



U.S. Food and Drug Administration

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## **NDA 22-250: Fampridine AC Backgrounder**

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# MEMORANDUM

## DEPARTMENT OF HEALTH & HUMAN SERVICES

### Public Health Service

### Food and Drug Administration

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**Date:** September 16, 2009  
**From:** Eric Bastings, MD. Deputy Director, Division of Neurology Products  
**Through:** Russell Katz, MD. Director, Division of Neurology Products  
**To:** Members of the Peripheral and Central Nervous System Drugs Advisory Committee  
**Subject:** NDA 22250 for Fampridine Sustained Release (Amaya)

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As you know, the Peripheral and Central Nervous System Drugs Advisory Committee will meet on October 14, 2009 to discuss New Drug Application (NDA) 22250 for Fampridine Sustained Release (Amaya). In preparation for that meeting, the division is providing the following reviews for your consideration:

- Clinical safety, by Dr. Gerald Boehm (team leader Dr. Sally Yasuda)
- Clinical efficacy, by Dr. Kachi Illoh (team leader Dr. Billy Dunn)
- Statistics, by Dr. Sharon Yan (team leader Dr. Kun Jin)
- Clinical Pharmacology/Biopharmaceutics, by Dr. Dr. Jagan Parepally and Dr. Joo-Yeon Lee (team leader Dr. Angela Men and Dr. Yaning Wang).

## 1. Introduction

Acorda submitted a new drug application (NDA) to support the marketing of fampridine Sustained Release (Amaya) for the (symptomatic) improvement of walking ability in patients with multiple sclerosis (MS). This is a new indication, never granted by the Agency, as currently approved MS drugs are indicated to decrease relapse rate, and in some cases to prevent the accumulation of disability.

Fampridine (also known as 4-aminopyridine) is a potassium channel blocker that has a long history of use in the United States, even though it was never approved by the FDA. Prior to its investigational and off label use in humans, 4-aminopyridine has been known primarily as a bird poison (trade names Avitrol 200 and Avitroland, classified by the EPA as a Restricted Use Pesticide), and as a research tool to characterize subtypes of potassium channels in bench research. Based on non clinical evidence suggesting that 4-aminopyridine enhances action potential conduction in demyelinated nerve fibers, the drug has been compounded in pharmacies and used off-label with the goal of improving walking in a number of neurological conditions for more than 20 years. That off label use was not based on substantial evidence from adequate and well controlled studies.

4-aminopyridine has been investigated since the early nineties in a number of clinical studies, both by research and pharmaceutical sponsors (first by Elan, and since 1998 by Acorda). Various neurological disorders have been targeted, including Guillain-Barre syndrome, spinal cord injury and multiple sclerosis. Acorda has conducted a total of 56 studies for these three indications, but in recent years has concentrated their clinical



development on the latter indication, as studies in Guillain-Barre syndrome and spinal cord injury have been largely negative.

For the multiple sclerosis indication, the subject of this new drug application, the sponsor has conducted two pivotal efficacy studies under special protocol assessment (SPA) program. As stipulated in the SPA guidance, “having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident”. The SPA guidance also stipulates that “However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application”.

As discussed at greater length below, the proposed primary efficacy endpoint is novel, and has no precedent in regulatory use. As always, novel endpoints may pose clinical interpretation issues, and may turn out to be less than satisfactory. In that setting, the analysis of supportive secondary endpoints and sensitivity analyses are key to gauge the clinical significance of the trials results.

Both pivotal studies of this NDA met their primary endpoint, and met the requirements of the special protocol assessments. Results on secondary analyses, however, gave inconsistent results, and indicated a very limited effect on walking speed.

In its regulatory decisions, the Agency balances the risks and benefits of new drug products. In this NDA, the efficacy must be considered against a widely acknowledged safety signal for 4-aminopyridine, and other pyridine compounds: seizures.

## **2. Background**

4-aminopyridine was initially studied by research and pharmaceutical sponsors in MS patients using an immediate release formulation. Seizures occurred in 6/178 MS patients treated with immediate release formulations, all at doses higher than 20 mg/day. As noted by Acorda, “A potentially narrow therapeutic index, with C<sub>max</sub> related to the risk of seizure, was one important justification for the development of the sustained-release formulation of the drug, fampridine-SR”.

Phase 2 development for the MS indication using the SR formulation began with Study MS-F201. This was a multi-center, double-blind, placebo-controlled, dose-ranging study, with a primary objective to determine the tolerability of escalating doses of Fampridine-SR 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg administered twice daily. In that study, in which 36 patients were enrolled, two patients experienced convulsions, one at 30 mg b.i.d, and the other at 35 mg b.i.d. Acorda also noted discontinuations due to adverse events at doses of 25mg b.i.d. and higher, and concluded that future studies should concentrate on evaluating doses in the range of 10-20 mg b.i.d.

Study MS-F202 followed. In that double-blind, placebo-controlled, parallel group, 20-week study (12 on stable dose treatment), Acorda investigated 206 patients, randomized 1:1:1:1 to placebo, 10 mg b.i.d., 15 mg b.i.d., and 20 mg b.i.d. of fampridine-SR tablets.



The primary efficacy variable was the percent change from baseline in average walking speed measured using the Timed 25-Foot Walk Test from the Multiple Sclerosis Functional Composite (MSFC). Two patients experienced seizures while on 20 mg b.i.d. fampridine-SR. One patient experienced two complex partial seizures after taking an overdose of study drug, resulting in a dose of 40 mg at the time of seizure, and one patient experienced a tonic-clonic seizure. An additional patient experienced an “altered mental state” while on 15 mg b.i.d., also after taking an overdose of study drug, receiving 30 mg at one time. No significant effect was demonstrated on the primary endpoint.

An end-of-phase 2 meeting in August 2004 followed, to discuss the results of study MS-F202. The division observed that Study MS-F202 appeared to be a negative study, with no significant difference between any of the doses tested and placebo for the primary outcome measure (p-values respectively 0.82, 0.40 and 0.78 for the 20mg, 30mg and 40mg dose groups). The division also questioned the clinical significance of the change in walking speed observed over the up- titration and stable-dose visits (estimated by Acorda at 0.179 ft/sec). The division noted that even if statistical significance was reached with an effect size of that magnitude (i.e. with a larger sample size), the division would not be convinced of the clinical significance of that change.

At the end-of-phase 2 meeting, Acorda proposed as a primary endpoint for the phase 3 pivotal trials the change from baseline in walking speed on the Timed 25 Foot Walk, and proposed to study the dose of 15mg of 4-aminopyridine b.i.d.. The division required that Acorda propose a co-primary outcome measure to validate the clinical significance of any change observed on the 25-ft Timed Walk Test in phase 3 studies, or submit data to validate the functional significance of changes on that scale. The division expressed concern about the occurrence of seizures in the trials to date, and at doses close to those proposed for the pivotal trials. The division noted that even though this represents an expected side effect with a drug of this class, this may be a significant issue if the drug is not shown to have a robust and significant clinical benefit. The division indicated that long term safety studies need to well define the risk of seizures in MS patients.

After the end-of-phase 2 meeting, Acorda performed additional post-hoc analyses of study MS-F202. Acorda informed the division that these analyses suggested that patients who met a responder criterion for a consistent response (increase in walking speed in  $\geq 3$  visits on drug compared to the fastest walking speed in several pre-treatment sessions) experienced a  $>25\%$  average increase in walking speed over the treatment period and that this increase did not diminish across the treatment period. Acorda proposed to use that responder definition in phase 3 as a primary outcome measure.

In a December 2004 telecon, the division responded that Acorda had not established the clinical meaningfulness of the proposed responder analysis, and asked Acorda to either to validate the proposed primary outcome before conducting the proposed study (Acorda suggested using published literature for that purpose), or to prospectively define a co-primary endpoint (such as the Subject Global Impression scale) to support the clinical meaningfulness of changes seen in a responder analysis.



Acorda recognized that the proposed responder criterion did not define the full characteristics of the response, and did not specify the amount of improvement nor that the improvement must be stable over time. As presented by Acorda, a progressive decline in effect during the course of the study period, even one resulting in speeds slower than the maximum non-treatment value, would not be excluded by the criterion. The division also observed that since responders are only expected to have an improvement in three out of four visits, patients may have no positive drug effect remaining at the last visit, and still be declared responders.

Acorda sent in March 2005 a special protocol assessment request for the first pivotal efficacy Study (MS-F203), which was a double-blind, placebo-controlled, 21-week, parallel group study evaluating fampridine SR 10 mg b.i.d. For that study, Acorda proposed a sequential analysis that would define the primary endpoint as follows: (1) Acorda would test if there are significantly more responders in the treatment group than in the placebo group (2) Acorda would then compare the responders and non-responders for their improvement on the MSWS-12 score as a measure of the global impact of walking improvements on perceived disability. A statistically significant improvement in responders compared to non-responders in this measure would serve to validate the clinical meaningfulness of the responder criterion (3) Acorda would test for significant improvement in walking speed at the last visit on drug for the Fampridine-treated responders versus the placebo-treated group (responders plus non-responders).

The Division agreed that Acorda had addressed some of FDA concerns with regard to the responder criterion [by adding the second step of the primary analysis]; however, the Division had remaining concerns regarding the maintenance of the effect, which were discussed during an April 2005 teleconference. In particular, the Division remained concerned that the proposed endpoint did still allow that the treatment may result in a negative response slope among responders, with no clinically significant drug effect at the last visit. The Division emphasized that the endpoint as defined allows that one could lose effect during the treatment period and still be positive on the analysis- that one could do very much worse on drug at the end of the treatment period than at the beginning yet still beat placebo. The Division also remarked that for the 3rd step of the analysis testing, the fampridine responder group is a small selective group which is very likely to beat the placebo group regardless of the treatment effect. The division observed that in fact, if the roles of comparison groups were reversed, it is likely that the responders in the placebo group would beat the Fampridine group (responders and non-responders) as well. Acorda agreed that this might be the case, but pointed out that the endpoint analysis is not meant to prove efficacy, but only to prove that some treatment effect is maintained at the final visit for the Fampridine responders. The Division, at the time, accepted the argument.

It was concluded that MS-F203 with the minor changes discussed could, if positive, be one of the adequate and well controlled studies that demonstrate efficacy. FDA emphasized that “as usual, the division will evaluate the risk and benefits of the treatment to determine approvability.” [emphasis added]



In December 2006, Acorda requested a special protocol assessment for their second pivotal phase 3 study (MS-F204), and asked FDA whether “pending the availability of clinical results, does the Division agree that the two studies (MS-F203 and MS-F204) would be adequate to support an NDA for Fampridine-SR”. Study MS-F204 had a design similar to Study MS-F203, and in particular used the same responder definition. The main difference was a shorter duration (13 weeks), which FDA accepted as Study MS-F203 had the potential to provide sufficient information regarding the long-term efficacy of fampridine. However, Acorda initially did not include in Study MS-F204 several of the key secondary endpoints of Study MS-F203, in particular the Ashworth Assessment of Spasticity, MSWS-12, SGI, and CGI. FDA asked Acorda to include these secondary endpoints in Study MS-F204. FDA noted that while statistical significance need not be demonstrated for these secondary endpoints in the new trial, this information would be considered in the review of all of the evidence available on efficacy. FDA also asked for data to evaluate whether the drug effect on gait is present throughout the dosing interval, or if there is an end-of-dose wearing off of efficacy. FDA noted that this could be accomplished by, at least at one of the visits, evaluating patients at various times during the dosing interval, or by evaluating patients at different times at the various visits, to cover the dosing interval. FDA also noted that the labeled indication would be based on substantial evidence from clinical trials, and that while it was premature to finalize the indication at that time, but it was not clear that Acorda would have the evidence required to support the indication proposed by Acorda, which included disability claims.

Acorda revised their study protocol, and FDA expressed agreement to the changes in May 2007.

In February 2008, FDA contacted Acorda to express concern regarding frequency of seizures reported in recent submissions to the Agency. FDA noted that several cases had occurred at doses of 10 mg b.i.d (the dose investigated in pivotal efficacy studies), which was a new finding at the time (and a finding that was identified after special protocol agreement was reached). FDA asked Acorda to address this issue in the NDA submission. FDA noted that while there appears to be a dose relationship between the drug and seizures, the rate at doses higher than 10 mg b.i.d cannot be ignored, and emphasized that the proposed indication [symptomatic treatment to increase walking speed] drove the concern. FDA insisted that the risk/benefit of the drug is always considered while reviewing a new drug application.

A pre-NDA meeting took place on October 27, 2008. At that meeting, FDA requested as a secondary efficacy analysis the change from baseline at each double-blind visit and at the last visit. FDA stressed the importance of preserving type 1 error in secondary comparisons. FDA asked Acorda to provide analyses not only of patients identified as responders, but also of entire treatment groups (i.e. drug vs. placebo). The indication was also discussed. Acorda proposed that “Fampridine-SR is indicated for the treatment of walking disability in people with Multiple Sclerosis to improve mobility and leg strength and related activities of daily living”. FDA indicated that any claim must be supported by independent substantiation of an effect on a relevant and valid endpoint. The Agency noted the data appeared to have demonstrated an effect on walking speed in at least 2



independent clinical trials, but not to support any additional claim (i.e. disability, strength). The sponsor would need to show an effect on relevant endpoints in the entire randomized population (i.e. limiting that analysis to only the subgroup of responders would not be valid). One suggestion was to design a study where the sponsor first identify responders, and then re-randomize these patients to active drug or placebo, prospectively conducting the primary analysis on the disability and leg strength endpoints. FDA also commented that the MSWS-12 walking scale has not been fully validated to support a disability claim, and that a full validation would be required, in collaboration with the FDA patient-reported outcome (PRO) review group.

The NDA was submitted on April 22, 2009.

### **3. CMC**



### **4. Clinical/Statistical- Efficacy**

Acorda conducted two pivotal efficacy studies: Study MS-F203 and MS-F204.

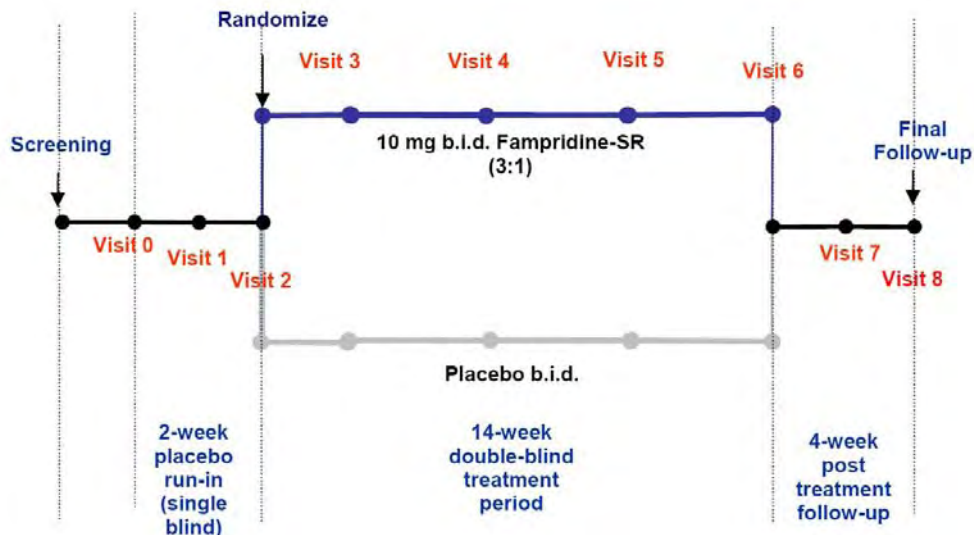
Study MS-F203 was a double-blind, placebo-controlled, 21-week, parallel group study. A single dose, 10 mg b.i.d. was evaluated in 304 patients with MS. To be included, patients had to carry a diagnosis of clinically definite MS, be aged 18 to 70 years, and be able to perform two trials of timed 25 foot walk within 8-45 seconds at the screening visit. Study design is summarized in Figure 1.

As discussed by Dr. Yan and Dr. Illoh, eligibility for the study was evaluated at Visit -1, after which subjects returned to clinic one week later for a new assessment of walking at Visit 0, which represented the beginning of a single-blind two-week placebo run-in



period. Subjects returned for another assessment at Visit 1 after one week. Immediately following the placebo run-in, patients were randomized at Visit 2 to fampridine or placebo (in a 3:1 ratio) to begin 14 weeks of treatment. Figure 1, copied from the statistical review, shows the design of Study MS-F203.

**Figure 1: Design of Study MS-F203**



Visit 6 marked the end of the 14-week randomized treatment period. At this visit, patients began a four-week follow-up period during which no study medication was to be taken. Patients returned to the clinic after two weeks and after 4 weeks for follow-up assessments at Visit 7 and Visit 8.

The primary efficacy variable was based on a responder definition. To be considered a responder, a patient had to have 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).

As discussed above, the division had no precedent for use of such a responder definition, and was concerned about the clinical significance of a response based on the proposed criteria. In response to the division's concerns, the second step of the primary analysis consisted of testing whether the responders identified registered a significant improvement in MSWS-12 score, when compared to non-responders, regardless of treatment group. The MSWS-12 is based on 12 questions asking patients to rate their limitations in mobility during the preceding two weeks on a 5-point scale (from 1 = not at all to 5 = extremely). In response to another FDA concern regarding the possibility of a negative response slope, the third step of the primary endpoint analysis tested whether patients who responded to Fampridine-SR would still register a significant improvement in walking speed relative to placebo-treated patients at the last observed double-blind visit (i.e., the change from baseline in walking speed at the double-blind endpoint). The



reader is referred to the background discussion above for a more detailed discussion of the proposed endpoints and the interactions between Acorda and FDA regarding the endpoints.

Several secondary analyses were either proposed by the sponsor or required by the FDA, including an evaluation of lower extremity motor strength (LEMMT), spasticity (Ashworth), clinician global impression of change (CGI), and subject global impression of change (SGI). As noted by Dr. Illoh, the CGI, as administered in the study, is uninterpretable, because the assessor had access to the findings of the Timed 25 Foot Walk, Ashworth or LEMMT when conducting the CGI. Therefore, I will not discuss it further.

As discussed by Dr. Yan and Illoh, Study MS-F203 showed statistically significant results for all three steps of the primary analysis, with 35% of the 224 Fampridine-treated subjects and 8% of the 72 placebo-treated subjects meeting the responder definition ( $p < .0001$ ). The mean reduction from baseline in average MSWS-12 over the double-blind period in fampridine or placebo responders was 6.84, compared to an increase of 0.05 among the non-responders ( $p = 0.0002$ ). The mean change in walking speed from baseline to the end of the double-blind was 0.10 ft/sec for the placebo group and 0.52 ft/sec for the fampridine responder group ( $p < .001$ ).

A major limitation of the second step of the primary analysis (MSWS-12) is that as the MSW12 measures the same domain as the time 25-foot walk (walking), and both are correlated, it is not unexpected that patients doing better on the 25-foot also do better on the MSW12. Therefore, a posteriori, it is not clear that this truly validates the significance of the responder definition analysis.

Considering the known safety issues with fampridine (seizure risk), and to better understand the risk/benefit profile of the product, the review team conducted additional analyses, which were based on a more traditional assessment of drug effects, comparing the fampridine and placebo groups (without using the “responder” definition). In the supportive analyses shown in Table 1, no adjustment for multiple comparisons was applied, and the p value estimates must be interpreted in that context.



**Table 1: FDA analyses of Study MS-F203**

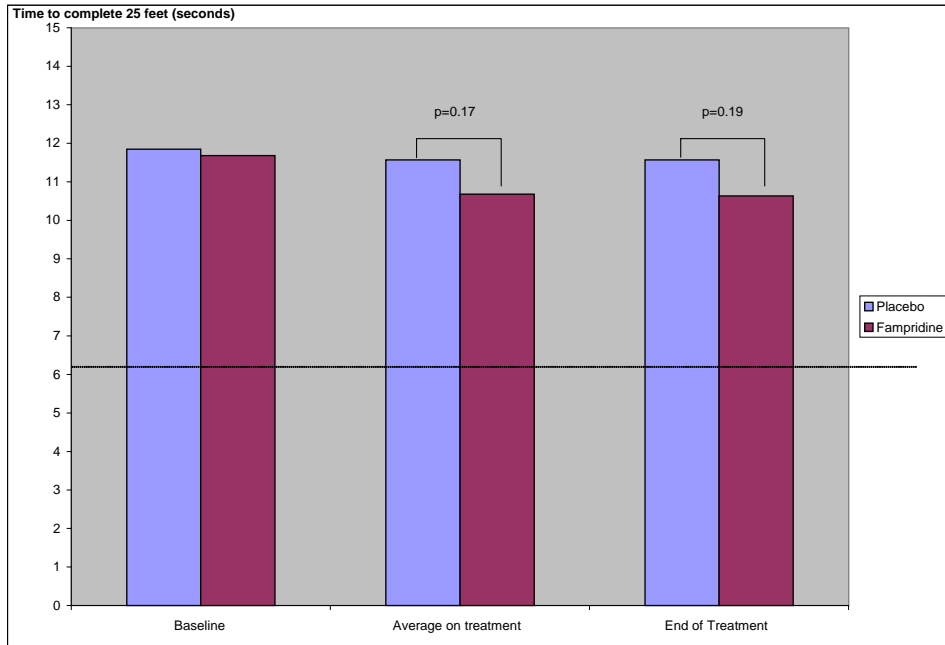
<b>Study MS-F203</b>	<b>Placebo (n=72)</b>	<b>Fampridine (n=224)</b>	<b>p value</b>
Baseline walking speed (ft/sec)	2.12	2.14	0.88
Visit 6 Walking speed (ft/sec)	2.16	2.35	0.19
Walking speed change Visit 6 vs. baseline (ft/sec)	0.05	.21	0.03
Walking speed change Visit 6 vs. baseline (%)	5.58	10.90	0.24
Walking speed on drug (average)	2.16	2.34	0.17
Walking speed change (ft/sec) on drug (average) vs. baseline	0.10	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

Table 1 shows that the average walking speed during the double-blind treatment was not significantly different between fampridine and placebo ( $p=0.17$ ). Likewise, the walking speed at the end of the double-blind treatment (Visit 6) was not different between fampridine and placebo ( $p=0.19$ ). As noted by Dr. Illoh and Dr. Yan, despite the lack of significant difference between the treatment groups for walking speed during the treatment periods, the comparison of the walking speed change between the baseline period and the average of the entire double-blind period, and between Visit 6 and baseline both had p values under 0.05 (unadjusted for multiple comparisons). Changes were however of small magnitude, with a walking speed increased of 0.21 ft/sec for fampridine group between baseline and Visit 6, and a 0.05 ft/sec increase for placebo group. That change translated into a 0.88 seconds difference between fampridine and placebo to complete the 25-foot walk.

To illustrate this drug effect, I plotted the time to complete the 25-foot walk for the placebo and fampridine group at baseline, on average during the treatment period, and at the end of the treatment period (Figure 2). The dotted line on Figure 2 is based on a normal walking time (4ft/sec, which corresponds to 6.25 seconds to complete the 25-foot walk).



**Figure 2: Time to complete the 25 feet distance in Study MS-F203 (dotted line represents normal time in healthy subjects)**



The other contrasts with a p value under 0.05 in Study MS-F203 were for the comparison of lower extremity strength and Ashworth score between fampridine and placebo. The modified British Medical Research Council (BMRC) manual muscle testing procedures were to be followed to estimate muscle strength bilaterally in four groups of muscles: hip flexors, knee flexors, knee extensors, and ankle dorsiflexors. On that scale, strength is rated from 0 (no movement) to 5 (normal strength). The effect size difference (0.09) between the treatment groups is clinically difficult to interpret. Similarly, the effect size difference (0.09) on the Ashworth score (which averaged the spasticity score for the hip adductors, knee flexors and knee extensors, on a scale 0-4) is of questionable clinical meaningfulness.

While there was a (not significant) trend favoring fampridine for the change from baseline to Visit 6 in MSWS-12 scores ( $p=0.06$ ), most of the improvement occurred during the pre-treatment period (before patients were exposed to fampridine), which again leads to question the meaningfulness of that change.

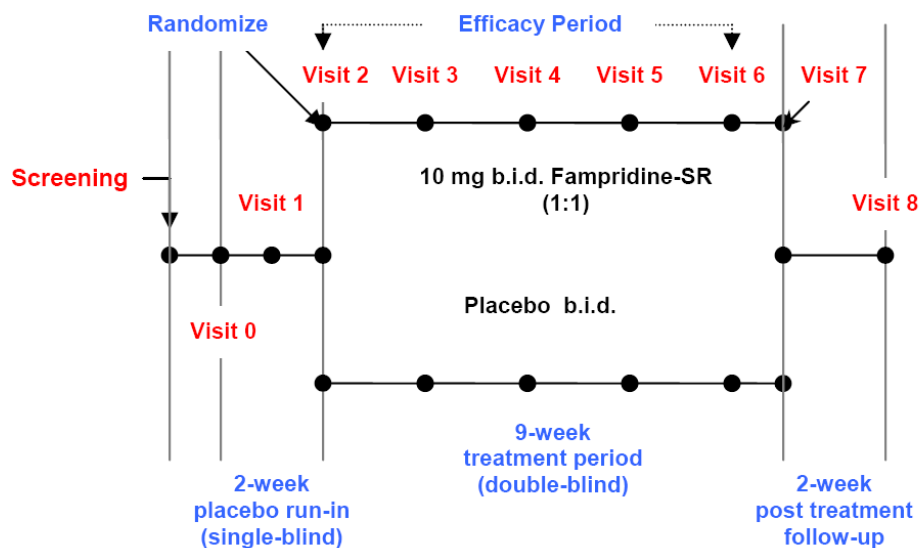
Finally, the Subject Impression of Change (SGI) was no better for fampridine than for placebo ( $p=0.122$ ). SGI was evaluated by asking patients to rate themselves based on the following question: “how do you feel about the effects of the study medication over the past 7 days?”, on a scale 0-7, where 0 was “terrible” and 7 “delighted”. The lack of significant difference on that endpoint also questions the clinical relevance of the effect noted on the responder rate and the MSW12.

Overall, Study MS-F203 met its primary efficacy endpoint, but improvement in walking speed was of questionable clinical significance.



Study MS-F204 had a design similar to that of F203, with the exception of a shorter (9 weeks) double-blind treatment period. The treatment group comparisons with respect to efficacy were based on the first eight weeks of double-blind treatment; end of dosing interval activity (pharmacokinetics and pharmacodynamics of drug) was also evaluated at the end of the final (9<sup>th</sup>) week of double-blind treatment. A total of 239 patients were randomized into the study; 119 were assigned to placebo and 120 to 10 mg b.i.d. Fampridine-SR. Figure 3, copied from the statistical review, displays the general scheme.

**Figure 3: Design of Study MS-F204**



The primary efficacy variable was based on the same responder definition as used in Study MSF-203. The same secondary endpoints as in Study F-203 were also assessed: Ashworth spasticity scores, MSWS-12, SGI, and CGI). The study met its primary efficacy endpoint, as the number of “responders” was significantly higher ( $p < 0.01$ ) for fampridine (43%) than for placebo (9%).

The review team conducted the same analyses comparing the entire treatment groups (without regard to responder status) as in Study MS-F203 (Table 2).

**Table 2: FDA analyses of Study MS-F204**

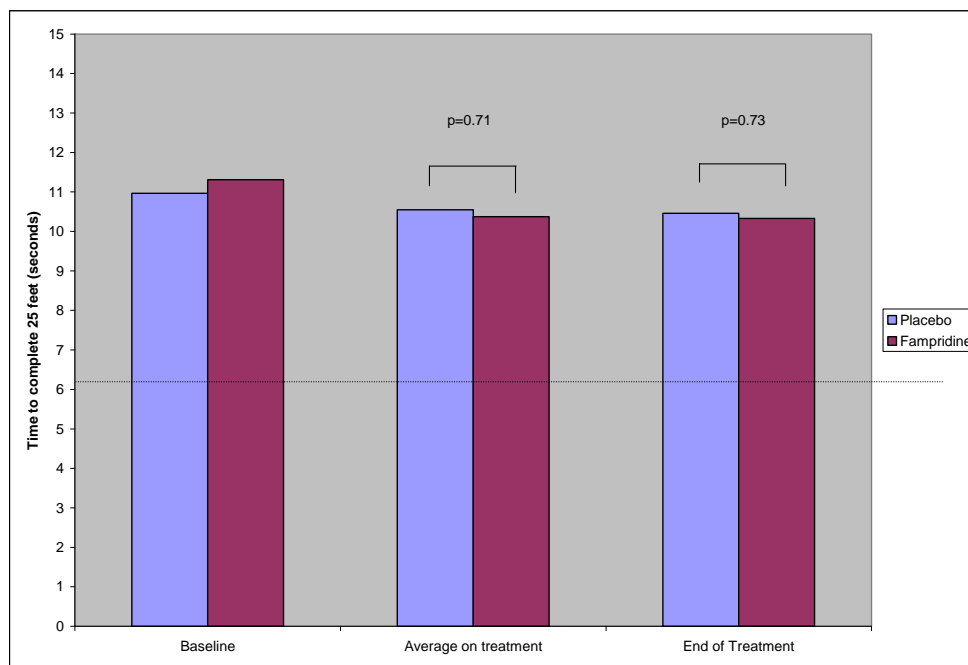
Study MS-F204	Placebo	Fampridine	p value
Baseline walking speed (ft/sec)	2.28	2.21	0.5463
Visit 6 Walking speed (ft/sec)	2.39	2.42	0.7284
Walking speed change Visit 6 vs. baseline (ft/sec)	.11	.22	0.0425
Walking speed change Visit 6 vs. baseline (%)	4.87%	10.64%	0.0392
Walking speed on drug (average)	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



Study MS-F204	Placebo	Fampridine	p value
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	.1059
Ashworth change on drug vs. baseline	-0.06	-0.18	0.0153

The results of FDA analyses are very similar to those of Study MS-F203: no significant difference between fampridine and placebo either for the average walking speed during the double-blind period or Visit 6, but contrast under  $p=0.05$  (unadjusted for multiple comparisons) for the change between baseline and Visit 6. Dr. Yan calculated that the walking speed change between baseline and visit 6 (end of double blind period) favored fampridine by 0.11 feet/seconds, which translates into a 0.5 second difference to complete the 25 feet distance. As for Study MS-F203, I plotted the time to complete the 25-foot walk for the placebo and fampridine group at baseline, on average during the treatment period, and at the end of the treatment period in Study MS-F204 (Figure 4). The dotted line on Figure 2 is based on a normal walking time (4ft/sec).

**Figure 4: Time to complete the 25 feet distance in Study MS-F204 (dotted line represents normal time in healthy subjects)**



In Study MS-F204, the contrast for the MSW12 score changes was under  $p=0.05$ , but there was no significant difference between fampridine and placebo for the SGI ( $p=0.19$ ), or the lower extremity strength test ( $p=0.11$ ). The contrast for Ashworth change favored fampridine ( $p=0.015$ ), but the magnitude of change was clinically small (fampridine-placebo difference of 0.12 on a scale 0-4) .

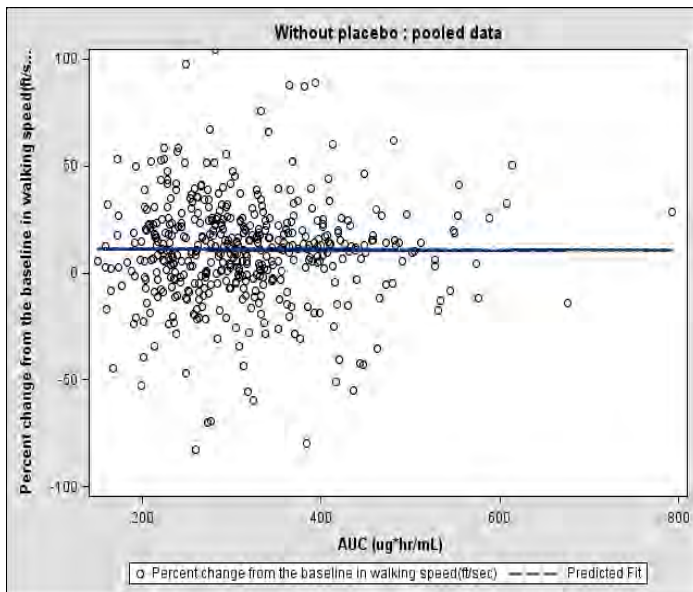


## 5. Pharmacometrics

Dr. Joo-Yeon Lee analyzed fampridine exposure-response relationship, based on the percent change in walking speed from baseline to the end of double blind phase. The methodology applied is described in detail in her review.

Briefly, Dr. Lee conducted a linear regression analysis for the pooled data of Study MS-F202, 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 b.i.d, 15 mg b.i.d or 20 mg b.i.d. Figure 5 (adapted from the clinical pharmacology and biopharmaceutics review) 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 bid, and did not improve with increased exposure.

*Figure 5: Dose-response analysis for efficacy*



Of course, this also indicates that a lower dose may be as efficacious as 10 mg bid, and that the lowest effective dose has not been identified by the development program. The identification of the lowest effective drug is particularly important for drugs with narrow therapeutic index, such as fampridine.

## 6. Safety

As discussed by Dr. Boehm, the safety database exceeds ICH guidelines for the standard experience needed to characterize common adverse events. Acorda included safety information on 917 MS subjects, 583 SCI subjects and 382 non-patient subjects. That experience includes comparative results from MS (fampridine  $n=507$ , placebo  $n=238$ ) and SCI controlled trials (fampridine  $n=277$ , placebo  $n=229$ ). In the NDA database, 780



subjects were exposed to fampridine for at least 6 months (601 MS subjects) and 444 were exposed for at least 1 year (405 MS subjects), with the majority receiving doses of at least 10 mg bid.

Dr. Boehm notes that deaths occurred infrequently in the fampridine clinical trials and the reported causes of death (oxycodone overdose, aortic dissection, suicide, unknown/found dead in bed, intracerebral hemorrhage, and fall) did not appear related to fampridine.

Dr. Boehm further notes that 15.1% of MS and SCI subjects experienced one or more serious adverse events (SAEs). Table 3 (adapted from Dr. Boehm's review) shows that the most commonly reported (in 3 patients or more) SAEs were multiple sclerosis relapse (2.5%), convulsion (1.3%), urinary tract infection (1.2%), and cellulitis (1.1%).

***Table 3: SAEs in MS and SCI clinical studies***

SAE Preferred Term	N (%)
Multiple sclerosis relapse	38 (2.5%)
Convulsion	19 (1.3%)
Urinary tract infection	18 (1.2%)
Cellulitis	16 (1.1%)
Pneumonia	13 (0.9%)
Sepsis	7 (0.5%)
Muscle spasticity	5 (0.3%)
Pulmonary embolism	4 (0.3%)
Deep venous thrombosis	4 (0.3%)
Nausea	4 (0.3%)
Asthenia	4 (0.3%)
Fall	4 (0.3%)
Anemia	3 (0.2%)
Atrial fibrillation	3 (0.2%)
Chest pain	3 (0.2%)
Influenza	3 (0.2%)
Urosepsis	3 (0.2%)
Hip fracture	3 (0.2%)
Osteoarthritis	3 (0.2%)
Breast cancer	3 (0.2%)
Complex partial seizures	3 (0.2%)
Encephalopathy	3 (0.2%)
Syncope	3 (0.2%)
Anxiety	3 (0.2%)
Decubitus ulcer	3 (0.2%)

Dr. Boehm observes that in MS controlled trials, SAEs were 3 times more frequent among fampridine-treated subjects (6.5%) than in placebo-treated subjects (2.1%) and the risk for all SAEs appeared dose related.

Dr. Boehm notes that 14.6% of MS and SCI subjects experienced one or more AEs leading to discontinuation. Table 4 (adapted from Dr. Boehm's review) shows the most common AEs leading to discontinuation among fampridine-treated subjects, that include



dizziness (2.5%), insomnia (1.5%), convulsion (1.3%), asthenia (1.3%), nausea (1.1%), anxiety (1.1%), and paresthesia (1.0%).

**Table 4: Most frequent discontinuations due to adverse dropouts in MS and SCI clinical studies**

AE Preferred Term	N (%)
Dizziness	38 (2.5%)
Insomnia	22 (1.5%)
Convulsion	19 (1.3%)
Asthenia	19 (1.3%)
Nausea	17 (1.1%)
Anxiety	17 (1.1%)
Paresthesia	15 (1.0%)
Headache	14 (0.9%)
Muscle spasticity	12 (0.8%)
Tremor	12 (0.8%)
Muscle spasms	10 (0.7%)
Difficulty in walking	9 (0.6%)
Fatigue	9 (0.6%)
Confusional state	9 (0.6%)
Vision blurred	7 (0.5%)

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.

Table 5 (copied from Dr. Boehm's review) shows common adverse events that were more common on fampridine than on placebo and had a frequency of 1% or more in MS controlled trials. Highlighted rows indicate an incidence at least 2 times higher in a fampridine dosage group than on placebo.

**Table 5: Common AEs in MS controlled 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)
Urinary tract infection	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)
Multiple sclerosis 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)
Paresthesia	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)



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)
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)
Diarrhea	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
Dyspnea	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

The principal safety issue with fampridine is the risk of seizures. Dr. Boehm notes that data from the controlled clinical trials at the 10mg bid dose did not suggest a difference in seizure risk compared to placebo, but this comparison relied on only 400 Fampridine SR treated patients, 238 placebo patients and only 2 seizure events (1 fampridine, 1 placebo). Dr. Boehm further observes that in these same studies, at 20 mg bid (only a doubling of the dose intended to be marketed), the seizure risk was 10-fold higher (based on 2 events



in 57 subjects), a concerning finding suggesting to Dr. Boehm a narrow therapeutic index.

Dr. Boehm notes that in open-label trials, the seizure risk at 10mg bid was similar to the risk seen in controlled trials. Dr. Boehm cautions that the results from this open label population must be considered very 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 2/3 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.

The review team also tried to identify from available pharmacokinetic data if patients who experienced seizures represented outliers (with unusually high fampridine exposure), which would provide some reassurance regarding the safety of the 10 mg b.i.d. dosing. For the 5 patients who had a seizure in controlled trials (Studies MS-201,-202,-203 and -204), Dr. Lee and Dr. Wang looked into each patient narrative to identify the date and time (if available) of seizure incidence, and then compared these to the time of fampridine plasma concentration collection time. The principal limitations of these data is that the plasma level and seizure occurrence were separate by a delay of several hours or days. Nevertheless, the data suggest that seizures occurred at exposure levels within the range expected for the 10 mg b.i.d. dose, as the maximum fampridine concentration observed for the 10 mg b.i.d dosing regimen was 87.3 ng/ml (see Table 6).

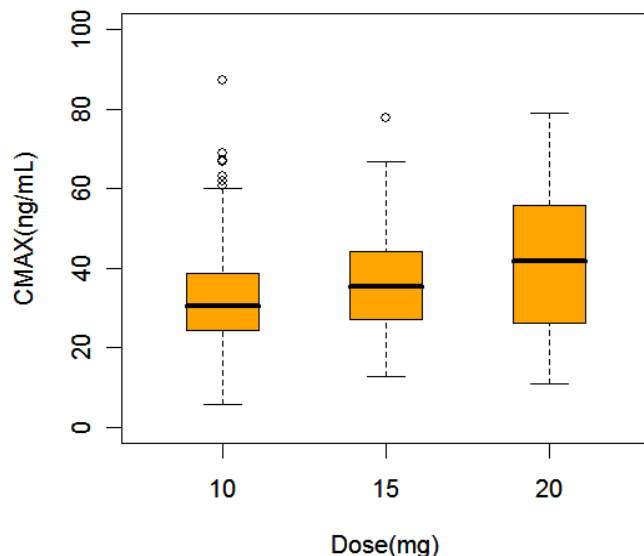
**Table 6: Fampridine exposure in patients who experience seizures**

Study	Subject	PK (ng/ml)	PK date and time	Previous dosing date and time	Time after dose(hr)	Previous dose (mg)	Seizure date and time	PK at seizure time (ng/ml)
MS-F203	14003	63	Dec 12, 2005, 10:23AM	Dec 12, 2005, 8:36AM	1.8	10	Dec 17, 2005, no specific time	~63 (assume dose was taken regularly)
MS-F202	04006	35.5	Aug 21, 2003, 2:52PM	Aug 21, 2003, 9:00AM	5.9	20	Aug 26, 2003, no specific time	>35.5 (Aug 21 is the first dose titrated to 20mg)
MS-F202	07019	79	Sep 23, 2003, 12:32PM	Sep 23, 2003, 8:00AM	4.5	40	Sep 23, 2003, 2 hr during afternoon and evening	<79 (close to trough)
MS-F201	03002	117	Mar 27, 2001, 1:10PM	Mar 27, 2001, 9:15AM	3.9	25	Mar 30, 2001, no specific time	~117*30/25=140 (Mar 27 is the first dose titrated to 30mg)
MS-F201	02006	99.6	May 16, 2001, 12:45PM	May 16, 2001, 8:00AM	4.75	25	May 27, 2001, no specific time	~99.6*35/25=139(May 27 is the first dose titrated to 35mg)



Pharmacokinetic data (Figure 6) also indicate that there is a large overlap of exposure between the dose proposed for marketing (10 mg b.i.d), and the first dose associated to an increased incidence of seizures (20 mg b.i.d).

**Figure 6: Distribution of Cmax at each dose group (pooled data from Study MS-F202, 203 and 204)**



Dr. Boehm emphasizes that comparing the seizure risk in the Fampridine SR clinical trial population with background data or data from other MS drug development programs must also be viewed with caution. Dr. Boehm believes that the screening in the fampridine trials and usual concerns about potentially important differences among the Fampridine SR population and the general MS background population or other drug development program populations make these comparisons problematic.

Dr. Boehm concludes that the current evidence supports a dose-related risk of seizure with fampridine, with limited experience at the dose intended for treatment, and some evidence of increasing risk just above the therapeutic dose. I concur.

Dr. Boehm also reviewed results from the pooled analysis of AEs from the controlled MS trials that demonstrated an apparent dose-related increased risk of multiple sclerosis relapse among fampridine-treated subjects compared to placebo. Dr. Boehm notes that the difference in MS relapse risk between fampridine and placebo was driven by differences in the post-treatment period, when subjects were not taking Fampridine SR. He notes that this finding is based on very limited observation time (2 weeks), and that the MS relapse risk in the fampridine-treated group prior to initiating treatment was 4-fold higher (30.3/100PY) than the risk in the placebo group during the pre-treatment phase (7.3/100PY). The reason for the observed difference in MS relapse risk between



Fampridine SR subjects and placebo subjects is not clear to Dr. Boehm. Dr. Boehm notes that the available data presented in the narratives for these events are not sufficient to allow differentiation between waning therapeutic effect (as suggested by Acorda) and relapse of the MS disease process. Dr. Boehm observes that some of these events appeared to be true relapses to clinicians because they resulted in hospitalization and treatment with steroids. Finally, Dr. Boehm comments that data from patients who experienced relapse during the post treatment phase and who continued in open label extension phases is reassuring, as they did not suggest continued increased MS relapse risk among these patients. Furthermore, there did not appear to be an increased MS relapse risk in the extension trial patients compared to the RCT patients. Overall, I agree with Dr. Boehm that there is not a clear signal for increased relapses in fampridine-treated patients.

Another safety issue identified by Dr. Boehm is an increased risk for urinary tract infections in fampridine-treated patients compared to placebo patients. Dr. Boehm notes that in many cases, these events were diagnosed based only on symptoms and UA and/or urine cultures were not performed. Dr. Boehm believes that there is insufficient evidence to evaluate Acorda's hypothesis that these UTI events represent drug related sensory symptoms rather than actual infections. As there was no consistent increase in SAEs related to these infections, appropriate description in labeling should be appropriate to address this issue.

Lab data, vital sign data and ECG data collected during the clinical trials did not find evidence of Fampridine SR related deleterious effects. A formal QT study did not find evidence of QT prolongation in subjects exposed to Fampridine SR.

## **7. Summary and Questions to the Peripheral and Central Nervous System Drugs Advisory Committee**

The sponsor has submitted the results of two adequate and well-controlled trials in which statistically significant between-treatment differences were seen on the primary outcome in both studies: the proportion of patients who met responder criteria. Analyses of the drug-placebo difference in the change from baseline in time to complete the 25 foot timed walk reached statistical significance in both studies, but was numerically quite small, and the average time to complete the 25 foot walk was not different between the treatment groups in either study. For these reasons, it appears that the clinical meaning of the differences seen on the primary outcomes is in question.

Further, fampridine causes seizures in a dose-dependent fashion. Although the risk of seizures in the MS controlled trials at 10 mg BID was the same as in placebo (1 seizure in each group), and the risk of seizures in the open-label experience at this dose was the same as in the controlled trials, an increased risk was seen at 20 mg BID. Importantly, although the plasma levels of fampridine at which seizures were seen is not completely clear, there is reason to believe that a not insignificant proportion of patients treated with 10 mg BID might achieve the levels associated with seizures, and in any event there is



considerable overlap in the plasma exposures at 10 and 20 mg BID. In addition, it is difficult to compare the risk of seizures in the sample of MS patients included in these studies to published background seizure rates in MS patients, because patients in these trials were screened and were shown to have no evidence of seizure activity on EEG prior to receiving treatment with fampridine.

We are asking the Committee's help in addressing whether the benefit to be obtained with fampridine is justified by the risk (primarily of seizures) to be expected in a population of MS patients who would be expected to receive the treatment if the application is approved. In this regard, we would like the Committee to consider the following questions:

- 1) Has the sponsor demonstrated substantial evidence of effectiveness of fampridine as a treatment to improve walking in patients with MS?
- 2) If so, has the sponsor demonstrated that this effect is clinically meaningful, either in the group of fampridine-treated patients as a whole, or in a specific subset?
- 3) If so, should the sponsor be required to evaluate the effects of doses lower than 10 mg BID?
- 4) If so, should this be required prior to approval?
- 5) If substantial evidence of a clinically meaningful effect has been demonstrated, do you conclude that there are conditions under which fampridine SR could be considered safe in use for this indication?
- 6) If so, what are those conditions (e.g., specific enrollment criteria, specific monitoring, etc.)?

We look forward to seeing you in October, and thank you for the work you have done in preparation for the meeting, and for your efforts at the meeting itself.



## CLINICAL REVIEW – EFFICACY

Application Type	NDA 505 (b)(1)
Application Number(s)	22-250
Priority or Standard	Priority

Submit Date(s)	04/22/2009
Received Date(s)	04/22/2009
PDUFA Goal Date	09/22/2009

Reviewer Name(s)	Kachi Illoh, MD, MPH
Review Completion Date	09/22/2009

Established Name	Fampridine Sustained Release (4-aminopyridine)
(Proposed) Trade Name	Amaya
Therapeutic Class	Selective potassium channel blocker
Applicant	Acorda Therapeutics, Inc.

Formulation(s)	Sustained Release 10 mg tablets
Dosing Regimen	Single tablet taken orally twice a day
Indication(s)	Improvement of walking ability
Intended Population(s)	Multiple sclerosis patients



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## **5 Sources of Clinical Data**

A total of 56 clinical studies (table listing below) were conducted in the development of fampridine, of which 19 were in healthy volunteers, 24 in MS patients, 11 in spinal cord injury (SCI), and 2 in Guillain-Barré Syndrome. In these studies, over 1,900 subjects were exposed to fampridine, of which over 1,600 were exposed to the Fampridine-SR formulation. Five of the MS investigations were extension studies that continued from completed trials. Excluding the extension studies, the MS trials enrolled 1,156 subjects.

The review of efficacy focuses more on two adequate and well-controlled phase 3 trials conducted under separate Special Protocol Assessments (SPAs), and to a less extent on a phase 2 dose ranging trial. The two phase 3 trials enrolled 539 subjects with MS to test the proposed indication dose.

### **5.1 Tables of Studies/Clinical Trials**



**Table , Listing of Clinical Studies/Trials (from sponsor's submission)**

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
<b>Clinical Trials in Non-Patients</b>						
<b>Open-Label Clinical Trials</b>						
0193-002 <sup>#</sup> 1 Healthy Volunteers	Open-label, single- dose, food effect, crossover 09-Mar-93 14-Mar-93	10 mg FAM-CR capsule 20 mg q.d., 30 mg and 40 mg b.i.d.	6	6 (100%), 0 — (18, 30) 100% Caucasian	Completed	Module 5.3.1.1
0195-006 1 Healthy Volunteers	Open-label, 2-way crossover 24-Feb-95 09-Mar-95	12.5 mg FAM-CR (with or without phosphate buffer) Single oral dose	4	4 (100%), 0 35.3 yrs. (16, 40) 100% Caucasian	Completed	Module 5.3.1.1
0494-006 <sup>#</sup> 1 Healthy Volunteers	Open-label, single- dose, 3-way crossover, relative bioavailability 07-June-1994 06-July-1994	12.5 mg FAM-SR tablet, 12.5 mg IR capsule	12	12 (100%), 0 24.4 (18, 32) 100% Caucasian	Completed	Module 5.3.1.1
0497-010 <sup>#</sup> 1 Healthy Volunteers	Open-label, single- dose, 5-way crossover, IVIVC	15 mg FAM-SR tablet, 15 mg FAM-IR tablet 15 mg	12	12 (100%), 0 27.2 (19, 38) —	Completed	Module 5.3.1.1
0791-011 <sup>#</sup> 1 Healthy Volunteers	Open-label, single- dose, food effect, 4- way crossover 1991	5 mg FAM-IR capsule, 20 mg FAM-CR capsule 20 mg	12	12 (100%), 0 — —	Completed	Module 5.3.1.1
Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
0792-001 1 Healthy Volunteers	Open-label, single-dose, randomized, 4-way crossover 22-Feb-93 04-May-93	10 mg FAM-IR 20 mg FAM-CR Single oral dose	13	13 (100%), 0 29.7 yrs. (25, 33) —	Completed	Module 5.3.1.1
0496-002 1 Healthy Volunteers	Open-label, single-dose 20-Jun-96 23-Jul-96	15 mg <sup>14</sup> C FAM solution Single oral dose	4	4 (100%), 0 20.7 yrs. (18, 22) 100% Caucasian	Completed	Module 5.3.3.1
1194-002 1 Healthy Volunteers	Open-label, randomized, 3-way crossover 31-Mar-94 31-May-94	12.5 mg FAM-SR tablet 12.5 mg FAM-SR capsule 12.5 mg FAM-IR capsule Single oral dose	12	12 (100%), 0 27.0 yrs. (23, 35) 100% Caucasian	Completed	Module 5.3.4.1
BE10-25F- SR100S122003 1 Healthy Volunteers	Open-label, single-dose, randomized, 3-way crossover 04-Dec-03 20-Dec-03	10 mg FAM-SR tablet 25 mg FAM-SR tablet 10 mg FAM solution Single oral dose	30	17 (57%), 13 (43%) 25.4 yrs. (19, 42) 83.3% Caucasian, 6.6% Black, 3.3% European/Middle Eastern, 3.3% Hispanic, 3.3% American Indian	Completed	Module 5.3.1.2
BE10F-SR22004 1 Healthy Volunteers	Open-label, single-dose, randomized, 2-way crossover 16-Mar-04 25-Mar-04	10 mg FAM-SR tablets (from 2 manufacturers, Patheon and Elan Corporation) Single oral dose	18	10 (56%), 8 (44%) 29.4 yrs. (20, 45) 100% Caucasian	Completed	Module 5.3.1.2



Clinical Review  
{Kachi Illoh, MD, MPH}  
{NDA 22-250}  
{Amaya, Fampridine Sustained Release}

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
BE25F-SRO22004 1 Healthy Volunteers	Open-label, single-dose, randomized, 2-way crossover 05-Mar-04 14-Mar-04	25 mg FAM-SR tablets (from 2 manufacturers, Patheon and Elan Corporation) Single oral dose	22	10 (45%), 12 (55%) 24.2 yrs. (19, 38) 95.5% Caucasian, 4.5% Black	Completed	Module 5.3.1.2
FeFa25F-SR112003 1 Healthy Volunteers	Open-label, single-dose, 2-way crossover 06-Nov-03 15-Nov-03	25 mg FAM-SR tablets Single oral dose	14	5 (36%), 9 (64%) 34.0 yrs. (26, 5) 78.6% Caucasian, 14.3% Asian, 7.1% Black	Completed	Module 5.3.1.2
0593-005 1 Healthy Volunteers	Open-label, randomized, single-dose, 5-period, crossover 08-Nov-93 14-Dec-93	15 mg FAM-IR capsule 15 mg FAM-CR capsule Single oral dose	10	10 (100%), 0 34.0 yrs. (27, 40) 100% Caucasian	Completed	Module 5.3.1.3
RD10F SR012004 3 15 Patients with Renal Impairment 5 Healthy Volunteers	Open-label, single-dose, non-randomized, 2-stage, parallel group 10-Feb-04 28-Jul-04	10 mg FAM-SR tablets Single oral dose	20	9 (45%), 11 (55%) 60.5 yrs. (19, 80) 75% Caucasian, 25% Black	Completed	Module 5.3.3.3
0194-002 1 Healthy Volunteers	Open-label, single-dose, randomized, 3-way crossover 31-Mar-94 31-May-94	15 mg FAM-CR 10 mg Baclofen 15 mg FAM-CR and 10 mg Baclofen Single oral dose	12	13 (100%), 0 29.8 yrs. (18, 40) 100% Caucasian	Completed	Module 5.3.3.4
Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
<b>Blinded Clinical Trials</b>						
ELA/G-9101 <sup>#</sup> 1 Healthy Volunteer	Double-blind, placebo- controlled, single ascending dose May-1991 June-1991	5 mg FAM-IR capsule up to 25 mg	8	8 (100%), 0 22.6 (20, 26) —	Completed	Module 5.3.3.1
0492-004 1 Healthy Volunteers	Single-blind, randomized, multiple-dose, 4-period, crossover 17-Jun-92 04-Aug-92	20 mg FAM-CR Oral b.i.d.	14	14 (100%), 0 28.8 yrs. (21, 47) 100% Caucasian	Completed	Module 5.3.4.1
TQTc-F-SR001 1 Healthy Volunteers	Double-blind, placebo-controlled, randomized, double-dummy, parallel group 17-Oct-07 03-Dec-07	10 mg FAM-SR Oral q12h 30 mg FAM-SR Oral q12h Placebo Oral q12h 400 mg Moxifloxacin/ Placebo Oral q12h	208	113 (54%), 95 (46%) 25.0 yrs. (18, 44) 87% Caucasian, 5% Black, 6% American Indian/ Alaskan Native, 2% Asian	Completed	Module 5.3.4.1
<b>Clinical Trials in MS Patients</b>						
<b>Open-Label Clinical Trials</b>						
0195-001US 1 MS Patients	Open-label, single-dose, 3-way crossover Mar-95 Apr-95	12.5 mg FAM-SR tablets Oral 12.5 mg FAM-SR capsules Single oral dose	13	7 (54%), 6 (46%) 47.5 yrs. (30, 60) 92% Caucasian, 8% Asian	Completed	Module 5.3.3.2



Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
0296-003US 1 MS Patients	Open-label study 14-May-96 27-Jul-98	12.5 mg FAM-SR tablet 17.5 mg FAM-SR tablet 22.5 mg FAM-SR tablet Oral b.i.d.	20	10 (50%), 10 (50%) 52.0 yrs. (31, 67) 95% Caucasian, 5% Asian	Completed	Module 5.3.3.2
0893-001US 1 MS Patients	Open-label, single-dose, 3-way crossover Mar-93 Dec-93	7.5 and 15 mg FAM-SR capsules Single oral dose	12	6 (50%), 6 (50%) 50.4 yrs. (41, 64) 100% Caucasian	Completed	Module 5.3.3.2
1293-001US 1 MS Patients	Open-label, dose escalation 07-Feb-94 13-Apr-94	7.5 mg FAM-SR Oral b.i.d., increased by 2.5 mg b.i.d. weekly	12	6 (50%), 6 (50%) 51.3 yrs. (41, 65) 100% Caucasian	Completed	Module 5.3.3.2
AN751-101 2 MS Patients	Open-label, single-escalating doses 21-Oct-97 21-Jan-98	5 mg FAM-SR 10 mg FAM-SR 15 mg FAM-SR Single oral dose	24	10 (42%), 14 (58%) 45.4 yrs. (29, 56) 100% Caucasian	Completed	Module 5.3.3.2
AN751-102 2 MS Patients	Open-label, multi-center, single treatment period multiple dose study 25-Nov-97 10-Feb-98	20 mg FAM-SR Oral b.i.d. for 13 consecutive days, with a single administration on Day 14	21	10 (48%), 11 (52%) 45.1 yrs. (29, 57) 100% Caucasian	Completed	Module 5.3.3.2
Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
Rush 001# 1 MS Patients, Healthy Volunteers	Open-label, single- dose pharmacodynamic study 11-Nov-1983 06-Sept-1985	1 to 5 mg i.v. solution 7 to 30 mg	17	17 (100%), 0 34.7 (24, 56) —	Completed	Module 5.3.3.2
1194-001US 1 MS Patients	Open-label, single, and multiple dosing 13-Jan-95 25-Mar-95	7.5 mg FAM-IR capsules Oral 8M units Betaseron IM	12	4 (33%), 8 (67%) 43.8 yrs. (38, 55) 92% Caucasian, 8% Native American	Completed	Module 5.3.3.4
<b>Blinded Clinical Trials</b>						
0293-001US 1 MS Patients (Study terminated prior to planned crossover)	Double-blind, placebo-controlled, 3-period crossover comparison of slow-release fampridine 30 and 40 mg in MS patients 12-May-93 25-Jun-93	30 mg FAM-SR 40 mg FAM-SR Placebo Oral doses administered b.i.d. for 10 days	9	4 (44%), 5 (56%) 50.8 yrs. (41, 58) 100% Caucasian	Terminated early by sponsor	Module 5.3.1.1
MS-F201 4 MS Patients	Double-blind, randomized, placebo-controlled 08-Nov-00 18-Sep-01	5, 10, 15, 20, 25, 30, 35, and 40 mg FAM-SR Placebo Oral doses administered b.i.d. for 8 weeks	36	17 (47%), 19 (53%) 47 yrs. (30, 61) 97% Caucasian, 3% Black	Completed	Module 5.3.5.1



Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
MS-F202 24 MS Patients (Adequate/well- controlled study)	Double-blind, placebo-controlled, 20-week, parallel group 27-Feb-03 18-Dec-03	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR Placebo Oral doses administered b.i.d. for 15 weeks	206	75 (36%), 131 (64%) 49.8 yrs. (28, 69) 92% Caucasian, 5% Black, 1.5% Hispanic, 1% Other, 0.5% Asian/ Pacific Islander	Completed	Module 5.3.5.1
MS-F203 33 MS Patients (Adequate/well- controlled study)	Double-blind, randomized, placebo-controlled 07-Jun-05 28-Jun-06	10 mg FAM-SR Placebo Oral doses administered b.i.d. for 14 weeks	300	95 (32%), 205 (68%) 51.4 yrs. (26, 70) 92.7% Caucasian, 4.3% Black, 1.3 % Hispanic, 1.3% Asian/Pacific Islander, 0.3% Other	Completed	Module 5.3.5.1
MS-F204 35 MS Patients (Adequate/well- controlled study)	Double-blind, randomized, placebo-controlled 22-May-07 27-Feb-08	10 mg FAM-SR Placebo Oral doses administered b.i.d. for 9 weeks	239	77 (32%), 162 (68%) 51.7 yrs. (24, 73) 91.2% Caucasian, 5.0% African- American, 1.7% Hispanic, 1.7% Other, 0.4% American Indian/Alaskan Native	Completed	Module 5.3.5.1
MS-F200 1 MS Patients	Double-blind, randomized, placebo-controlled, 4-way, single-ascending dose, crossover 11-Oct-99 11-May-00	5 mg FAM-SR 15 mg FAM-SR 25 mg FAM-SR Placebo Single oral dose	24	8 (33%), 16 (67%) 46.2 yrs. (23, 56) 92% Caucasian, 4% Hispanic, 4% Other	Completed	Module 5.3.1.2
Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
1091-001 <sup>#</sup> 1 MS Patients	Double-blind, placebo- controlled, 3-period crossover, concentration controlled study 10-Sept-1991 02-Jan-1992	2.5 mg FAM-IR capsule, 5 mg FAM-IR capsule	8	5 (56%), 4 (44%) 47.5 (35, 62) 100% Caucasian	Completed	Module 5.3.3.2
Rush 002 <sup>#</sup> 1 MS Patients	Single-blind, placebo- controlled, single-dose 06-Dec-1985 17-Sept-1985	2.5 mg FAM-IR capsule, 5 mg FAM-IR capsule to 25 mg	15	15 (100%), 0 37.2 (25, 48) —	Completed	Module 5.3.3.2
Rush 003 <sup>#</sup> 1 MS Patients	Double-blind, placebo- controlled 17-Feb-1987 12-Jan-1989	2.5 mg FAM-IR capsule, 5 mg FAM-IR capsule 7.5 mg to 53.5 mg	17	8 (47%), 9 (53%) 39.8 (28, 53) —	Completed	Module 5.3.3.2
0494-001US 9 MS Patients	Double-blind, randomized, placebo-controlled, parallel group 12-Sep-94 16-Dec-94	12.5, 17.5, and 22.5 mg FAM-SR Placebo Oral doses administered b.i.d. for 6 weeks	161	70 (43%), 91 (57%) 48.9 yrs. (29, 74) 95% Caucasian, 3% African-American, 2% Other	Completed	Module 5.3.4.2
0995-001US 1 MS Patients	Double-blind, placebo-controlled, crossover Sep-95 Nov-95	17.5 mg FAM-SR tablets Placebo Oral doses administered b.i.d. for 1 week/treatment	10	4 (40%), 6 (60%) 48.4 yrs. (33, 57) 100% Caucasian	Completed	Module 5.3.4.2



Clinical Review  
{Kachi Illoh, MD, MPH}  
{NDA 22-250}  
{Amaya, Fampridine Sustained Release}

Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
<b>Extension Studies</b>						
<b>0195-001US EXT</b> 1 MS Patients	Open-label extension study 15-Jun-95 22-May-96	12.5 mg FAM-SR tablets Oral b.i.d.	12	7 (58%), 5 (42%) 48.9 yrs. (31, 61) 92% Caucasian, 8% Asian	Completed	Module 5.3.5.2
<b>1293-001US EXT</b> 1 MS Patients	Open-label extension study 14-Mar-94 15-May-96	10-22.5 mg FAM-SR Oral b.i.d., switched from capsule to tablet during extension phase	12	6 (50%), 6 (50%) 51.3 yrs. (41, 65) 100% Caucasian	Completed	Module 5.3.5.2
<b>MS-F202 EXT</b> 21 MS Patients	Open-label extension study 15-Mar-04 (ongoing)	10 mg FAM-SR tablet 15 mg FAM-SR tablet 20 mg FAM-SR tablet Oral	177	66 (37%), 111 (63%) 51.9 yrs. (29, 70) 96.6% Caucasian, 2.3% Hispanic, 1.1% Black	Ongoing	Module 5.3.5.2
<b>MS-F203 EXT</b> 33 MS Patients	Open-label extension study 13-Dec-05 (ongoing)	10 mg FAM-SR tablet Oral b.i.d.	267	87 (33%), 180 (67%) 52.0 yrs. (26, 71) 93.3% Caucasian, 4.1% Black, 1.1% Hispanic, 1.1% Asian/Pacific Islander, 0.4% Other	Ongoing	Module 5.3.5.2
<b>MS-F204 EXT</b> 38 MS Patients	Open-label extension study 27-Aug-07 (ongoing)	10 mg FAM-SR tablet Oral b.i.d. Placebo	239	77 (32%), 162 (68%) 51.7 yrs. (24, 73) 91.2% Caucasian, 5.0% Black, 1.7% Hispanic, 0.4% American Indian/ Alaskan Native, 1.7% Other	Ongoing	Module 5.3.5.2
Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
<b>Clinical Trials in SCI Patients</b>						
<b>Open-Label Clinical Trials</b>						
<b>SCI-101</b> 1 SCI Patients	Open-label, escalating dose 24-Mar-98 19-Jun-98	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR Single oral dose	14	9 (64%), 5 (36%) 38 yrs. (17,61) 86% Caucasian, 7% Black, 7% Other	Completed	Module 5.3.5.4
<b>SCI-102</b> 1 SCI Patients	Open-label, escalating dose 24-Mar-98 10-Jul-98	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR Oral b.i.d.	16	14 (88%), 2 (12%) 40 yrs. (22, 59) 100% Caucasian	Completed	Module 5.3.5.4
<b>SCI-103</b> 1 SCI Patients	Open-label, escalating dose 26-Feb-99 30-Jul-99	5 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR 30 mg FAM-SR 35 mg FAM-SR 40 mg FAM-SR b.i.d.	16	13 (81%), 3 (19%) 35.7 yrs. (18, 60) 100% Caucasian	Completed	Module 5.3.5.4
<b>Blinded Clinical Trials</b>						
<b>0295-001US</b> 2 SCI Patients	Double-blind, randomized, placebo-controlled, dose titration, 3-way crossover in chronic SCI patients Sep-95 Jan-96	12.5 mg FAM-SR 17.5 mg FAM-SR Placebo Oral b.i.d. for 1 week	29	28 (97%), 1 (3%) 40.4 yrs. (23, 63) 90% Caucasian, 7% Hispanic, 3% African-American	Completed	Module 5.3.5.4



Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
SCI-001 1 SCI Patients	Double-blind, randomized, placebo-controlled 05-Nov-96 23-Dec-96	5 mg FAM-IR Placebo Oral doses administered b.i.d. for 7 days	4	4 (100%), 0 44 yrs. (28, 52) —	Terminated early by sponsor	Module 5.3.5.4
SCI-200 6 SCI Patients	Double-blind, placebo-controlled, escalating dose, crossover in SCI patients 23-Oct-97 28-Apr-98	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR Oral b.i.d. for 1 week	59	49 (82%), 11 (18%) 38.9 yrs. (20, 64) 82% Caucasian, 13% Black, 1.7% Asian, 3.3% Other	Completed	Module 5.3.5.4
SCI-F201 10 SCI Patients	Double-blind, placebo-controlled, parallel group in chronic incomplete SCI patients 27-Jun-00 06-Mar-01	25 mg FAM-SR 40 mg FAM-SR Placebo Oral b.i.d.	91	72 (79%), 19 (21%) 41.5 yrs. (19, 67) 93% Caucasian, 4% Black, 1% Asian, 2% Other	Completed	Module 5.3.5.4
SCI-F203 1 SCI Patients	Double-blind, placebo-controlled, parallel group in chronic complete and incomplete SCI patients 04-Jun-02 29-Oct-03	15 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR Oral b.i.d.	9	5 (56%), 4 (44%) 46.0 yrs. (30, 73) 100% Caucasian	Completed	Module 5.3.5.4
Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
SCI-F301 51 SCI Patients	Double-blind, placebo-controlled, fixed dose, 2-way crossover 8-Jul-02 16-Feb-04	25 mg FAM-SR Placebo Oral b.i.d.	212	185 (87%), 27 (13%) 40.9 yrs. (17, 70) 82.5% Caucasian, 14% Black, 1% American Indian/ Alaskan Native, 1% Asian, 1.5 % Other	Completed	Module 5.3.5.4
SCI-F302 33 SCI Patients	Double-blind, placebo-controlled, parallel group study in chronic SCI patients 11-Jun-02 14-Nov-03	25 mg FAM-SR Placebo Oral b.i.d.	203	172 (85%), 31 (15%) 40.9 yrs. (18, 73) 88% Caucasian, 9% Black, 0.5% Asian/ Pacific Islander, 2.5% Other	Completed	Module 5.3.5.4
<b>Extension Studies</b>						
SCI-F201 EXT 12 SCI Patients	Open-label, multicenter, extension study 04-Jun-02 07-Jul-04	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR 30 mg FAM-SR 35 mg FAM-SR 40 mg FAM-SR Oral b.i.d.	132	111 (84%), 21 (16%) 42 yrs. (19,68) 93.2% Caucasian, 3.8% Black, 3% Other	Terminated early by sponsor	Module 5.3.5.2
SCI-F300 EXT 40 SCI Patients	Open-label, multicenter, extension study 03-Oct-03 25-Jun-04	10 mg FAM-SR 15 mg FAM-SR 20 mg FAM-SR 25 mg FAM-SR Oral b.i.d.	230	201 (87%), 29 (13%) 42 yrs. (19,74) 82.2% Caucasian, 15.2% Black, 0.9% American Indian/Alaskan Native, 1.7% Other	Terminated early by sponsor	Module 5.3.5.2



Study ID No. of Centers Population	Design Start/End Dates	Planned Doses Route Regimen	No. of Patients Receiving at Least One Dose	Demographics Male, Female Mean Age (min, max) Race <sup>1</sup>	Study Status	Location
<b>Clinical Trials in Guillain-Barre Patients</b>						
<b>Blinded Clinical Trials</b>						
<b>CGBS-2a<sup>#</sup></b> 1 Guillain-Barre Patients	Double-blind, placebo- controlled, crossover, dose escalation 30–June–1999 01–Dec–1999	5 mg FAM-IR capsules 5 mg to 30 mg daily	8	3 (38%), 5 (62%) 57 (27, 73) 100% Caucasian	Completed	Module 5.3.5.4
<b>CGBS-2b<sup>#</sup></b> 1 Guillain-Barre Patients	Double-blind, placebo- controlled, crossover, dose escalation 19–Mar–2003 16–Mar–2005	5 mg FAM-IR capsules 5 mg to 30 mg daily	16	11 (69%), 5 (31%) 55.5 (23, 77) —	Completed	Module 5.3.5.4

## Differences between Efficacy and Safety Databases

For the purpose of this review, the efficacy database includes MS-F203 and MS-F204 trials, especially the modified intent-to-treat population. The sponsor used an extended pooled analysis database for efficacy by adding a part of MS-F202 (10 mg dose and placebo subjects) trial to the pool of the MS-F203 and MS-F204 trials. In contrast, the safety database included data from healthy subjects and from those with various diseases as MS, SCI, and renal impairment.

No pediatric patients were included in the efficacy database. Despite age limits for trials as low as 18 years, the youngest age enrolled was 24 years.

The overall clinical report is a joint review with input from efficacy, safety, and biometrics reviewers. All the reviewers are jointly responsible for the synthesis and documentation of the overall conclusions for the application review.

## 5.2 Review Strategy

For the efficacy analysis, we provide an overview of the two pivotal trials (MS-F203 and MS-F204) individually in section 5.3 of this document. We discuss the results of the two trials and pooled analysis in section 6. In contrast to the sponsor's approach, this review did not include MS-F202 in the main pooled efficacy analysis as it was a dose response trial with additional arms evaluating other doses, its efficacy analysis using the responder definition was post hoc, and it did not include a category of MS patients (progressive relapsing).

Another different approach we used in the pooled analyses was comparing the overall fampridine group to the placebo group, without the differentiation by responder status. The sponsor largely compared three groups – fampridine responders, fampridine non-responders, and placebo. Since the responders were not identified a priori, such responder groups based on the results of the trials are prone to have related variables trend in the same manner. Such a bias can limit the usefulness of the results of the different variables.



### 5.3 Discussion of Individual Studies/Clinical Trials

#### **MS-F203 “Double-Blind, Placebo-Controlled, 21-Week, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine-SR (10 mg B.I.D.) in Subjects with Multiple Sclerosis” (Final version 1.2; 20 September, 2005)**

Design: MS-F203 was a phase 3, multicenter, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of oral Fampridine-SR (10 mg twice daily) in 240 MS subjects. The trial was planned to run over 21 weeks consisting of one week pre-screening, two weeks of placebo run-in, **14 weeks of double-blind treatment**, and four weeks of follow-up. Subjects were randomized to one of two treatment groups, Fampridine-SR or placebo, in a 3: 1 ratio. Note, the initial plan changed from a phase 2 to a phase 3 trial in September 2005. Also, the trial enrolled 304 subjects instead of the planned 240.

#### Protocol:

Summary of inclusion criteria: Subjects with clinically definite MS, aged 18 to 70 years, able to perform two trials of Timed 25 foot Walk within 8-45 seconds at the screening visit.

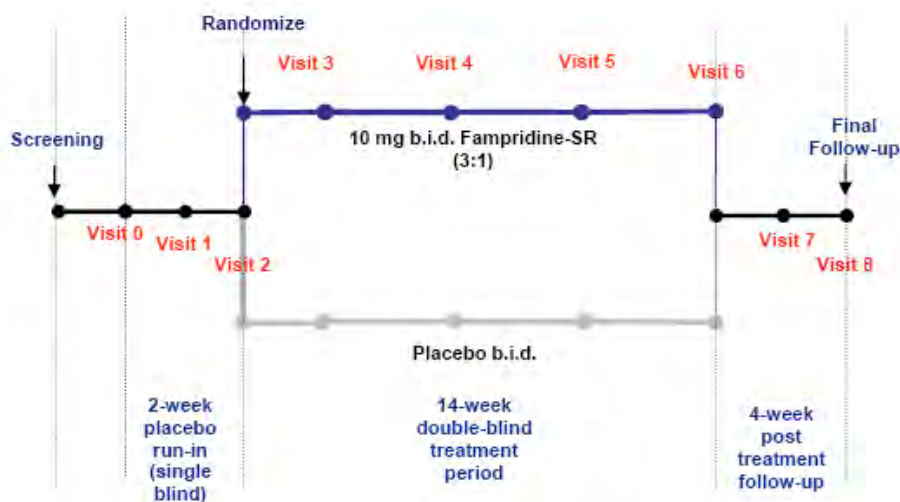
Summary of exclusion criteria: Female who is either pregnant or breastfeeding, and female of child-bearing potential not on birth control measures; history of seizures or evidence of epileptiform activity on EEG; known allergy to pyridine-containing substances or any of the inactive ingredients of the Fampridine-SR tablet; an investigational drug trial 30 days prior to Screening Visit or plans to enroll in an investigational drug trial at any time during the trial; starting immunomodulatory treatment within 90 days prior to the Screening Visit or any change in the dosing regimen of these drugs within 30 days prior to the Screening Visit; onset of MS exacerbation within 60 days prior to the Screening Visit; corticosteroids treatment within 30 days prior to the Screening Visit or expected to receive regularly scheduled steroid treatments during the trial; cyclophosphamide or mitoxantrone for MS within six months prior to the Screening Visit; any medical condition (including psychiatric disease) that would interfere with the interpretation of the trial results or the conduct of the trial; clinically significant abnormal laboratory values or an abnormal ECG; subject has angina, uncontrolled hypertension, cardiac arrhythmias, or any cardiovascular abnormality judged to be clinically significant by the investigator; subject started a concomitant medication regimen within the preceding three weeks, or their concomitant medication regimen expected to change during the course of the trial; subject with a history of drug or alcohol abuse within the past year; subject previously treated with fampridine; and subject administered botulinum toxin in the lower extremities within 6 months prior to the Screening Visit or expected to receive botulinum toxin in the lower extremities during the trial.

Trial procedure of interest: An ***Evaluator*** performed the Timed 25 Foot Walk test, Ashworth and LEMMT examinations. The evaluator remained blinded to the subject's overall clinical and safety assessments, Clinician Global Impression (CGI) and Subject Global Impression (SGI). An independent ***Clinician*** performed other assessments and had access to the findings of Timed 25 Foot Walk, Ashworth or LEMMT when conducting the CGI. At each visit during double blind treatment, the clinician and evaluator performed the required scales as in table below. **This**



arrangement that allows the clinician access to the findings of the evaluator is a potential source of bias.

### MS-F203 Trial Treatment Schedule



**Table : Schedule of procedure for MS-F203 (provided in sponsor's protocol)**

		2-Week Placebo Run-In		14-Week Randomized Treatment						4-Week No Treatment Follow-up	
Procedure/Drug Dispensed	Screening Visit	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7/Early Term <sup>+</sup>	Visit 8/Early Term Follow-up <sup>+</sup>	
Double-Blind Study Day	-21	-14 <sup>a</sup>	-7 <sup>a</sup>	0 <sup>a</sup>	14 <sup>a</sup>	42 <sup>b</sup>	70 <sup>b</sup>	98 <sup>b</sup>	112 <sup>a</sup>	126 <sup>a</sup>	
Written Informed Consent	C										
Medical and MS Histories	C										
SGH			C	C	C	C	C	C	(C) <sup>‡</sup>		
MSWS-12		C		C	C	C	C	C	C	C	
Timed 25 Foot Walk	E	E	E	E	E	E	E	E	E	E	
Ashworth	E	E	E	E	E	E	E	E	E	E	
LEMMIT	E	E	E	E	E	E	E	E	E	E	
Physical Exam/Vital Signs	C		C	C	C	C	C	C	C	(C)	
Concomitant Meds/Therapy	C	C	C	C	C	C	C	C	C	C	
Adverse Events		C	C	C	C	C	C	C	C	C	
ECG	C					C		C	(C) <sup>‡</sup>		
EEG	C*								[C] <sup>‡</sup>		
EDSS	C										
Chem/Hem/UA	C					C		C	(C) <sup>‡</sup>		
Urine Pregnancy Test	C							C	(C) <sup>‡</sup>		
PK Serum Analysis		C	C	C	C	C	C	C	C		
Drug Accountability			C	C	C	C	C	C	[C] <sup>‡</sup>		
CGI								C	[C] <sup>‡</sup>		
SSQ									C		
CSQ									C		
Final Status Assessment										C	
Dispense Drug		1 bottle	1 bottle	2 bottle	4 bottles	4 bottles	4 bottles				
Schedule next visit	C	C	C	C	C	C	C	C	C		

C= Assessments obtained by the study Clinician

E= Assessments obtained by the study Evaluator

<sup>a</sup> Visit should take place +/- 1 day. <sup>b</sup> Visit should take place +/- 4 days

\*EEG can be performed anytime between Screening Visit and Study Visit 0 (or must be obtained within 30 days prior to the Screening Visit)

<sup>†</sup> Complete all procedures if subject terminates from study early, including those in parentheses; complete all Visit 8 procedures in a two-week follow up.

C) Complete if necessary (e.g., if clinically significant abnormal value was collected at previous visit). <sup>‡</sup>Must be performed if subject terminates early.

C)<sup>†</sup> Only if subject terminates early. [C]<sup>‡</sup> Required only if the subject experienced a seizure while on study.



Endpoints:

Timed 25-Foot walk: At each subject visit, there were two tests of the Timed 25-Foot walk. The Timed 25-Foot walk is derived from the Multiple Sclerosis Functional Composite Score (MSFC). Each test derived walking speed (in feet per second) by dividing 25 feet by the time (in seconds) required to complete the walk. The walking speed for a visit was equal to the average of the walking speeds for the 2 tests walked. The Timed 25 Foot walk was obtained at the screening visit and all subsequent visits.

The 12-Item MS Walking Scale (MSWS-12): Assessed the subject's subjective response to questions regarding ability to walk, run, and climb over the preceding 2 weeks. Typically, the total score on MSWS-12 items is transformed to a scale with a range of 0 to 100. High scores indicate greater walking disability.

Ashworth assessment of spasticity: was used to evaluate the lower extremities for degree of spasticity. Specifically, the evaluator assessed 3 muscle groups (the hip adductors, knee flexors, knee extensors) on a 0-4 scale of spasticity. The Ashworth score is the average of all non-missing assessments. A negative change in Ashworth score signifies improvement in spasticity.

Lower extremity Manual Muscle (LEMMT) Testing: This testing estimated the muscle strength of lower extremities using the modified British Medical Research Council (BMRC) manual muscle testing procedures. It provides estimates of muscle strength bilaterally in four groups of muscles (hip flexors, knee extensors, ankle dorsiflexors, and knee flexors) with scores ranging from 0.0 to 5.0. Higher values indicated better muscle strength. The LEMMT score was the average of all non-missing assessments.

Subject Global Impression (SGI): Used to evaluate how patient felt on a 7-point scale (from terrible to delight) about the effects of trial medication on the subject's wellbeing over the preceding 7 days.

Clinician Global Impression (CGI): A documentation on a 7-point scale of the clinician's impression of the subjects neurological status on the evaluation date relative to baseline (screening visit). This is highly subject to bias.

Subject Summary Questionnaire (SSQ): This assessed the arm of treatment the subjects believed they were in and their willingness to continue same treatment. SSQ was obtained at visit 7.

Clinician Summary Questionnaire (CSQ): This assessed the arm of treatment the clinicians believed the subjects were in and their willingness to continue subject on the same treatment. CSQ was obtained at visit 7.

The Expanded Disability Status Scale (EDSS) was obtained only at the **Screening Visit** for baseline characterization.

Blood samples were obtained at **Visit 0** and at each subsequent visit (except Visit 8) to determine plasma fampridine concentrations.



Analysis:

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 (i.e., the four pre-treatment 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 MS-F203 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 Non-responders. 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 ( i.e., the change from baseline in walking speed at the double-blind endpoint).

The intent-to-treat population was based on all randomized subjects who received treatment and had at least one efficacy (timed 25 foot walk and MSWS-12) evaluation during the double-blind treatment period.

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

The sponsor compared the average change from baseline in the MSWS-12 score over the double blind treatment period between responders vs. non-responders (i.e. responder status) using an analysis of variance model with effects for responder status and center. The sponsor performed similar analyses for responders compared to non-responders 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:

Objective Secondary Variables

- 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 (Source MS-F203 Study Report body, section 5.3.5.1.3 of sponsor's submission):

- Addition of consistency of improvement in the LEMMT.
- Ordering of secondary endpoints. On meeting the primary endpoint, the secondary endpoints were to be analyzed in the following 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 non-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;
  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 non-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.

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 MSWS-12, 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;



- The Fampridine-SR responders would show a significantly larger improvement in average LEMMT score during the treatment period relative to the placebo-treated group;
- The Fampridine-SR non-responders would not show significant improvement relative to the placebo-treated group with respect to improved walking speed but would show statistically significant improvement on LEMMT;
- An approach equivalent to that of the primary variable, examining consistent improvement in LEMMT would show a higher rate of response in the Fampridine-SR treated patients, compared to the placebo group;
- The consistent improvement criterion for LEMMT was expected to be validated by the SGI, comparing patients with and without consistent improvement in LEMMT;
- The Ashworth score was not expected to show any treatment-related, or responder group effects, based on the lack of a recruitment criterion for spasticity, and the expectation of low Ashworth scores at baseline.

### Subject disposition For MS-F203 Trial

MS-F203 trial screened 401 patients from 33 centers in the United States and Canada. The trial enrolled 304 subjects, and randomized 301 subjects. Of the randomized, 18 (6%) discontinued the trial. One subject discontinued from the placebo group and 17 from the active drug group, as shown in the table below:

Table Disposition of subjects in randomized population MS-F203 trial

Status	Placebo	Fampridine-SR	Total
Randomized Patients	72	229	301
ITT Population	72 (100.0%)	224 (97.8%)	296 (98.3%)
Completed Study	71 (98.6%)	212 (92.6%)	283 (94.0%)
Discontinued Study:	1 (1.4%)	17 (7.4%)	18 (6.0%)
Adverse Event	0 (0%)	11 (4.8%)	11 (3.7%)
Non-Compliance with Protocol	0 (0%)	0 (0%)	0 (0%)
Subject Withdrew Consent	0 (0%)	4 (1.7%)	4 (1.3%)
Subject Lost to Follow-Up	1 (1.4%)	0 (0%)	1 (0.3%)
Other	0 (0%)	2 (0.9%)	2 (0.7%)

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The Per Protocol population included randomized subjects who received trial drug, remained compliant to treatment, and completed all planned assessments of walking speed and MSWS-12. This population (N = 260) included 90.3% (65/72) in the placebo group and 85.2% (195/229) fampridine.

### Demographic, Background, and Baseline Variables for MS-F203 Trial

Though MS-F203 trial enrolled 304 subjects, the trial had 300 subjects who received at least one dose of treatment. Of the 300 subjects, 68% (205/300) were females. The ethnic composition was: 92.7% Caucasian, 4.3% Black, 1.3% Hispanic, 1.3% Asian or Pacific Islander, and 0.3% others. The mean age of the subjects was 51.4 years (range 26 to 70 years). There were more



females in the fampridine group (71%, 163/229) compared to placebo (60%, 43/72), but this difference was not significant ( $p = 0.07$ ). As shown in table below, there were no differences between the treatment groups in age, ethnicity, MS subtype, EDSS and walking speed, and disease duration. The rate of concomitant drug treatment between the groups was comparable (table below).

Table Characteristics of subjects in randomized population of MS-F203 trial

Characteristics	Placebo (N = 72)	Fampridine-SR (N = 229)	Total (N = 301)	P value
Age (CI) years	51.5 (49.5-53.6)	52.1 (51.0-53.2)	51.4	0.6271
Gender Female %	60 (43/72)	71 (163/229)	301	0.0720
Race %				0.9676
Caucasian	93(67/72)	93 (212/229)	93 (279/301)	
Black	4 (3/72)	4 (10/229)	4 (13/301)	
Hispanic	1 (1/72)	1 (3/229)	1 (4/301)	
Asian/Pacific Islander	1 (1/72)	1 (3/229)	1 (4/301)	
Other	0 (0/72)	<1 (1/229)	<1 (1/301)	
MS Subtype %				0.6502
Primary Progressive	19.4 (14/72)	14.4 (33/229)	15.6 (47/301)	
Progressive Relapsing	2.8 (2/72)	4.4 (10/229)	4.0 (12/301)	
Relapsing Remitting	29.2 (21/72)	27.1 (62/229)	27.6 (83/301)	
Secondary Progressive	48.6 (35/72)	54.2 (124/229)	52.8 (159/301)	
Duration of MS in years	12.7 (10.8-14.6)	13.4 (12.3-14.5)	13.2	0.5326
EDSS at baseline	5.75 (5.52-5.99)	5.76 (5.63-5.90)	5.76	0.9708
Walking Speed at baseline ft/sec (CI)	2.07 (0.09-1.90)	2.06 (0.05-1.96)	2.06	0.9317

Table Concomitant drugs during double blind treatment in Safety Population of MS-F203 trial

Characteristics	Placebo (N = 72)	Fampridine-SR (N = 228)	Total (N = 300)
Glatiramer Acetate	25.0 (18/72)	21.9 (50/228)	22.7 (68/300)
Interferons	44.4 (32/72)	43.9 (100/228)	44.0 (132/300)
Glucocorticoids (different formulations)	15.3 (11/72)	11.8 (27/228)	12.7 (38/300)
HMG-CoA Reductase Inhibitors	18.1 (13/72)	21.9 (50/228)	21.0 (63/300)

Note inconsistency in table result: Table A.9 of MS-F203 Clinical report presented total interferons for the placebo group as 32 (44.4%). However, there were 9 subjects on Betaseron and 24 listed as interferon beta, giving a total of 33 on interferon. The number also conflicts with the numbers given in table 14.1.6.2 of the Clinical study report in section 5.3.5.1.3 of the sponsor's submission.

### Efficacy Variables at Baseline for MS-F203 Trial



There were no differences between the treatment groups with walking speed or other efficacy variables at baseline (table below).

Table Summary of Efficacy Variables at Baseline in ITT Population (Source: Sponsor's submission – Table 7 MS-F203 Clinical Study Report 5.3.5.1.3)

Parameter	Treatment Group: Mean (SD)		Total N=296	Treatment p-value
	Placebo N=72	Fampridine-SR N=224		
Walking Speed (ft/sec)	2.07 (0.711)	2.05 (0.749)	2.06 (0.739)	0.853
LEMMT Score	3.97 (0.737)	4.06 (0.586)	4.04 (0.626)	0.245
Ashworth Score	0.95 (0.670)	0.90 (0.713)	0.91 (0.702)	0.718
MSWS-12 Score	68.48 (22.304)	70.68 (18.551)	70.14 (19.513)	0.472
SGI Score	4.67 (0.939)	4.59 (0.941)*	4.61 (0.939)	0.460

\* Two ITT patients did not have a baseline value.

### Efficacy Outcome Results

Please see Section 6 (Review of Efficacy) for the outcome results of MS-F203 trial.

### MS-F204 “Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine-SR (10 mg b.i.d.) in Patients with Multiple Sclerosis” (Final version 1.3; 10 September, 2007)

The primary objective of MS-F204 was to demonstrate more patients treated with fampridine experienced consistent improvements in walking speed on drug compared to placebo. The secondary objective was to demonstrate improved leg strength in both fampridine responders and non-responders compared to placebo, and measure the maintenance of efficacy towards the end of the dosing interval.

Design: MS-F204 was a phase 3, multicenter, double-blind, placebo-controlled, parallel-group trial to evaluate the safety and efficacy of oral Fampridine-SR (10 mg twice daily) in 200 MS subjects. The trial was planned to run over 14 weeks consisting of one week pre-screening, two weeks of placebo run-in, **9 weeks of double-blind treatment**, and two weeks of follow-up. Subjects were randomized to one of two treatment groups, Fampridine-SR or placebo, in a 1: 1 ratio.

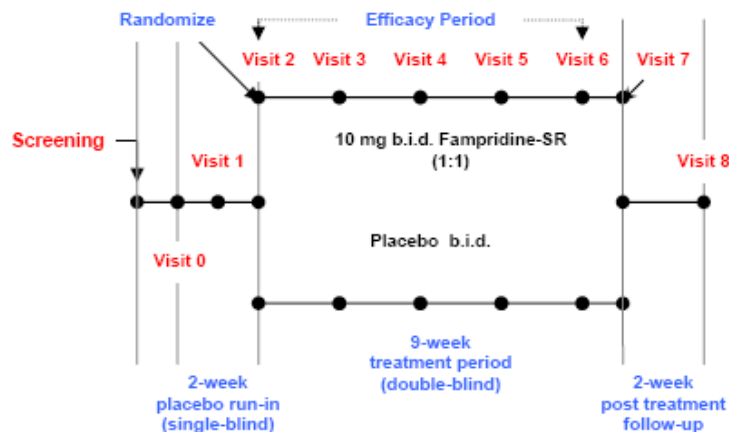
MS-F204 differed from MS-F203 by the following characteristics of MS-F204: shorter duration of the double-blind treatment period (9 weeks rather than 14); 1:1 randomization to active drug and placebo; and an additional visit at the end of the treatment period to obtain data on efficacy and drug plasma concentration near the end of the dosing interval.

### Protocol

The inclusion and exclusion criteria, trial procedures, and assessed endpoints were similar to the MS-F203 trial.



## MS-F204 Trial Treatment Schedule



## MS-F204 Trial Flow Chart

Study Procedures <sup>1</sup>	Screening Visit	2-Week Placebo Run-In		9-Week Randomized Treatment 8-Week Efficacy Period						2-Week Follow-up
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7*	Visit 8/Early Term
Double-Blind Study Day	-21	-14 <sup>2</sup>	-7 <sup>2</sup>	0 <sup>2</sup>	14 <sup>2</sup>	28 <sup>2</sup>	42 <sup>2</sup>	56 <sup>2</sup>	63 <sup>2</sup>	77 <sup>2</sup>
Written Informed Consent	C									
Medical and MS Histories	C									
SGI			C	C	C	C	C	C		C <sup>4</sup>
MSWS-12		C		C	C	C	C	C		C
Timed 25 Foot Walk	E	E	E	E	E	E	E	E	E <sup>7</sup>	E
Ashworth	E	E	E	E	E	E	E	E	E	E
LEMMT	E	E	E	E	E	E	E	E	E	E
Physical Exam/Vital Signs	C		C	C	C	C	C	C	C	C
Concomitant Meds/Therapy	C	C	C	C	C	C	C	C	C	C
Adverse Events		C	C	C	C	C	C	C	C	C
ECG	C					C		C	C	C <sup>4,5</sup>
EEG	C <sup>3</sup>									C <sup>6</sup>
EDSS assessment	C									
Chem/Hem/UA	C					C		C	C	C <sup>4,5</sup>
Urine Pregnancy Test	C							C	C	C <sup>4,5</sup>
Fampridine Plasma Sample		C	C	C	C	C	C	C	C	C
Investigational Drug Accountability			C	C	C	C	C	C	C	C <sup>4</sup>
CGI								C		C <sup>4</sup>
SSQ										C
CSQ										C
Final Status Assessment										C
Dispense Investigational drug		1 bottle	1 bottle	2 bottles	2 bottles	2 bottles	2 bottles	1 bottle		
Schedule next visit	C	C	C	C	C	C	C	C	C	

\*End of treatment visit, as detailed in Section 5.3.6 of this protocol

C= Assessments obtained by the study Clinician E= Assessments obtained by the study Evaluator

<sup>1</sup> Procedures should be performed (when possible) in the order listed, with the exception of Visit 7 (obtain PK sample immediately after first set of Timed Walk tests, and see Section 5.3.6 of the protocol for the order of other assessments)

<sup>2</sup> Visit should take place +/- 1 day.

<sup>3</sup> EEG can be performed anytime between Screening Visit and Study Visit 0 (or obtained up to 60 days prior to the Screening Visit). EEG results must be reviewed by the Investigator prior to dispensing Visit 0 investigational drug.

<sup>4</sup> Only performed for early termination visits.

<sup>5</sup> For Visit 8, complete assessment only if clinically significant abnormal value was collected at Visit 7.

<sup>6</sup> Required only for early termination visits due to a seizure. <sup>7</sup> This assessment will be performed three times during Visit

## Analysis

The efficacy measurements in MS-F204 included the Timed 25 Foot Walk Test and LEMMT. Additional measurements obtained include Ashworth spasticity assessment, MSWS-12, SGI, and CGI.



The primary efficacy variable in MS-F204 was responder status, based on consistency of response in walking speed on the Timed 25 Foot Walk. The secondary efficacy variable was average change from baseline in LEMMT during the eight-week, double-blind treatment period.

Similar to the earlier phase 3 trial, MS-F204 defined a responder as a subject with a faster walking speed for at least three of the first four double-blind visits (Visits 3 through 6) compared to the maximum walking speed for any of the pre-treatment visits (Screening Visit, Visits 0, 1 and 2) and the post-treatment visit (Visit 8). Visit 7 was not included in the responder criterion because the visit's purpose was to obtain data on efficacy and drug plasma concentration near the end of the normal 12 hour dosing interval.

Also, the sponsor conducted a sensitivity analysis of the responder criterion. It considered this analysis as a worst-case scenario sensitivity analysis that defined a modified responder as a responder using the previously outlined definition but with the following restriction: A fampridine-treated subject considered a responder in the primary analysis but who missed the post-treatment visit (Visit 8) was considered a non-responder for the modified responder variable. In this analysis, the restriction did not apply to the placebo group such that a placebo responder in the primary analysis remained a modified responder in the sensitivity analysis even when the patient missed Visit 8.

The plan included the use of Cochran-Mantel-Haenszel (CMH) test to determine differences between the treatment groups in the proportion of walking speed responders, while controlling for center. Differences in the continuous variables were analyzed by t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis group and center.

## Results of MS-F204 trial

### Subject disposition for MS-F204 Trial

MS-F204 trial screened 362 patients from 35 centers in the United States and Canada. The trial enrolled 240 subjects between May 22, 2007 and February 27, 2008; and randomized 239 subjects. Twelve subjects (5%) discontinued the trial, five from the placebo group and seven from the fampridine group, as shown in the table below:

Table Disposition of subjects in MS-F204 trial

Status	Placebo	Fampridine-SR	Total
Randomized Patients	119	120	239
ITT Population	118 (99.2%)	119 (99.2%)	237 (99.2%)
Completed Study	114 (95.8%)	113 (94.2%)	227 (95.0%)
Discontinued Study:	5 (4.2%)	7 (5.8%)	12 (5.0%)
Adverse Event	4 (3.4%)	4 (3.3%)	8 (3.3%)
Non-Compliance with Protocol	1 (0.8%)	2 (1.7%)	3 (1.3%)
Subject Withdrew Consent	0 (0%)	0 (0%)	0 (0%)
Subject Lost to Follow-Up	0 (0%)	0 (0%)	0 (0%)



Other	0 (0%)	1 (0.8%)	1 (0.4%)
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### Demographic, Background, and Baseline Variables for MS-F204 Trial

Of the 239 randomized subjects, 68% (162/239) were females. Most of the patients were Caucasian (88%). The mean age of the subjects was 51.7 years (SD, 9.67 years). As shown in table below, there were no differences between the treatment groups in age, gender, ethnicity, MS subtype, and walking speed, and disease duration. The EDSS score was higher in the fampridine group (p=0.024). Concomitant drug treatment included interferons (35.6%) and glatiramer acetate (23.0%) among others.

Table Characteristics of subjects in randomized population of MS-F204 trial

Characteristics	Placebo (N = 119)	Fampridine-SR (N = 120)	Total (N = 239)	P value
Age (SD) years	51.7 (9.83)	51.8 (9.55)	51.7 (9.67)	0.923
Gender Female n (%)	74 (62.2%)	88 (73.3%)	162 (67.8%)	0.077
Race n (%)				0.375
White	105 (88.2%)	113 (94.2%)	218 (91.2%)	
Black	9 (7.6%)	3 (2.5%)	12 (5.0%)	
Hispanic	2 (1.7%)	2 (1.7%)	4 (1.7%)	
American Indian or Alaskan Native	1 (0.8%)	0	1 (0.4%)	
Asian/Pacific Islander	0	0	0	
Other	2 (1.7%)	2 (1.7%)	4 (1.7%)	
MS Subtype n (%)				0.175
Primary Progressive	21 (17.6%)	10 (8.3%)	31 (13.0%)	
Progressive Relapsing	2 (1.7%)	5 (4.2%)	7 (2.9%)	
Relapsing Remitting	40 (33.6%)	43 (35.8%)	83 (34.7%)	
Secondary Progressive	56 (47.1%)	62 (51.7%)	118 (49.4%)	
Duration of MS in years	13.10 (8.69)	14.43 (9.51)	13.76 (9.12)	0.212
EDSS Score at baseline (SD)	5.55 (1.17)	5.83 (0.97)	5.69 (1.09)	0.024
Walking Speed at baseline ft/sec (SD)	2.202 (0.681)	2.117 (0.752)	2.159 (0.717)	0.364

### Efficacy Variables at Baseline for MS-F204 Trial

At baseline, there were no differences between the treatment groups with walking speed or LEMMT score. However, the fampridine group had a higher baseline MSWS-12 score as shown in the table below.

Table Summary of Efficacy Variables at Baseline in ITT Population for MS-F204 Trial (Source: Sponsor's submission – Table 10 MS-F204 Clinical Study Report 5.3.5.1.2)



	<b>Treatment Group: Mean (SD)</b>			
<b>Parameter</b>	<b>Placebo N=118</b>	<b>Fampridine-SR N=119</b>	<b>Total N=237</b>	<b>Treatment p-value</b>
Walking Speed (ft/sec)	2.202 (0.6812)	2.117 (0.7517)	2.159 (0.7172)	0.364
LEMMT Score	3.962 (0.5803)	3.908 (0.6028)	3.935 (0.5911)	0.457
Ashworth Score	0.800 (0.6722)	0.910 (0.6111)	0.855 (0.6433)	0.258
MSWS-12 Score	67.68 (22.562)	73.80 (17.751)	70.75 (20.478)	0.006
SGI Score	4.36 (0.847)	4.29 (0.877)	4.32 (0.861)	0.508

### **Efficacy Outcome Results for MS-F204 Trial**

Please see Section 6 (Review of Efficacy) for the outcome results of MS-F204 trial.



## 6 Review of Efficacy

### Efficacy Summary

Overall, the sponsor shows Timed Walk Responder rates were higher with fampridine treatment compared to placebo. This result was consistent across the individual trials that constitute the efficacy database and the pooled analysis of the pivotal trials. Though there is a change in walking speed from baseline with fampridine treatment, the magnitude of the change is not large enough for the average walking speed to differ from placebo. This suggests the improvement in walking speed among many treated is not clinically meaningful. It is important to note that the patients included in the trials are able to walk 25 feet over 8-45 seconds. Patients with abilities beyond the time limits were excluded. So, there is little information of the benefit of the drug beyond these limits. The sponsor in 2005 alluded to the lack of reliability of the data in more disabled subjects when walking speed exceeded 45 seconds.

### 6.1 Indication

The proposed indication for Fampridine-SR is for the improvement of walking ability in adult patients with MS.

#### 6.1.1 Methods

The efficacy review is limited, to a large extent, to two pivotal trials (MS-F203 and MS-F204) that prospectively defined the primary endpoint of relevance to the stated indication. Both trials compared a single fixed dose of fampridine (10 mg twice daily) to placebo. The sponsor performed a pooled analysis of three trials (MS-F202, MS-F203 and MS-F204) to show efficacy of fampridine for the stated indication. The overall designs of the two pivotal trials are discussed in more details in Section 5.3 and summarized as modified from the sponsor's table below.



Table

Trial, Protocol Name, Design	No. Patients	Double Blind Period	Total Trial Duration	Primary Endpoints	Secondary Endpoints
<b>MS-F203:</b>  Double-Blind, Placebo-Controlled, 21-week, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine-SR (10 mg b.i.d.) in Subjects with Multiple Sclerosis Design: Double-blind, randomized, placebo controlled study	304 enrolled  301 randomized (72, placebo; 229, Fampridine-SR)	14 weeks	21 weeks	<p>Prospective primary endpoint, as defined in the SPA: Timed Walk Response, based on the Timed 25 Foot Walk.</p> <p>A responder was defined as a patient who had faster walking speed for at least three of four during the double-blind period as compared to the maximum speed among the first five of the non double-blind (off) treatment visits.</p> <p>Additional requirements of the SPA:            Maintenance of effect defined as significantly greater improvement in walking speed at the last double-blind assessment for Fampridine-SR treated Timed Walk Responders compared to placebo treated patients.</p> <p>Validation of Timed Walk Response criterion – statistically significant greater improvement in MSWS-12 score for Timed Walk Responders compared to Timed Walk Non-responders.</p>	<p>Prospective, stepwise analysis of secondary endpoints:</p> <ul style="list-style-type: none"> <li>• Change from baseline in LEMMT averaged over the double-blind treatment period and compared separately for Timed Walk Responders and Non-responders</li> <li>• Change from baseline in the Average Ashworth Score over the double-blind treatment period, and compared separately for Timed Walk Responders and Non-responders.</li> </ul>



<b>MS-F204:</b>	240 enrolled	9 weeks	14 weeks	Prospective primary endpoint, as defined in the SPA: Timed Walk Response, based on the Timed 25 Foot Walk. A responder was defined as a patient who had faster walking speed for at least three of the first four visits during the double-blind period as compared to the maximum speed among all five of the non double-blind (off) treatment visits.	Prospective secondary endpoint: Average change from baseline in LEMMT during the eight-week, double-blind treatment period, comparing Timed Walk Responders and Timed Walk Non-responders separately and sequentially against placebo treated patients.  Pharmacokinetic data was to be collected at an additional fifth double-blind treatment visit (Visit7) that was not part of the overall efficacy analysis.  Additional assessments, including MSWS-12, SGI, CGI and Ashworth score, were collected for purposes of a pooled analysis with other studies and were not formal secondary endpoints.
Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate Safety and Efficacy of Oral Fampridine-SR (10 mg b.i.d.) in Patients with Multiple Sclerosis	239 randomized (119, placebo; 120, Fampridine-SR)				
Design: Double-blind, randomized, placebo controlled study					

Note: MSWS-12 = The 12 Item Multiple Sclerosis Walking Scale; SGI = Subject Global Impression; CGI = Clinician Global Impression; LEMMT = Lower Extremity Manual Muscle Test



The third trial included in the sponsor's pooled analysis is shown below.

Table: Overall Design of MS-F202 Trial

Study No., Protocol Name, Design	No. Patients	Dose, Regimen Route	Study Duration (weeks)		Study Endpoints	
			Double Blind Period	Total Study	Primary	Secondary
<b>MS-F202:</b> Double-Blind, Placebo-Controlled, 20-Week, Parallel Group Study to Evaluate Safety, Tolerability and Activity of Oral Fampridine-SR in Patients with Multiple Sclerosis  <i>Design:</i> Double-blind, randomized, placebo controlled, dose comparison study	211 enrolled  206 Randomized  (47, placebo; 52, 10 mg b.i.d. 50, 15 mg b.i.d. 57, 20 mg b.i.d. Fampridine-SR)	FAM-SR Tab; 10, 15, 20 mg; b.i.d.; Oral	15 weeks	20 weeks	<i>Prospective primary endpoint:</i> percent change from baseline in average walking speed measured using the Timed 25-Foot Walk  <i>Post hoc responder analysis:</i> Consistency of walking speed improvement (Timed Walk Response). A responder was defined as a patient who had faster walking speed for at least three of four during the double-blind period as compared to the maximum speed among all five of the non double-blind (off) treatment visits.	<i>Prospective secondary endpoints:</i> a response criterion based on an average improvement of >20% in walking speed during the double-blind treatment period; average improvement in Lower Extremity Manual Muscle Test (LEMMT) score and 9-Hole Peg; Paced Auditory Serial Addition Test scores (both from the MS Functional Composite - MSFC); the MSFC combined score; spasticity assessment (Ashworth Score); Clinician's Global Impression of Change (CGI); Subject's Global Impression (SGI); the 12-Item MS Walking Scale (MSWS-12); and the Multiple Sclerosis Quality of Life Inventory (MSQLI).

Both pivotal trials (MS-F203 and MS-F204) had similar inclusion and exclusion criteria. They enrolled adult clinically definite MS subjects, able to perform two trials of Timed 25 foot Walk within 8-45 seconds at the screening visit. Among a host of exclusion criteria were: female pregnant or breastfeeding subjects; and history of seizures or evidence of epileptiform activity on EEG.

### 6.1.2 Demographics of Pooled Analysis of MS-F203 and MS-F204 Trials

Demographics for the individual trials are presented in Section 5.3 of this review, while that for the pooled analysis is presented in this section. Of the 540 randomized subjects, 368 (68%) were females. As in the individual trials described in section 5, most of the subjects were Caucasian (92%). The mean age of the subjects was 52 years (SD, 9 years) with average disease duration of at least 13 years.

There were imbalances between the treatment groups at baseline. As shown in table below, there were no differences at baseline between the treatment groups in age, proportion of ethnic groups, MS subtype, median EDSS score, walking speed, LEMMT, and disease duration. However, there were imbalances between the groups in gender, height, weight, and MSWS-12 score. There were fewer females ( $p=0.011$ ) in the placebo group (61%) compared to the fampridine group (72%).

Table Characteristics of Subjects in Randomized Population of Pooled Efficacy Trials

Characteristics	Placebo (N = 191)	Fampridine-SR (N = 349)	Total (N = 540)	P value
Age (SE, standard error) years	51.6 (0.67)	52.0 (0.49)	51.9 (0.40)	0.664
Gender Female n (%)	117 (61.3%)	251 (71.9%)	368 (68.2%)	0.011



Race n (%)				0.640
White	172 (90.1%)	325 (93.1%)	497 (92.0%)	
Black	12 (6.3%)	13 (3.7%)	25 (4.6%)	
Hispanic	4 (2.1%)	6 (1.7%)	10 (1.9%)	
American Indian or Alaskan Native	1 (0.8%)	0	1 (0.4%)	
Asian/Pacific Islander	1 (0.5%)	3 (0.9%)	4 (0.7%)	
Other	2 (1.1%)	2 (0.6%)	4 (0.7%)	
Height in cm (SE)	169.6 (0.70)	167.9 (0.52)	168.6 (0.42)	0.0483
Weight in kg (SE)	78.6 (1.36)	74.8 (1.00)	76.1 (0.82)	0.0225
Body Mass Index (SE)	27.3 (0.44)	26.5 (0.33)	26.8 (0.26)	0.1078
MS Subtype n (%)				0.128
Primary Progressive	35 (18.3%)	43 (12.3%)	78 (14.4%)	
Progressive Relapsing	4 (2.1%)	15 (4.3%)	19 (3.5%)	
Relapsing Remitting	61 (31.9%)	105 (30.1%)	166 (30.7%)	
Secondary Progressive	91 (47.6%)	62 (51.7%)	186 (53.3%)	
Duration of MS in years (SE)	13.05 (0.63)	13.80 (0.47)	13.64 (0.38)	0.332
EDSS Score median (IQL)	6.0 (3.5-6.5)	6.0 (6.0-6.5)	6.0 (6.0-6.5)	0.254
Walking Speed at baseline ft/sec (SE)	2.15 (0.05)	2.08 (0.04)	2.10 (0.03)	0.285
LEMMT at baseline (SE)	3.96 (0.04)	4.01 (0.03)	3.99 (0.03)	0.356
MSWS-12 at baseline (SE)	67.85 (1.44)	71.67 (1.06)	70.41 (0.86)	0.033
Ashworth score (SE)	0.86 (0.05)	0.89 (0.04)	0.89 (0.03)	0.554
SGI score (SE)	4.48 (0.05)	4.48 (0.05)	4.48 (0.04)	0.979

### 6.1.3 Subject Disposition of Pooled Analysis of MS-F203 and MS-F204 Trials

Both efficacy trials screened a total of 763 subjects, enrolled 544, and randomized 540 subjects. Of the subjects screened, 29% failed screening. Thirty subjects (6%) of the randomized discontinued the trials; 24 were in the fampridine group and 6 in the placebo group. The reasons for screen failures were not stated clearly in the sponsor's submission.

Table Disposition of subjects in Pooled MS-F203 and MS-F204 trials

Status	Placebo	Fampridine-SR	Total
Randomized Patients	191	349	540
ITT Population	190 (99.5%)	343 (98.3%)	533 (98.7%)
Completed Study	185 (96.9%)	325 (93.1%)	510 (94.4%)
Discontinued Study:	6 (3.1%)	24 (6.9%)	30 (5.6%)
Adverse Event	4 (2.1%)	15 (4.3%)	19 (3.5%)
Non-Compliance with Protocol	1 (0.5%)	2 (0.6%)	3 (0.6%)
Subject Withdrew Consent	0 (0%)	4 (1.2%)	4 (0.7%)
Subject Lost to Follow-Up	1(0.5%)	0 (0%)	1 (0.2%)
Other	0 (0%)	3 (0.9%)	3 (0.6%)



## 6.1.4 Analysis of Primary Endpoint(s)

### Primary Endpoints for MS-F203 Trial

#### *Responder Status Rates Between Treatment Groups*

The responder rate was higher in the fampridine group compared to placebo. The primary efficacy variable was responder status, based on consistent improvement in walking speed on the Timed 25-Foot Walk. This section analysis used the ITT population (N = 296). The responder rate in the fampridine group was 34.8% (78/224), and in the placebo group 8.3% (6/72); the difference was significant between the treatment groups ( $p < 0.001$ ). Interestingly, the results closely resemble the predictions from the protocol's sample size calculation. Then, the protocol power calculation predicted responder rates of 35.3% for fampridine and 8.5% for placebo with a sample size of 240 subjects. Regardless, the fampridine group achieved a higher proportion of responder status compared to placebo.

#### *Treatment Groups by Responder Status*

The subjects grouped by responder status in treatment arms are as follows: placebo responders (N = 6), placebo non-responders (N = 66), fampridine responders (N = 78), fampridine non-responders (N = 146). According to the pre-specified analysis plan, the sponsor largely compared the placebo group (responders and non-responders) to the fampridine responders in the ITT population.

#### *MSWS-12 Score in Timed Walk Responders and Non-responders*

The sponsor reported a significant improvement in the 12-Item MS Walking Scale (MSWS-12) for walking responders compared to non-responders. MSWS-12 assessed a patient's subjective response to questions regarding ability to walk, run, and climb over the preceding 2 weeks. The sponsor compared the 84 responders (78 in the Fampridine-SR group and 6 in the placebo group) against the 212 non-responders (146 in the Fampridine-SR group and 66 in the placebo group) on the average change from baseline in MSWS-12 to determine if patients with consistently improved walking speeds could perceive benefit relative to those patients who did not. For the comparison, the sponsor performed an analysis of variance model with effects for responder status and center. The responders had average change from baseline in MSWS-12 of -6.84 (standard deviation, SD of 12.97) in the fampridine responders compared to 0.05 (SD, 11.25) in the non-responder group ( $p < 0.001$ ). These MSWS-12 results suggested the responders' assessment of greater improvements in their ability to walk, run, and climb. The sponsor indicated that MSWS-12 results establish the clinical meaningfulness of walking speed response with respect to overall walking ability.

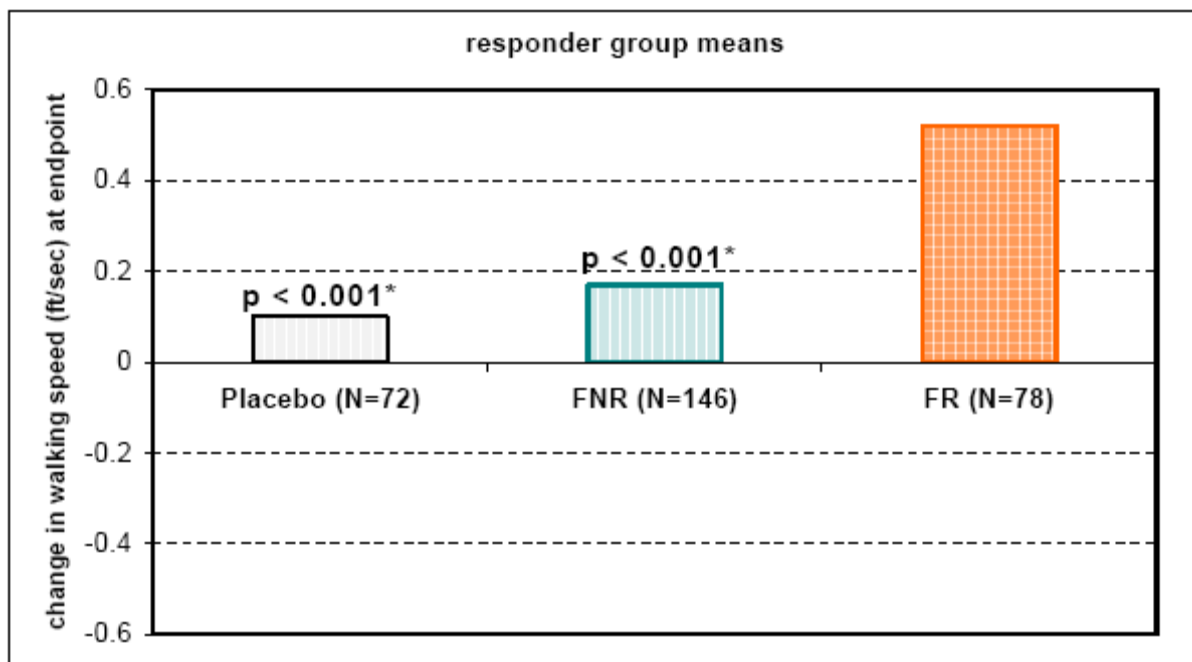
#### *Maintenance of Walking Speed Improvement at Last Treatment Visit in Fampridine Responders*

The sponsor reported maintenance of walking speed improvement to the last treatment visit by fampridine responders. The mean changes in walking speed at the double-blind endpoint from baseline were 0.10 ft/sec for the placebo group and 0.53 ft/sec for the fampridine responder group. The corresponding change in walking speed for fampridine non-responder was 0.17 ft/sec



(as shown in Figure below). The difference between the fampridine responder and placebo groups was significant ( $p < 0.001$ ).

Figure Change from Baseline in Walking Speed (ft/sec) at the Double-Blind Endpoint by Responder Analysis Group (ITT Population) – Source Figure 4 MS-F203 Clinical Study Report 5.3.5.1.3)



ABBREVIATIONS: FNR=Fampridine-SR non-responders; FR=Fampridine-SR responders  
 \*: p-value versus Fampridine-SR responder group;  $p=0.483$  for the other comparison (FNR vs. placebo).

The sponsor reported that all three components of the multi-stage primary endpoint for the trial were successfully achieved.

### Primary Efficacy Endpoint in MS-F204 Trial

As in MS-F203 trial, the primary efficacy variable for MS-F204 trial was responder status, based on consistency of response in walking speed on the Timed 25 Foot Walk

#### *Responder Status Rates Between Treatment Groups*

The responder rate was higher in the fampridine group compared to placebo. The difference in responder rate, between the fampridine group 42.9% (51/119) and the placebo group 9.3% (11/118), was significant ( $p < 0.001$ ). Though not a part of the primary analysis, the mean change in walking speed during the double-blind period ranged from 21.45% to 26.80% for fampridine responders compared to 7.07% to 8.78% for the placebo group at every visit.

#### *Treatment Groups by Responder Status*

The subjects were grouped into the following treatment groups: placebo responders (N = 11), placebo non-responders (N = 107), fampridine responders (N = 51), fampridine non-responders



(N = 68). In the same manner as the MS-F203 trial, MS-F204 compared the placebo group (responders and non-responders) to the fampridine responders in the ITT population.

### **Primary Efficacy Endpoint of Pooled Analysis of MS-F203 and MS-F204 Trials**

The same primary efficacy variable for both phase 3 trials was used in this pooled efficacy analysis. The variable is 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 sponsor analyzed the primary efficacy variable by comparing the proportion of responders in the treatment groups.

Problems exist with the use of the sponsor's primary endpoint. It has not been frequently used as a primary endpoint in MS clinical trials of other drugs. In MS patients, it is not clear what extent of improvement in walking speed improves walking ability or quality of life. The responder variable ignores the importance of the extent of improvement in walking speed. So, a small benefit in many patients receiving the active drug may result in a positive trial, even when the benefit is not clinically significant or meaningful for the patient. Statistical significance can be achieved without clear clinical significance. Supportive endpoints such as EDSS could be helpful, especially when MSWS-12 is not clearly validated by the Agency for MS trials. Only baseline EDDSS was performed in the sponsor's trials.

The overall design of the trials appears appropriate to test the efficacy of fampridine in MS patients with walking impairment. The two trials in the pooled efficacy analysis meet the conditions for adequate and well-controlled trials; this assessment is based on adequacy of blinding, randomization, prospective statistical analytic plan. A limiting factor of the trial is the inclusion of only patients able to perform two trials of Timed 25 foot Walk within 8-45 seconds. It is difficult to extrapolate the findings of the trial results to patients who have walking disability but are unable perform at the set time limits at baseline. Thus the finding of drug efficacy does not confer effectiveness for all MS patients with walking impairment.

### *Responder Status Rates between Treatment Groups in Pooled Analysis*

As with the individual trials, the pooled analysis responder rate was higher in the fampridine group compared to placebo. The primary efficacy variable was responder status, based on consistent improvement in walking speed on the Timed 25-Foot Walk. The responder rate in the fampridine group was 37.6% (129/343), and in the placebo group 9.0% (17/190); the difference was significant between the treatment groups ( $p < 0.001$ ).

### *Treatment Groups by Responder Status in Pooled Analysis*

The subjects were grouped into the following treatment groups: placebo responders (N = 17), placebo non-responders (N = 173), fampridine responders (N = 129), fampridine non-responders (N = 214).

I performed an analysis of the modified walking speed responder, and arrived at the same conclusion. The modified walking speed responder supposes the worst-case-scenario that assigns a responder in the fampridine group with a missing visit to the non-responder group. This yielded



37.0% (127/343) responders in the fampridine group to 9.0% (17/190) placebo ( $p < 0.001$ ). On mixed models analysis using modified walking speed responder status as the response variable, only treatment arm (fampridine) significantly predicted odds of response ( $p = 0.001$ ). The odds of response were not predicted by the other covariates: walking speed at baseline ( $p = 0.388$ ), height (0.570), weight ( $p = 0.177$ ), MSWS-12 at baseline ( $p = 0.813$ ), and gender (0.866).

The sponsor suggested that MSWS-12 validates timed walk response as a clinically meaningful endpoint. The sponsor makes the case for MSWS-12 results being a useful validation for the time walk response. The change in MSWS-12 ranged between -6.04 to -11.79 for responders in the individual and pooled analyses compared to 0.85 to -2.49 in non-responders (all  $p = 0.001$ ). With respect to treatment group differences, I obtained from the pooled analysis, a change from baseline MSWS-12 of -2.69 (CI, -3.95 to -1.42) for fampridine treatment compared to 0.69 (CI, -1.001 to 2.39) for placebo ( $p = 0.0018$ ). The change was different from that of placebo ( $p = 0.0018$ ). However, the average MSWS-12 score during the double-blind treatment was not different between treatment groups ( $p = 0.8348$ ).

The sponsor demonstrated the maintenance of time walk response in fampridine responders during treatment. The sponsor showed significant differences in the change from baseline in walking speed at the end of double-blind treatment for fampridine responders compared to non-responders and placebo (all  $p < 0.001$ ).

In my pooled analysis of the whole groups (disregarding responder status) fampridine treatment was associated with improvement in walking speed from baseline to the end of double blind treatment. The change from baseline in walking speed at the end of double-blind treatment was 0.30 ft/sec for fampridine and 0.15 ft/sec for placebo ( $p = 0.0016$ ). Note that despite the significant change, **the walking speed at the end of double-blind treatment was not different between the treatment groups** (2.37 ft/sec versus 2.30 ft/sec,  $p = 0.4269$ ), suggesting that the magnitude of change is small.

In the average change during double blind treatment from baseline in walking speed, the sponsor showed significant improvement with fampridine responders compared to non-responders and placebo. In my pooled analysis, the average change from baseline in walking speed is improved ( $p < 0.001$ ) in the fampridine group (0.29 ft/sec) over placebo (0.14 ft/sec). Again discounting responder status, the average walking speed during treatment is not different between treatment groups (2.36 ft/sec versus 2.29 ft/sec,  $p = 0.3825$ ).

To determine the variables that predicted the change from baseline in walking speed, I performed two mixed models analyses. In the first, the response (dependent) variable was change from baseline in double blind walking speed; the independent variables adjusted for were baseline walking speed, treatment arm, height, weight, and baseline MSWS-12 score. Only baseline walking speed ( $p < 0.001$ ) and fampridine treatment ( $p < 0.001$ ) were predictive of change in walking speed from baseline in the pooled efficacy population. In second mixed models analysis that excluded treatment arm, only baseline walking speed predicted change in walking speed ( $p = 0.0015$ ) while the following variables did not predict the change: center, gender, MS subtype,



and EDSS. This suggests that among the variables examined a subject's baseline walking speed and fampridine treatment contribute to the subject's improvement in walking speed.

## 6.1.5 Analysis of Secondary Endpoints

### Secondary Endpoints of MS-F203 Trial

#### *Average percent change from baseline walking speed in MS-F203 Trial*

The average percent change from baseline walking speed to the double-blind period was higher in the fampridine responders group compared to placebo. The mean (SD) change from baseline in walking speed was 0.51 (SD, 0.43) ft/sec for fampridine responders, 0.16 (SD, 0.31) for fampridine non-responders, and 0.10 (SD, 0.29) for placebo. The difference between placebo and fampridine non-responders in average change from baseline ( $p=0.297$ ) or percent change from baseline in walking speed ( $p=0.335$ ) was not significant. The average improvement (percent change from baseline) in walking speed for the fampridine responders group during the double-blind period was 25.2% (SD, 16.2%) compared to 4.7% (SD, 15.7) for the placebo group ( $p<0.001$ ). The average percent change for the fampridine responders group during the double-blind period ranged from 24.2% to 26.1% compared to 2.1% to 7.4% for the placebo group ( $p<0.001$  at every visit).

#### *Lower extremity Manual Muscle (LEMMT) Testing in MS-F203 Trial*

The fampridine responders showed higher improvements in LEMMT score that estimated the lower extremities muscle strength. The average improvement in the LEMMT scores for the fampridine responders was 0.18 (SD, 0.19) compared to 0.04 (SD, 0.22) for placebo ( $p<0.001$ ). The average improvement in the LEMMT scores for the fampridine non-responders was 0.11 (SD, 0.21), an improvement compared to placebo ( $p=0.046$ ). The LEMMT score improvement for the fampridine responders group during the double-blind period ranged from 0.16 to 0.20 compared to 0.03 to 0.05 for the placebo group at every visit. The difference between the treatment groups was significant at each visit ( $p<0.01$ ) except at the last visit ( $p=0.07$ ). The sponsor was unsuccessful at validating the clinical significance of LEMMT variable using the SGI to compare subjects with and without consistent improvements in LEMMT ( $p=0.808$ ).

#### *Ashworth assessment of spasticity in MS-F203 Trial*

There was no significant change in the Ashworth assessment of spasticity with fampridine treatment. A reduction from baseline in the Ashworth score suggests improvement. The average reduction from baseline in the Ashworth score was 0.13 for the fampridine responders, 0.17 for fampridine non-responders, and 0.07 for the placebo group. The difference between the placebo group and the fampridine responders was not significant ( $p=0.09$ ). Following the stepwise analytical procedure for evaluation of secondary endpoints, the difference in the Ashworth assessments between the fampridine non-responders and placebo ( $p=0.024$ ) is technically not significant.

#### *Subject Global Impression (SGI) and Clinician Global Impression (CGI) in MS-F203 Trial*

These variables were not part of the prespecified secondary analyses, but the sponsor included SGI and CGI variables to bolster its argument for the clinical meaningfulness of the walking



speed responder criterion. The sponsor showed both variables were scored higher in the walking speed responders compared to non-responders ( $p<0.001$ ).

### **Secondary efficacy Endpoint in MS-F204 Trial**

The secondary efficacy variable in MS-F204 Trial was average change from baseline in LEMMT during the eight-week, double-blind treatment period.

#### *Lower extremity Manual Muscle (LEMMT) Testing*

The fampridine responders showed higher improvements in LEMMT score that estimated the lower extremities muscle strength. The average improvement in the LEMMT scores for the fampridine responders was 0.15 (SD, 0.21) compared to 0.04 (SD, 0.25) for placebo ( $p=0.028$ ). The average improvement in the LEMMT scores of 0.05 (SD, 0.22) for the fampridine non-responders was not different from the placebo group ( $p=0.600$ ) or from the fampridine responders ( $p=0.134$ ). The LEMMT score improvement for the fampridine responders group during the double-blind period ranged from 0.09 to 0.18 compared to 0.02 to 0.07 for the placebo group at every visit.

**In the reviewer's analysis, there was no clinical difference in leg strength between the overall treatment groups in MS-F204.** The average improvement in LEMMT for the overall fampridine group during the double-blind period was 0.09 (CI, 0.05-0.13) units compared to 0.04 (CI, -0.001 to 0.085) units for the placebo group ( $p=0.125$ ). The average improvement from baseline in LEMMT for the overall fampridine group at the last observed double-blind visit was 0.10 (CI, 0.04-0.16) units compared to 0.07 (CI, 0.01-0.13) units for the placebo group ( $p=0.406$ ). The average LEMMT for the overall fampridine group during the double-blind period was 4.00 (CI, 3.89-4.11) compared to 4.00 (CI, 3.90-4.11) for the placebo group ( $p=0.927$ ). Likewise, the average LEMMT for the overall fampridine group at the last observed double-blind period was 3.91 (CI, 3.8-4.01) compared to 3.96 (CI, 3.86-4.07) for the placebo group ( $p=0.478$ ). These results indicate there was no change clinically in the leg strength between treatment groups for this trial.

### **Secondary Endpoints of Pooled Analysis of MS-F203 and MS-F204**

#### *LEMMT Testing in Pooled Analysis of MS-F203 MS-F204 Trial*

The fampridine group showed better results on the secondary efficacy variable used for both phase 3 trials, average improvement in LEMMT. In the pooled results conducted by the sponsor, the average improvement in LEMMT for fampridine responders during the double-blind period was 0.16 units compared to 0.03 units for the placebo group ( $p<0.001$ ).

In the reviewer's pooled analysis, the average improvement in LEMMT for the overall fampridine group (irrespective of responder status) during the double-blind period was 0.12 units compared to 0.04 units for the placebo group ( $p=0.0002$ ). Also, the average LEMMT for the overall fampridine group (irrespective of responder status) during the double-blind period was 4.12 units compared to 4.01 units for the placebo group ( $p=0.0307$ ).



The results, from combining both pivotal trials, indicate that there was a statistically significant improvement in leg strength with fampridine treatment. However, the magnitude of the improvement is so small as to question its clinical significance. On the LEMMT scale, the average score for both treatment groups fall under the same degree of leg strength (level 4), which is voluntary movement against moderate resistance applied by the examiner. The variability of moderate resistance as applied by different examiners further limits the usefulness of small improvement in length strength as observed with the fampridine group.

## 6.1.6 Other Endpoints

### Other Endpoints in MS-F203 Trial

#### *Efficacy Endpoints at Follow-up in MS-F203 Trial*

At the last follow-up visit when the subjects were four weeks from double blind treatment, there no differences in walking speed ( $p=0.802$ ), LEMMT (0.607), or Ashworth score (0.587) between the fampridine responders or placebo.

#### *Adjustment for Covariates in MS-F203 Trial*

There were no significant differences between the treatment groups in terms of demographics and other baseline characteristics. Yet, the sponsor reported performing further analysis while controlling for center and gender and came to the same conclusion in favor of fampridine.

#### *Analyses of Per Protocol Population in MS-F203 Trial*

The conclusions from the analysis of the per protocol population were supportive of the primary analysis. The responders were 9.2% (6/65) for placebo and 35.4% (65/195) for fampridine treatment ( $p<0.001$ ).

### Reviewer's Additional Efficacy Results of ITT analysis in MS-F203

At baseline, average walking speed was not different ( $p=0.8990$ ) between fampridine (2.05 ft/sec; CI, 1.96-2.15) compared to placebo (2.06 ft/sec; CI, 1.86-2.34)

The average walking speed during the double-blind treatment **was not different** ( $p=0.1527$ ) between fampridine (2.34 ft/sec; CI, 2.22-2.46) compared to placebo (2.16 ft/sec; CI, 1.95-2.37). Likewise, the walking speed at the end of the double-blind treatment **was not different** ( $p=0.1709$ ) between fampridine (2.35 ft/sec; CI, 2.22-2.48) compared to placebo (2.16 ft/sec; CI, 1.93-2.39).

The change in walking speed during treatment from baseline increased in the fampridine group. The difference in the average percent change from baseline walking speed was higher ( $p=0.0002$ ) with fampridine (13.6%; CI, 11.4-15.9) compared to placebo (4.7%; CI, 0.7-8.7). The average change in the double-blind walking speed from baseline was higher ( $p=0.0002$ ) with fampridine (0.28; CI, 0.24-0.33) compared to placebo (0.10; CI, 0.01-0.18). The change from baseline in walking speed at the end of double-blind treatment was 0.29 (CI, 0.22-0.37) ft/sec for fampridine and 0.10 (-0.03-0.22) ft/sec for placebo ( $p=0.0072$ ).



Lower extremity strength, tested by LEMMT, increased in the fampridine group. The average change in LEMMT during the treatment from baseline was 0.13 (CI, 0.11-0.16) in the fampridine group compared to 0.04 (CI, 0.00-0.09) in the placebo group (p=0.0016). Baseline LEMMT was not different (p=0.2439) between fampridine (4.06; CI, 3.98-4.15) and placebo (3.97; CI, 3.82-4.11) groups.

### Other Endpoints in MS-F204 Trial

#### *Additional Variables in MS-F204 Trial*

The sponsor further analyzed two objective and three subjective variables; these were not part of the definitive endpoints. One of the objective variables, average percent change in walking speed, was analyzed *post hoc*. The descriptive summaries of the additional variables are shown in the sponsor's tables below.

Table Summary of Additional Objective Variables in ITT Population of MS-F204 Trial

	Placebo (N=118)	Fampridine-SR Non-responder (N=68)	Fampridine-SR Responder (N=51)
Baseline Walking Speed in ft/sec: Mean (SD)	2.202 (0.6812)	2.083 (0.7988)	2.162 (0.6892)
Average Percent Change in Walking Speed *			
Mean (SD)	7.67 (18.166)	5.96 (15.523)	24.69 (13.117)
Median	5.16	4.05	22.64
Min, Max	-38.7, 141.1	-42.8, 52.1	5.3, 60.6
Baseline Ashworth Score: Mean (SD)	0.800 (0.6722)	0.884 (0.6045)	0.946 (0.6241)
Average Change in Ashworth Score *			
Mean (SD)	-0.064 (0.3437)	-0.159 (0.3065)	-0.202 (0.3721)
Median	-0.042	-0.125	-0.167
Min, Max	-1.08, 1.04	-0.88, 0.42	-1.08, 0.88

Note: For the Ashworth Score, a negative change is indicative of patient improvement.

\*The double-blind average was derived by taking the average of the unmissed visits during Visits 3 through 6.



Table Summary of Additional Subjective Variables in ITT Population of MS-F204 Trial

	Non-responder (N=175)	Responder (N=62)
n	175	62
Baseline MSWS-12: Mean (SD)	70.03 (21.092)	72.78 (18.649)
Average Change in MSWS-12 Score*		
Mean (SD)	0.85 (10.539)	-6.04 (13.880)
Median	1.04	-3.65
Min, Max	-38.0, 41.1	-55.2, 25.0
Average SGI Score*		
n	175	62
Mean (SD)	4.21 (1.008)	4.76 (0.965)
Median	4.00	4.63
Min, Max	1.0, 7.0	2.0, 6.8
	Non-responder (N=175)	Responder (N=62)
CGI Score at the End of Double-Blind **		
n	162	60
Mean (SD)	3.8 (0.61)	3.4 (0.80)
Median	4.0	3.5
Min, Max	2, 5	1, 5

Note: For the MSWS-12 Score, a negative change is indicative of patient improvement.

For the SGI, a larger value is indicative of a positive patient evaluation.

For the CGI Score, a smaller value is indicative of a positive patient evaluation (7 patients did not have a CGI score at the end of the double-blind).

\* The double-blind average was derived by taking the average of the unmissed visits during Visits 3 through 6.

\*\*Evaluated at double-blind Visit 6.

#### Additional Post hoc Analyses for MS-F204Trial

The sponsor reported additional analyses that showed reduction in disability score based on average change in MSWS-12 score in the fampridine responder group compared to non-responders. Similar advantages were reported for the responder group for the average SGI score and CGI score at the end of double-blind treatment.

The sponsor assessed the potential for treatment unblinding using the summary questionnaires. In the placebo group, 45 % of the subjects felt they received placebo. Similarly, 45% of subjects in the fampridine group felt they received the active drug. In the clinician's assessments, 40-44% of the clinicians were unsure of patient receiving active drug.

#### Adjustment for Covariates for MS-F204Trial

Adjusting for covariates yielded the same results on reanalyzing the primary and secondary efficacy variables. The sponsor adjusted for the following covariates individually while also adjusting for trial center: gender, weight, height, baseline EDSS score, baseline MSWS-12 score, and baseline SGI score. The primary efficacy variable (percentage of responders in the treatment



groups) showed greater proportion of responders in the fampridine group ( $p < 0.001$ ) with each adjustment for covariance. Likewise, the average change in LEMMT by responder group was analyzed adjusting for the following covariates: age, weight, height, duration of disease, baseline EDSS score, baseline MSWS-12 score, and baseline SGI score. Following the adjustments, the fampridine responders had more improvements in the average LEMMT score compared to placebo ( $p < 0.05$  for each covariate adjustment).

#### *Analyses of Per Protocol Population for MS-F204Trial*

The conclusions from the analysis of the per protocol population ( $N = 197$ ) were supportive of the primary analysis. The responders were 8.2% for placebo and 47.0% for fampridine treatment ( $p < 0.001$ ).

#### *Plasma Concentration and Fampridine Response for MS-F204Trial*

The sponsor analyzed plasma concentrations of fampridine and its metabolites for fampridine-treated subjects in the MS-F204 trial. The mean plasma concentrations at each visit ranged between 21 and 30 ng/mL during the double-blind period. The maximum concentrations at each visit during the double-blind period were between 56 and 87 ng/mL. The sponsor indicates the results were consistent with earlier PK studies.

#### **Reviewer's Additional Efficacy Results of ITT analysis for MS-F204Trial**

At baseline, average walking speed was not different ( $p = 0.3597$ ) between fampridine (2.12 ft/sec; CI, 1.99-2.25) compared to placebo (2.20 ft/sec; CI, 2.07-2.33)

The average walking speed during the double-blind treatment **was not different** ( $p = 0.7547$ ) between fampridine (2.41 ft/sec; CI, 2.25-2.56) compared to placebo (2.37 ft/sec; CI, 2.22-2.53). Likewise, the walking speed at the end of the double-blind treatment **was not different** ( $p = 0.8029$ ) between fampridine (2.42 ft/sec; CI, 2.26-2.58) compared to placebo (2.39 ft/sec; CI, 2.23-2.55).

However, the average change from baseline in the double-blind walking speed was higher ( $p = 0.0089$ ) with fampridine (0.29; CI, 0.23-0.35) compared to placebo (0.17; CI, 0.11-0.23). Similarly, the difference in the average percent change from baseline walking speed was higher ( $p = 0.0064$ ) with fampridine (14.0%; CI, 10.8-17.2) compared to placebo (7.7%; CI, 4.5-10.9). The average percent change from baseline in walking speed at the end of double-blind treatment was 14.8 (CI, 10.7-19.0) for fampridine and 8.5 (4.3-12.7) for placebo ( $p = 0.0358$ ).

For lower extremity strength tested by LEMMT, there **were no differences** between fampridine and placebo in the following parameters: average LEMMT during double-blind treatment [(4.00; CI, 3.89-4.11) versus (4.00; CI, 3.90-4.11);  $p = 0.9267$ ]; LEMMT at the last observed double-blind visit [(4.01; CI, 3.90-4.12) versus (4.03; CI, 3.92-4.14);  $p = 0.8109$ ]; change in LEMMT at the last observed double-blind visit [(0.10; CI, 0.04-0.16) versus (0.07; CI, 0.01-0.13);  $p = 0.4056$ ]; and average change from baseline in LEMMT [(0.09; CI, 0.05-0.13) versus (0.04; CI, 0.00-0.09);  $p = 0.1246$ ]. Baseline LEMMT was not different ( $p = 0.4784$ ) between fampridine (3.91; CI, 3.80-4.02) and placebo (3.96; CI, 3.86-4.07) treatment groups.



### Reviewer's Pooled Analysis of MS-F203 and MS-F204

Some of the sponsor's additional variables showed changes from baseline in the pooled analysis comparing the treatment groups as in table below. During the double blind period, there was no difference between the treatment groups in the Ashworth scores, SGI, and CGI. The lack of between treatment differences in Ashworth scores occurred in spite of a significant change in the score from baseline. Any of the observed changes in Ashworth scores do not appear to change the clinical degree of spasticity. On the average, the subjects remain between no increase in tone and slight increase in tone of muscles. The contribution of such a level of spasticity to walking disability or speed is unclear.

Table Additional Variables in the Pooled ITT population

Variable	Placebo	Fampridine-SR	Total	P value
Ashworth (SE)				
Baseline	0.86 (0.05)	0.89 (0.04)		0.5540
Double blind Average	0.79 (0.05)	0.74 (0.04)		0.4109
<b>Double blind Change from baseline</b>	-0.07 (0.02)	-0.17 (0.02)		0.0012
SGI (SE)				
N	190	343	533	
Baseline	4.47 (0.05)	4.48 (0.07)		0.9787
Double blind Average	4.38 (0.07)	4.51 (0.06)		0.1593
Double blind Change from baseline	-0.10	0.03 (0.07)		0.1201
CGI (SE)				
N	182	323	405	
<b>Double blind End</b>	3.8 (0.06)	3.5 (0.04)		0.0008

The sponsor also suggests that an improvement in spasticity may be independent of walking speed improvement. The sponsor's pooled results showed the average reduction in Ashworth Score for the fampridine responders during the double-blind period was 0.15 units compared to 0.07 units for placebo ( $p = 0.003$ ). The fampridine non-responders also had significantly reduced spasticity of 0.16 units compared to the placebo group ( $p = 0.009$ ), indicating that improvements in walking speed and spasticity with fampridine may be independent.

### 6.1.7 Subpopulations

#### Examination of Subgroups in MS-F203 Trial

All four subtypes of MS recorded an increase in the proportion of responders. The proportions of responders were not different between placebo and fampridine treatment ( $p=0.309$ ) as shown in the following table:

Table Proportion of Responders by MS Subtype in MS-F203 Trial

Characteristics	Placebo (N = 72)	Fampridine non- responder (N = 160)	Fampridine responder (N = 78)	Total (N = 300)
Relapsing Remitting	21 (29.2%)	47 (31.3%)	15 (19.2%)	83 (27.7%)



Primary Progressive	14 (19.4%)	20 (13.3%)	11 (14.1%)	45 (15.0%)
Secondary Progressive	35 (48.6%)	77 (51.3%)	48 (61.5%)	160 (53.3%)
Progressive Relapsing	2 (2.8%)	6 (4.0%)	4 (5.1%)	12 (4.0%)

### Examination of Subgroups for MS-F204 Trial

As in MS-F203 trial, MS-F204 had no formal subgroup analysis. All four subtypes of MS recorded an increase in the proportion of responders. The proportions of Timed Walk Responders among fampridine-treated subjects in the four MS types were: relapsing-remitting 37.2% (16/43); primary progressive 50.0% (5/10); secondary progressive 45.2% (28/62); and progressive-relapsing 40.0% (2/5).

### Examination of Subgroups in Pooled Analysis of MS-F203 and MS-F204 Trials

The Timed Walk Responder rates were consistent in the subgroups that the sponsor examined. The subgroups include: gender, race (Caucasians versus non-Caucasians), age, and BMI.

In the sponsor's pooled analysis, the MS subtype, duration of disease, and baseline EDSS did not affect the responder rates. Other baseline characteristics that did not influence the responder rates include: walking speed, LEMMT, Ashworth Score, MSWS-12, and SGI.

The sponsor examined the responder rates in subjects with renal impairment and found no significant change in responder rates. The subjects were categorized as normal (creatinine clearance of 80 mL/minute or above), or abnormal (creatinine clearance below 80 mL/minute). The responder rates were 47.6% in abnormal renal function group compared to 34.7% in normal renal function group ( $p = 0.825$ ).

With respect to concomitant immunomodulator use, there was a trend to a difference in responder rates between the users and non-users of immunomodulators. The responder rates for placebo-treated subjects were 6.1% for immunomodulator users and 14.9% nonusers, for fampridine-treated were 36.0% for immunomodulator users and 39.8% non-users ( $p=0.076$ ). The sponsor suggests the trend is likely driven by the high responder rates in placebo-treated nonusers.

## 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Increasing doses of fampridine do not appear to increase efficacy. However, there is a remarkable lack of investigation of doses below 10 mg twice daily.

## 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The efficacy variables returned to baseline values during follow-up visits after the double blind treatments. To address the issue of persistence of efficacy, the sponsor reported interim data from ongoing extension trials (MS-F202 EXT, MS-F203 EXT, and MS-F204 EXT). The extension trials included subjects who participated in the parent double blind trials and received at least one efficacy assessment in the extension trials.



In MS-F203 EXT, the extension Timed Walk Responders were 66 (24.9%). Of these responders, 29 were responders in the parent MS-F203 trial, 25 were nonresponders in the parent MS-F203 trial, and 12 were previously in the placebo group. Among the fampridine double blind responders, the extension responder rates were 42.9% for year 1 and 36.1% for year 2; for fampridine nonresponders, the extension responder rates were 19.7% for year 1 and 17.5% for year 2; and for the placebo patients, the extension responder rates were 16.2% for year 1 and 20.8% for year 2.

The average percent change from baseline in walking speed for the extension timed walk responders was over 30% in year 1, but declined about 10% in year 2 from preceding year level. Similarly, the average percent change in nonresponders improved by 20% in year 1, but declined 8% in year 2 from preceding year level. The sponsor attributed the decline in responder rates in the second year to the natural history of the underlying MS disease.

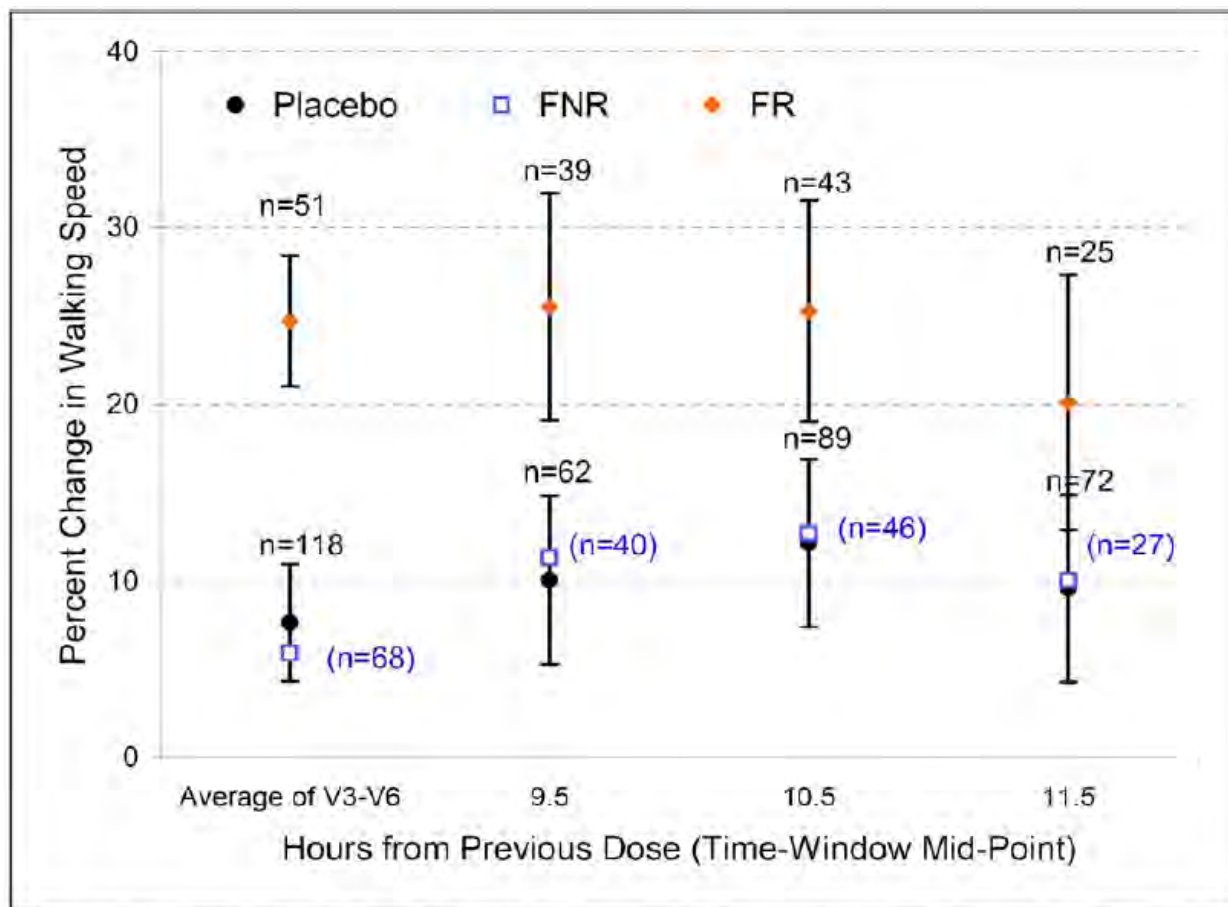
In MS-F204 EXT, the extension Timed Walk Responders were 105 (49.3%). Among the extension responders, 35 were responders in the parent MS-F204 trial, 18 were nonresponders in the parent MS-F204 trial, and 52 were in the placebo group. The sponsor suggests that these extension responder results indicate absence of tolerance to the treatment effect of fampridine.

#### **Efficacy with Respect to Time from Last Fampridine Dose**

The sponsor evaluated efficacy with respect to time from last dose of fampridine in MS-F204. The average walking speed among fampridine responders consistently increased up to 10.5 hours from last dose (Visits 3-6), but declined during the last hour of the 12 hour inter-dosing interval (Visit 7). The changes in average walking speed during the dose interval are shown in the sponsor's figure below.



Figure Percent Change from Baseline in Walking Speed versus Approximate Time from Previous Dose at Visits 3-6 and at the 3 Major Post-dose Time Windows at Visit 7 by Responder Analysis Group (ITT Population, Observed Cases, Mean, 95% CI)



Abbreviations: PBO=Placebo; FNR=Fampridine Timed Walk Non-responders; FR= Fampridine Timed Walk Responders.

Note: Sample sizes for Fampridine 10 mg b.i.d. Timed Walk Non-responders in parentheses. CI not shown for clarity of comparing FNR and PBO.

### 6.1.10 Additional Efficacy Issues/Analyses

The results of two pivotal trials showed improvements in walking speed in a greater proportion of subjects treated with fampridine compared to placebo. Yet, the magnitude of improvement in the active drug treatment is so small that the walking speed in that group is not significantly different from that of placebo. So, the clinical significance of the treatment benefits is in doubt. One of the major problems of the responder analysis is the inability to predict responders before treatment. If this were possible, a trial in such a population will help determine the real benefits of fampridine treatment. The efficacy of the individual pivotal trials is summarized as follows:



***Efficacy Conclusion for MS-F203***

The sponsor achieved all three steps of the primary endpoint. More subjects the fampridine group improvement in walking speed measured by the Timed 25-Foot Walk compared to placebo (34.8% vs. 8.3%,  $p < 0.001$ ). The improvement in walking speed, among responders, was maintained through the 14-week double-blind treatment period ( $p < 0.001$ ). Responders in both treatment groups showed improvement in MSWS-12 compared to non-responders ( $p < 0.001$ ). The sponsor presented analyses to support the results of the primary endpoint. The average increase in walking speed over the treatment period compared to baseline was significantly more in the fampridine responder group (25.2%) compared to placebo (4.7%). Leg strength increases occurred with fampridine treatment for both responders ( $p < 0.001$ ) and non-responders ( $p = 0.046$ ) compared to placebo.

***Efficacy Conclusion for MS-F204***

The sponsor achieved the primary endpoint. More subjects in the fampridine group showed improvement in walking speed as measured by the Timed 25-Foot Walk compared to placebo (42.9% vs. 9.3%,  $p < 0.001$ ). The secondary efficacy endpoint, leg strength, increased with fampridine treatment for responders ( $p = 0.028$ ) but not for non-responders ( $p = 0.600$ ) compared to placebo.

**Overall in both pivotal trials**, not considering the responder status, fampridine treatment is associated with increases in walking speed and in lower extremity strength from baseline. Despite these increases, there was no difference in walking speed between the fampridine and placebo groups during double-blind treatment.



## CLINICAL SAFETY REVIEW

Application Type	NDA
Application Number(s)	022-250
Priority or Standard	Priority

Submit Date(s)	
Received Date(s)	
PDUFA Goal Date	
Division / Office	DNP/ODE 1

Reviewer Name(s)	Gerard Boehm, MD, MPH
Review Completion Date	9/1/09

Established Name	Fampridine SR
(Proposed) Trade Name	Amaya
Therapeutic Class	Potassium Channel blocker
Applicant	Acorda Therapeutics

Formulation(s)	Controlled release tablet
Dosing Regimen	10mg BID
Indication(s)	Improvement of Walking Ability
Intended Population(s)	Multiple Sclerosis Patients



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## Review of Safety

### **Safety Summary**

This review considers the safety data for Fampridine SR as presented in Acorda's NDA 022-250. Fampridine SR is an orally administered, controlled release dosage form of 4-aminopyridine, a selective blocker of potassium channels. In addition to its proposed use as a therapeutic agent, 4-aminopyridine is used as a bird poison (trade names Avitrol 200 and Avitroland, classified by the EPA as a Restricted Use Pesticide) and as a research tool to characterize potassium channels

4-aminopyridine improves conduction in demyelinated nerve fibers and has been used to improve symptoms in multiple sclerosis (MS) patients. Since no dosage forms of 4-aminopyridine are currently approved for use, MS patients have depended on compounding pharmacies to obtain the drug. This has resulted in reports of toxicity related to compounding errors. The most concerning toxic effect of 4-aminopyridine is seizure. To limit seizure risk, the Fampridine SR formulation was developed and Acorda intends to limit recommend Fampridine SR doses to 10mg bid.

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-Barre 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 FDA approved treatments for MS but Fampridine SR would be the first approved treatment for improvement of walking ability in MS patients.

The Fampridine SR NDA submission summarizes pooled safety data from 45 trials including 2,115 subjects from studies in healthy volunteers and adults with MS and SCI. Acorda provided additional safety data for 138 subjects from 11 trials that could not be pooled due to lack of available datasets from previous IND holders. The overall pool of safety data includes information collected from MS subjects (clinical pharmacology, controlled, and uncontrolled trials), SCI subjects (clinical pharmacology, controlled, and uncontrolled trials), and non-patient subjects (healthy volunteers, volunteers with renal deficiency). Acorda also presents safety data using subsets of the pooled data. Acorda presents results for MS subjects and SCI subjects (clinical pharmacology, controlled, and uncontrolled trials n=1510). Acorda presents separately results for only MS subjects (n=917), only SCI subjects (n=583) and only non-patient subjects (n=382). In addition, Acorda presents comparative results from MS adequate and well controlled trials (Fampridine SR n=507, placebo n=238), and from SCI adequate and well controlled trials (Fampridine SR n=277, placebo n=229). Lastly, Acorda provides summaries of safety data for the 11 trials excluded from the pooled analysis. For overall event risk estimates, this review relied on the analyses of the pooled safety population for MS



subjects and SCI subjects. For comparative risk analyses, this review primarily relied on data from the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204).

The number of patients exposed to Fampridine SR in the NDA trials exceeds ICH guidelines and investigators exposed adequate numbers of subjects to the intended recommended dose (10 mg bid). The Fampridine SR NDA submission includes safety data for 2253 subjects. Acorda reported that 1,621 subjects were exposed to at least one dose of Fampridine SR, including 807 MS subjects. In the NDA submission, 780 subjects were exposed to Fampridine SR for at least 6 months (601 MS subjects) and 444 were exposed for at least 1 year (405 MS subjects). The majority of subjects were exposed to Fampridine SR doses of at least 10mg bid.

I identified no significant deficiencies in the NDA safety submission. Acorda submitted all necessary summaries and supporting data. There were no notable inconsistencies between the data sources. The routine clinical safety testing in the fampridine MS trials seemed appropriate and capable of identifying major safety signals with Fampridine SR. The Fampridine SR NDA included instances of coding inadequacies, but none are expected to impact our understanding of the safety profile of Fampridine SR.

Deaths occurred infrequently in the Fampridine SR clinical trials and there did not appear to be clusters of unusual causes of death. The reported causes of death for Fampridine SR clinical trial subjects were oxycodone overdose, aortic dissection, suicide, unknown/found dead in bed, intracerebral hemorrhage, and fall (positional asphyxia).

15.1% (228/1510) of MS and SCI subjects experienced one or more serious adverse events (SAEs). The System Organ Class (SOC) groupings with the most SAEs were Nervous system disorders (5.4%, 81/1510), and Infections and Infestations (4.3%, 65/1510). No subjects experienced SAEs of hepatic failure, hepatitis, rash, Stevens Johnson syndrome, Toxic epidermal necrolysis, angioedema, anaphylaxis, rhabdomyolysis, or aplastic anemia. The most commonly reported SAEs were multiple sclerosis relapse (2.5%), convulsion (1.3%), urinary tract infection (1.2%), and cellulitis (1.1%). In the MS adequate and well controlled trials, SAEs were 3 times more frequent among Fampridine SR subjects (6.5%, 33/507) compared to placebo subjects (2.1%, 5/238) and the risk for all SAEs among Fampridine SR subjects appeared dose related. Multiple sclerosis relapse was the only SAE that occurred in more than 2 Fampridine SR subjects (Fampridine SR n=7, 1.4%; placebo n=0).

14.6% of MS and SCI subjects experienced one or more AEs leading to discontinuation. The most common AEs leading to discontinuation among Fampridine SR subjects in the pool of MS and SCI study subjects were dizziness (2.5%), insomnia (1.5%), convulsion (1.3%), asthenia (1.3%), nausea (1.1%), anxiety (1.1%), and paresthesia (1.0%). In the MS adequate and well controlled trials, 3.4% (17/507) of Fampridine SR subjects had



one or more AEs leading to discontinuation compared to 2.1% (5/238) of placebo subjects. The AEs leading to discontinuation of at least 2 Fampridine SR subjects and that led to discontinuation more frequently compared to placebo were headache (Fampridine SR 0.8%, 4/507; placebo 0/238), balance disorder (Fampridine SR 0.6%, 3/507; placebo 0/238), dizziness (Fampridine SR 0.6%, 3/507; placebo 0/238), and confusional state (Fampridine SR 0.4%, 2/507; placebo 0/238).

Common AEs that occurred more frequently among Fampridine SR MS subjects and in some cases that exhibited evidence of a dose response relationship included urinary tract infection, insomnia, dizziness, headache, asthenia, nausea, fatigue, MS relapse, balance disorder, paresthesia, back pain, muscle spasms, nasopharyngitis, constipation, diarrhea, difficulty walking, pharyngolaryngeal pain, gastroenteritis viral, pollakiuria, vomiting, pyrexia, rash, anxiety, cough, and tremor.

As noted above, Fampridine SR causes seizures and Acorda evaluated the seizure risk at the dose intended for the treatment of MS patients (10mg bid). Data from the controlled clinical trials at the 10mg bid dose did not suggest a difference in seizure risk compared to placebo but this comparison relied on only 400 Fampridine SR treated patients, 238 placebo patients and only 2 seizure events (1 Fampridine SR, 1 placebo). In these same studies, at 20mg bid (only a doubling of the dose intended to be marketed), the seizure risk was 10-fold higher (based on 2 events in 57 subjects), a concerning finding suggesting a narrow therapeutic index. In the open label trials, the seizure risk in those treated with 10mg bid was similar to the risk seen in the Fampridine SR subjects treated with 10mg bid during controlled trials. The results from this open label population must be considered very carefully since this was a highly selected population. These patients were screened by history and EEG prior to the RCT, those with exposure to Fampridine SR in the RCT (roughly 2/3 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.

Comparing the seizure risk in the Fampridine SR clinical trial population with background data or data from other MS drug development programs must also be viewed with caution. The screening in the Fampridine SR trials and usual concerns about potentially important differences among the Fampridine SR population and the general MS background population or other drug development program populations make these comparisons problematic.

The current evidence supports a dose-related risk of seizure with Fampridine SR, with limited experience at the dose intended for treatment, and some evidence of increasing risk just above the therapeutic dose. If the risk benefit for Fampridine SR is favorable and the drug is approved, Fampridine SR should not be used in patients with seizure history and prospective patients should be screened with EEG prior to treatment, the conditions of use in the clinical trials. Fampridine SR labeling should include information about the potential for increased seizure risk at the intended dose, should strongly warn



about not increasing the dose above the recommended dose and urge caution in patients at risk for higher exposures (ex. renal insufficiency). A Medication Guide should explain the risk for patients and include information cautioning against increasing the dose.

Results from the pooled analysis of AEs from the adequate and well controlled MS trials demonstrated an increased risk of multiple sclerosis relapse TEAEs among Fampridine SR subjects compared to placebo subjects and the risk among Fampridine SR subjects increased with increasing dose. The difference in MS relapse risk between Fampridine SR and placebo in the RCT study data was driven by differences in the post-treatment period, when subjects were not taking Fampridine SR. The post treatment phase was short in duration (only 2 weeks) meaning that this finding is based on very limited observation time. Also complicating this assessment is the suggestion of differences between the placebo and Fampridine SR groups based on the pre-treatment, baseline data. The MS relapse risk in the Fampridine SR group prior to initiating treatment was 4-fold higher (30.3/100PY) than the risk in the placebo group during the pre-treatment phase (7.3/100PY).

The reason for the observed difference in MS relapse risk between Fampridine SR subjects and placebo subjects is not clear. Acorda's explanation, that the MS relapse TEAEs represent a waning therapeutic effect following discontinuation seems to be a reasonable explanation. Unfortunately the available data presented in the narratives for these events are not sufficient to allow differentiation between waning therapeutic effect and relapse of the MS disease process. In fact, in some cases, these events appeared to be true relapses to clinicians because the events resulted in hospitalization and treatment with steroids.

The data from patients who experienced relapse during the post treatment phase and who continued in open label extension phases is reassuring. These data did not suggest continued increased MS relapse risk among these patients. Furthermore, there did not appear to be increased MS relapse risk in the extension trial patients compared to the RCT patients.

Acorda suggests that patients and physicians should be counseled to expect the possibility of worsening MS symptoms after discontinuing treatment. Acorda did not suggest how this might be accomplished. Labeling language and discussion in the Medication Guide could accomplish this goal.

The AE data from the Fampridine SR clinical trials (both MS and SCI) suggested an increased risk for urinary tract infections in Fampridine SR patients compared to placebo patients. In many cases, these events were diagnosed based only on symptoms and UA and/or urine cultures were not performed. There did not appear to be consistent increases in risk among Fampridine SR subjects compared to placebo subjects for UTI SAEs (elevated risk in Fampridine SR MS patients, but not in SCI



Fampridine SR patients). There is insufficient evidence to evaluate Acorda's hypothesis that these UTI events represent drug related sensory symptoms rather than actual infections. Any future planned Fampridine studies should attempt to clarify the association between Fampridine and UTI, perhaps by questioning all study patients about urinary symptoms and collecting cultures and UAs in symptomatic patients.

Lab data, vital sign data and ECG data collected during the clinical trials did not find evidence of Fampridine SR related deleterious effects. A formal QT study did not find evidence of QT prolongation in subjects exposed to Fampridine SR.

#### Problem List/Recommendations

Labeling and the Medication Guide should describe the seizure risk with Fampridine SR.

Labeling and the Medication Guide should describe the possibility of worsening symptoms following discontinuation of Fampridine SR.

Any ongoing or planned fampridine clinical trials should incorporate testing to assess the risk for UTIs in Fampridine SR treated patients.

Acorda should closely follow up all reports of liver injury. Follow up should include complete description of the case, outcome information, lab test results, biopsy results, and post mortem test results. In addition, Acorda should submit any serious liver injury cases as 15-day reports.

Acorda should incorporate the labeling language that will be requested by the Division.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Acorda reported that 2253 subjects participated in the 56 clinical trials included in the Fampridine SR NDA (cutoff date 7/31/08). The Fampridine SR integrated safety database included 2115 subjects from 45 trials. Acorda could not include the remaining 138 subjects from 11 trials in the integrated safety database because they were unable to obtain from former IND holders the SAS data sets used as the basis for the integrated review (Summary of Clinical Safety, p.9). Acorda summarized separately the safety data for these 138 subjects not included in the integrated safety database.

Investigators collected safety data during trials that evaluated various fampridine treatment indications including multiple sclerosis, spinal cord injury (SCI), and Guillain-



Barre syndrome as well as during clinical pharmacology trials. The integrated safety database includes 382 healthy volunteers from 13 trials, 1029 subjects from 20 trials in MS patients, and 704 subjects from 12 trials in SCI patients (Summary of Clinical Safety, Table 1, p.12).

Acorda identified 1922 subjects exposed to one or more doses of fampridine (all formulations). Acorda summarized the exposure by indication in table 2 and I reproduce that table below.

Total Number of Patients Exposed to Fampridine and Placebo in all Clinical Trials

Trial Population	Trial Category	Trial Number	Placebo	First Use of Fampridine		
				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
		<i>Total</i>	<i>386</i>	<i>807</i>	<i>178</i>	<i>974</i>
Spinal Cord Injury	Clinical Pharmacology	All		14	4	18
	Placebo Controlled	All	322	372		372
	Uncontrolled	All		203		203
		<i>Total</i>	<i>322</i>	<i>589</i>	<i>4</i>	<i>593</i>
Renal Deficiency	Clinical Pharmacology	RD10F-SR012004		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
<i>All</i>	<i>All</i>	<i>Total from all studies with available data</i>	<i>797</i>	<i>1621</i>	<i>224</i>	<i>1793</i>
		<b>Grand Total</b>	<b>845</b>	<b>1621</b>	<b>353</b>	<b>1922</b>



Acorda's Safety Update (submitted on 6/22/09 with a data cutoff date of 11/30/08) included additional safety data for subjects continuing in ongoing MS extension trials (MSF-202 EXT, MSF-203 EXT, and MSF 204 EXT) and data for 30 subjects that participated in a newly completed PK study.

### 7.1.2 Categorization of Adverse Events

Acorda defined adverse events (AEs) as "any untoward medical occurrence in a clinical investigation patient that did not necessarily have a causal relationship with treatment." Acorda defined treatment emergent adverse events (TEAEs) as "AEs with the date of onset (or worsening severity) on or after the start of double-blind/active study medication and no more than 14 days after the last dose of study medication." In addition to providing analyses of TEAEs, Acorda provided additional analyses that examined TEAEs that occurred during active treatment and TEAEs that occurred during follow up (after treatment cessation).

In addition to the routine exploration of AEs, Acorda presented additional analyses of selected AEs of particular concern. Acorda considered seizure AEs of special interest because of the known causal association with fampridine. Following discussions with the Division, Acorda agreed to classify all seizure AEs as SAEs (Summary of Clinical Safety, p.22). Acorda coded AEs involving focal or generalized, grand mal type motor seizures that were often not well described by observers to the MedDRA term "convulsion". Four events reported as complex partial seizures were coded directly to the MedDRA term "complex partial seizures" and one event that Acorda considered severe and prolonged was coded to the MedDRA term "grand mal convulsion" (Summary of Clinical Safety, p.40). For a separate analysis, Acorda also pooled and analyzed AE terms that could be a response to underlying seizure activity. I list those AE terms are listed below:

Abnormal dreams, Agitation, Aphasia, Aphonia, Asthenia, Clonus, Cognitive disorder, Complex partial seizure, Confusional state, Convulsion, Daydreaming, Delirium, Delusion, Depressed level of Consciousness, Disorientation, Dissociation, Disturbance in attention, Dizziness, Encephalopathy, Hallucination, Hallucination auditory, Hallucination visual, Hypersomnia, Insomnia, Lethargy, Listless, Loss of consciousness, Mania, Memory impairment, Mental impairment, Mental status changes, Muscle contractions involuntary, Myoclonus, Nausea, Neurologic symptom, Nightmare, Panic attack, Paralysis, Parosmia, Psychomotor hyperactivity, Psychotic disorder, Seizures, Sensory disturbance, Somnolence, Suicidal ideation, Syncope, Tension, Thinking abnormal, and Transient ischemic attack (ISS Statistical Plan, p.34).

Acorda compared the frequency of the pool of these potential seizure AE terms for Fampridine SR and placebo.



In addition to seizures, Acorda analyzed the following AEs as AEs of special interest: other CNS AEs not characterized as seizures; psychiatric disorders; suicidal ideation and related events; MS relapse; urinary tract infections; injury, poisoning and procedural complications; and infections and infestations.

#### Coding Dictionary Evaluation

Adverse event verbatim terms were initially coded to either COSTART or MedDRA. The NDA safety analyses are based on AE terms that were ultimately coded to MedDRA Version 8.1 (Clinical Summary of Safety, p.22). Adverse events were voluntarily reported by trial subjects in response to the investigator's question regarding how the subject was feeling since the last visit and study protocols did not use checklists of potential AEs (ISS, p.133).

Coding the various AE verbatim terms reported by study subjects (ex. "my stomach hurts") to specific preferred terms (ex. abdominal pain) is an important task that allows for the analysis of AEs occurring during drug development programs. The output of the coding process must be evaluated for results that might hamper AE risk evaluation such as lumping unrelated events under single preferred terms, splitting similar events into multiple terms or coding events to preferred terms so vague that they have limited value. Such occurrences can be present in any NDA, usually with little consequence, but it is important to look for coding inadequacies that could impact the safety assessment.

The Fampridine SR NDA included instances of coding inadequacies, but none are expected to impact our understanding of the safety profile of Fampridine SR. I identified occasional examples of lumping unrelated AE terms into single preferred term. For example, the MedDRA term bacterial infection subsumed a collection of verbatim terms so diverse (bacterial infection in toenail, bacterial infection of stomach, left elbow infection) as to render the preferred term unhelpful. The Fampridine SR NDA also included instances where similar events were split into different preferred terms. For example, Acorda coded similar clinical events to the preferred terms cystitis, urinary tract infection, Escherichia urinary tract infection, and kidney infection. To take into account this coding approach, I conducted additional analyses by pooling these different preferred terms to assess urinary tract infection risk. Acorda used a number of preferred terms that were unhelpful in terms of describing the events they subsumed. Examples of unhelpful preferred terms include eye disorder, bladder disorder, liver disorder, hypersensitivity, feeling abnormal, and mental impairment. Assessing vague preferred term AEs requires examining the verbatim terms along with the preferred terms.



### 7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Acorda provides various pools of data to summarize the safety experience with Fampridine SR. The overall pool of safety data includes information collected from MS subjects (clinical pharmacology, controlled, and uncontrolled trials), SCI subjects (clinical pharmacology, controlled, and uncontrolled trials), and non-patient subjects (healthy volunteers, volunteers with renal deficiency). Acorda also presents safety data using subsets of the pooled data. Acorda presents results for MS subjects and SCI subjects (clinical pharmacology, controlled, and uncontrolled trials n=1510). Acorda presents separately results for only MS subjects (n=917), only SCI subjects (n=583) and only non-patient subjects (n=382). In addition, Acorda presents comparative results from MS adequate and well controlled trials (fampridine n=507, placebo n=238), and from SCI adequate and well controlled trials (fampridine n=277, placebo n=229). Lastly, Acorda provides summaries of safety data for the 11 trials excluded from the pooled analysis. For overall event risk estimates, this review will rely primarily on the analyses of the pooled safety population for MS subjects and SCI subjects. For comparative risk analyses, this review will primarily rely on data from the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204). This review will present data from other sub-groupings for specific safety issues, for clarification, or for further exploration of risk.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The number of subjects exposed to fampridine in the development program exceeds the subject exposure recommendations in the ICH guidance document.

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). The following table summarizes exposure by formulation, for MS subjects, and by duration, through the NDA cutoff date.

Exposure groups	Number exposed to all fampridine formulations	Number exposed to fampridine SR
<b>Total exposed</b>	<b>1922</b>	<b>1621</b>
Integrated database	1793	1621
<i>MS subjects</i>	<i>917</i>	<i>807</i>



Non-integrated	129	0
<i>MS subjects</i>	57	0
<b>Exposed ≥ 6 months</b>	<b>792</b>	<b>780</b>
Integrated database	792	780
<i>MS subjects</i>	601	601
Non-integrated	0	0
<b>Exposed ≥ 1 year</b>	<b>456</b>	<b>444</b>
Integrated database	456	444
<i>MS subjects</i>	405	405
Non-integrated	0	0

### Demographics

Acorda provided tables that summarized the demographic factors for the MS patients that participated in clinical trials. Below, I summarize demographic data for the adequate and well controlled MS trials that served as the basis for the majority of comparative analyses in the NDA safety data presentations.

### Demographic Factors for Subjects in the Adequate and Well Controlled MS Trials MS-F202, MS-F203, and MS-F204

Demographic Factor	Placebo	Fampridine SR			
	(n=238)	10mg bid (n=400)	15mg bid (n=50)	20mg bid (n=57)	Total (n=507)
Age (years)					
Mean	51.1	51.7	47.8	52.3	51.4
Median	51	53	47	53	52
Min, Max	24, 70	25, 73	30, 66	29, 67	25, 73
Sex					
Male	94 (40%)	114 (29%)	16 (32%)	23 (40%)	153 (30%)
Female	144 (60%)	286 (71%)	34 (68%)	34 (60%)	354 (70%)
Race					
Caucasian	216 (91%)	374 (94%)	44 (88%)	52 (91%)	470 (93%)
Black	14 (6%)	15 (4%)	3 (6%)	3 (5%)	21 (4%)
Asian	1 (<1%)	3 (<1%)	1 (2%)	0	4 (<1%)
Other	7 (3%)	8 (2%)	2 (4%)	2 (4%)	12 (2%)

From Table 4, Summary of Clinical Safety, p18)

There was a slightly higher percentage of females in the Fampridine SR group compared to the placebo group, but there did not appear to be meaningful differences in age or race between the treatment groups.



Acorda reported that for the Fampridine SR treatment group 27% of subjects were classified with relapsing remitting MS, 16% with primary-progressive MS, 54% with secondary progressive MS, and 3% with progressive relapsing MS. For the placebo group, 31% were classified with relapsing remitting MS, 20% with primary progressive MS, 48% with secondary progressive MS, and 2% with progressive relapsing MS (ISS Table 39).

In the following table, I summarize demographic data for MS patients that participated in clinical pharmacology trials and in the uncontrolled MS trials.

Demographic Factors for Subjects in Clinical Pharmacology Trials and in the Uncontrolled MS Trials

Demographic factor	Clinical Pharmacology Trials (Duration 1 week or less) (N=94)	Uncontrolled Trials (Duration > 1 week) (n=693)
Age (years)		
Mean	46.6	51.7
Median	47	51
Min, Max	23, 64	25, 71
Sex		
Male	38 (40%)	321 (35%)
Female	56 (60%)	454 (65%)
Race		
Caucasian	90 (96%)	655 (95%)
Black	0	21 (3%)
Asian	1 (1%)	4 (<1%)
Other	3 (3%)	9 (1%)

From ISS table 2.2.1

In the uncontrolled trials, Acorda reported that 26% of subjects were classified with relapsing remitting MS, 14% with primary-progressive MS, 50% with secondary progressive MS, and 3% with progressive relapsing MS (7% missing MS diagnosis type information) (ISS Table 40).

## 7.2.2 Explorations for Dose Response

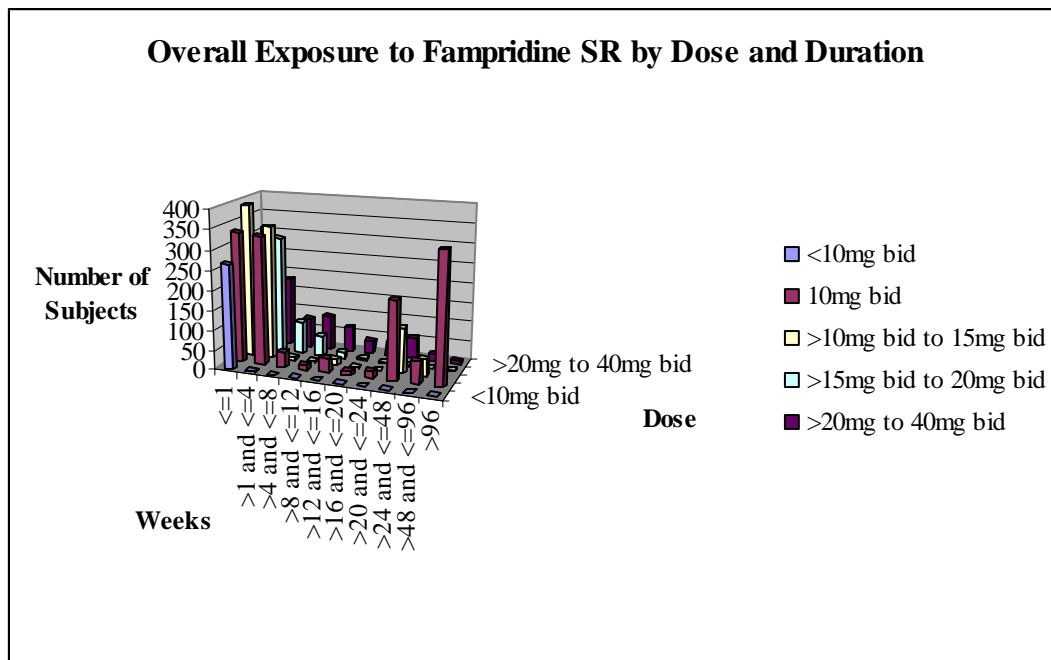
### Exposure by Dose

Acorda's ISS Table 7.0.1 summarizes the number of subjects exposed to the different doses used in the Fampridine SR development program trials. Table 7.0.1 demonstrates that most study subjects in the Fampridine SR development program were exposed to Fampridine SR doses  $\geq 10$ mg bid. Acorda's proposed labeling for Fampridine SR recommends a dose of 10mg bid.



#### Exposure by Dose and Duration

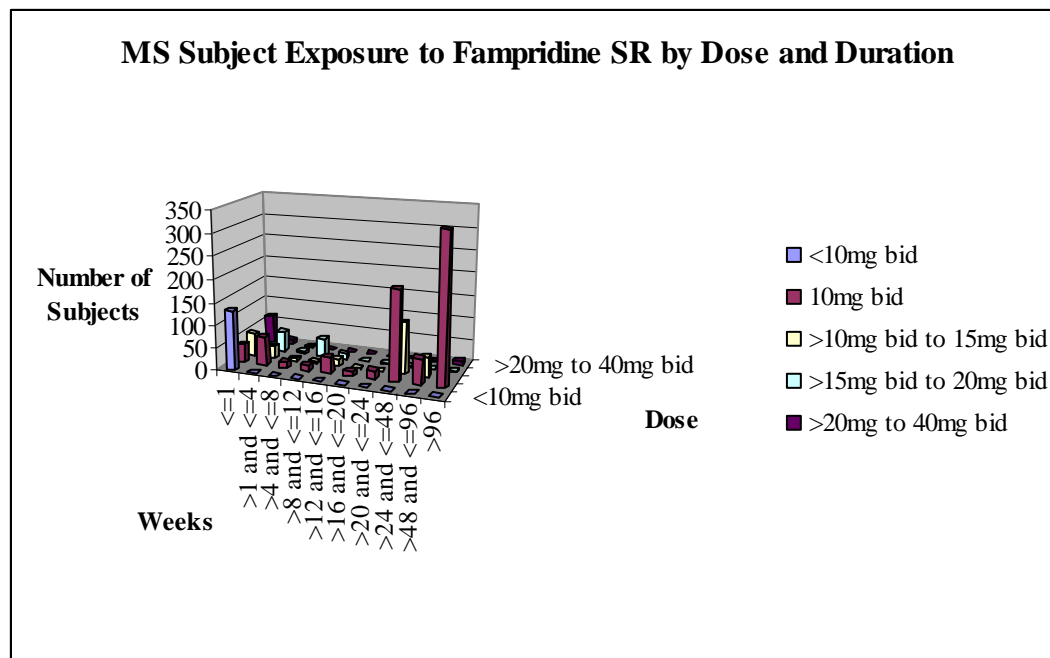
Acorda's ISS Table 7.0.2 summarizes exposure to Fampridine SR by dose and duration. I used the data from Table 7.0.2 to create the following graphs depicting exposure by dose and duration for the Overall population and the MS population.



This graph demonstrates that Acorda exposed most subjects to Fampridine SR doses of 10mg bid or greater with a number of subjects exposed more than 26 weeks.

The following graph summarizes exposure to Fampridine SR in MS trials included in the integrated safety database.





This graph demonstrates that most MS subjects were exposed to the 10mg bid dose and that a considerable number of subjects were exposed for more than 48 weeks. Few MS patients were exposed to Fampridine SR doses above 10mg bid.

### 7.2.3 Special Animal and/or In Vitro Testing

Acorda reported results of animal trials assessing the risk and mechanism of seizures. In addition, Acorda provide results from hERG channel testing, action potential testing in isolated dog Purkinje fibers, and cardiovascular effect observations in beagles. These data are examined in the Preclinical pharmacology section 4.3 of the NDA review.

### 7.2.4 Routine Clinical Testing

The routine clinical safety testing in the Fampridine SR MS trials seemed appropriate and capable of identifying major safety signals. In the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204), at each visit, subjects underwent AE assessment, physical exam, and vital signs testing, and at multiple visits, subjects underwent laboratory testing and ECG testing. These trials required follow-up visits up to 2 weeks after stopping Fampridine SR that allowed for assessment for potential late-occurring AEs and for withdrawal symptoms that could manifest following treatment cessation. In the open label extension trials (MS-F202EXT, MS-F203EXT, and MS-F204EXT) for the above RCTs, subjects were screened and then began treatment within 2 weeks of screening. Subjects were followed initially at 2 week intervals, with subsequent increases in interval of follow up. Subjects were ultimately seen in by



investigators at 26 week intervals with phone call follow up between clinic visits. Subjects were also seen for a follow up visit (up to 4 weeks after completing treatment). Subjects' safety assessments during these open label extension trials included AE assessments, physical exams, vital signs, lab testing, and ECGs.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor's in vitro and in vivo testing for fampridine metabolism, clearance and interactions seemed appropriate. Acorda found that Fampridine SR absorption was 96% and that 90% is excreted unchanged in urine. CYP2E1 is the major enzyme responsible for 3-hydroxylation of metabolized Fampridine SR. There were no identified inhibitors or inducers and fampridine is not an inhibitor or inducer of P450s. Fampridine SR is not a P-glycoprotein substrate or inhibitor. The half-life of Fampridine SR was 5.2-6.5 hours. Fampridine SR can be taken with or without food. Acorda found no evidence of drug-drug interactions with either baclofen or betaseron. Details of these assessments can be found in the Clinical Pharmacology Review.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Fampridine is a new molecular entity and does not belong to an approved class of drugs.

## 7.3 Major Safety Results

### 7.3.1 Deaths

Deaths occurred infrequently in the Fampridine SR clinical trials and there did not appear to be clusters of unusual causes of death.

Acorda reported six deaths that occurred within 30 days of last exposure to Fampridine SR during the clinical trials included in the integrated safety database. Five of these deaths were MS trial subjects and 1 was a SCI trial subject. One additional death (in an MS trial subject) occurred 5 weeks after last Fampridine SR exposure. Acorda also identified one death in a subject receiving placebo (SCI trial).

Five of the six deaths within 30 days of last Fampridine SR dose occurred in MS trial subjects (ISS, pp. 212-213). All five of these deaths occurred during open label extension phases of trials. The reported causes of death for these five trial subjects were oxycodone overdose, aortic dissection, suicide, unknown/found dead in bed, and intracerebral hemorrhage. Four of the 5 MS trial subjects that died within 30 days of last fampridine exposure were taking 10mg bid Fampridine SR doses at the time of death and one was taking 15mg bid. I summarize details for these five deaths below.



Subject 10001 in trial MS-202 EXT was a 57 year old female and was receiving Fampridine SR 10 mg bid. dose at the time of her death. She had been treated with Fampridine SR for almost 3 years at the time of her death. The patient's partner found her in bed and extremely lethargic. She became unresponsive and was transferred to the hospital where she was pronounced dead. Autopsy revealed that the patient died of accidental oxycodone toxicity. The narrative did not explain why this subject was taking oxycodone.

Subject 21007 in trial MS-F202 EXT was a 58 year old female and was receiving Fampridine SR 15 mg bid prior to death. She had been treated with Fampridine SR for approximately 3 weeks, and then stopped the medication after developing neck pain. Four days later she presented to the ER with complaint of neck pain. She experienced cardiopulmonary failure upon presentation. A CT scan revealed a ruptured aorta. During corrective surgery for the dissection, the patient experienced bleeding and hypoxia and developed several large cerebral infarcts. The patient died ten days after presenting to the ER. The patient had a history of elevated cholesterol and was taking atorvastatin (screening cholesterol 182mg/dL). Her screening blood pressure was 150/96mmHg and her on treatment blood pressure recorded in the CRF was 130/94mm Hg at her 2 study visits. The subject's internist prescribed atenolol for hypertension 5 days before the subject presented to the ER with aortic dissection but there is no information about the subject's blood pressure results that prompted her internist to start treatment.

Subject 220011 in trial MS-203 EXT was a 65 year old male who was receiving Fampridine SR 10 mg bid at the time of his death. The subject committed suicide by self-inflicted shotgun wound of the head, which was the immediate cause of death. The patient's wife had died one week prior to the subject's suicide.

Subject 34011 in trial MS-F203 EXT was a 45 year old female who was receiving Fampridine SR 10 mg bid at the time of her death. She had been treated with Fampridine SR for over 2 years. The patient retired to bed for the evening and was found deceased the next morning. According to the patient's family, she had expressed feeling tired and unwell at times since her MS diagnosis. The family requested there be no autopsy; therefore, the patient's cause of death is not known. The subject had a history of elevated cholesterol. She was taking a number of concomitant medications prior to death including atorvastatin, pinaverium (CCB for irritable bowel), tizanidine, citalopram, oxycontin, gabapentin, baclofen, amitriptyline, rabeprazole, clonazepam, nortriptyline, botulinum toxin, methylprednisone, ondansetron, and mitoxantrone. Adverse events reported during the trial included injuries from falls, MS exacerbation, difficulty sleeping, indigestion, upper respiratory infections fatigue, and feeling unwell.



Subject 35001 in trial MS-F203 EXT was a 51 year old male receiving Fampridine SR 10 mg bid at the time of his death. The subject had been treated with Fampridine SR for over a year when he presented to the emergency room after taking a dose of alprostadil for impotence. At an unknown time, he was unresponsive and his right eye was severely dilated at which time emergency services were called. Upon arrival to the ER, a CT scan was performed showing a “major hemorrhage”. The subject died the following day due to an intracranial hemorrhage caused by a brain aneurysm. The subject had a history of hypertension and was treated with lisinopril. \*Note this death was included in the ISS but not in the Summary of Clinical Safety

The death in the spinal cord injury patient within 30 days of last Fampridine SR exposure involved subject 03B10 in trial SCI-F201EXT. This 57 year old male was receiving Fampridine SR 40 mg bid prior to death. The subject was found dead on the floor in front of his wheelchair on his face and knees with his arms by his sides. His fall from the wheelchair resulted in positional asphyxia (compressed airway) which led to death. Acorda reported that no autopsy was performed.

The death in the MS subject that occurred 5 weeks after last Fampridine SR exposure (Subject 009/004, trial MS-F203) involved a 52 year old male and the cause of death documented by autopsy was ischemic and hypertensive heart disease. This subject had a history of smoking, hypertension and elevated triglycerides. Acorda noted that fampridine plasma concentration data collected at the two-week follow-up visit after completing the trial did not show detectable fampridine levels.

The death in the placebo subject (10119, Trial SCI-F302) was attributed to atherosclerotic disease complicated by morphine intoxication.

No deaths were reported from the fampridine trials excluded from the integrated safety analysis.

In the Safety Update, Acorda reported one addition death from an ongoing MS trial. I summarize that death below.

Subject 03001 from trial MS-F202 EXT was a 68 year old female receiving Fampridine SR 10 mg bid prior to death. The subject had been treated with Fampridine SR for over 4 years. She was found unresponsive by her husband. She was taken to a hospital by ambulance and was pronounced dead. She was diagnosed with an intracranial hemorrhage and no autopsy was performed.

### 7.3.2 Nonfatal Serious Adverse Events

#### MS and SCI Trials Pooled



Acorda reported that 15.1% (228/1510) of Fampridine SR MS and SCI subjects experienced one or more SAEs. The System Organ Class (SOC) groupings with the most SAEs were Nervous system disorders (5.4%, 81/1510), and Infections and Infestations (4.3%, 65/1510). No other SOC grouping of SAEs included >1% of subjects. In the table below, I identify the SAEs reported by at least 3 subjects in MS and SCI trials.

Serious Adverse Events Reported by at Least 3 Fampridine subjects in MS and SCI Trials

SAE Preferred Term	N (%)
Multiple sclerosis relapse	38 (2.5%)
Convulsion	19 (1.3%)
Urinary tract infection	18 (1.2%)
Cellulitis	16 (1.1%)
Pneumonia	13 (0.9%)
Sepsis	7 (0.5%)
Muscle spasticity	5 (0.3%)
Pulmonary embolism	4 (0.3%)
Deep venous thrombosis	4 (0.3%)
Nausea	4 (0.3%)
Asthenia	4 (0.3%)
Fall	4 (0.3%)
Anemia	3 (0.2%)
Atrial fibrillation	3 (0.2%)
Chest pain	3 (0.2%)
Influenza	3 (0.2%)
Urosepsis	3 (0.2%)
Hip fracture	3 (0.2%)
Osteoarthritis	3 (0.2%)
Breast cancer	3 (0.2%)
Complex partial seizures	3 (0.2%)
Encephalopathy	3 (0.2%)
Syncope	3 (0.2%)
Anxiety	3 (0.2%)
Decubitus ulcer	3 (0.2%)

Source: ISS Table 28.1.1a

In addition to the more frequently reported SAEs listed above, 1 subject experienced an SAE of pancytopenia and 1 subject experienced an SAE of pancreatitis. No subjects experienced SAEs of hepatic failure, hepatitis, rash, Stevens Johnson syndrome, Toxic epidermal necrolysis, angioedema, anaphylaxis, rhabdomyolysis, or aplastic anemia.



Below I summarize information for select SAEs of interest in the pooled safety population.

#### Encephalopathy

Three Fampridine SR subjects had SAEs of encephalopathy (subjects ACD-001246, ACD-001235, and ACD-000202). The encephalopathy SAE for subject ACD-001235 occurred approximately 15 days after stopping Fampridine SR (for seizure) and the event was attributed to baclofen. The encephalopathy event for subject ACD-000202 occurred after this subject mistakenly took up to 300mg of baclofen and then suddenly stopped. The event was attributed to baclofen withdrawal and the subject continued to take Fampridine SR in the trial. The event for subject ACD-001246 was not well described in the submitted narrative. This subject, a 55 year old female who received Fampridine SR for approximately 1 month (titrated to 30mg bid) experienced encephalopathy with associated hypokalemia and possible seizure. The patient, who had a history of episodes of dizziness worsening with migraines, had abruptly withdrawn from chronic use of clonazepam and Prozac® on the day of the event and was in a confused state. She experienced “tremulousness” without rhythmic jerking on the way to the emergency room and was treated with lorazepam and potassium replacement, after which she made a full recovery. The patient was discontinued from the trial (her last dose of Fampridine SR was on the day of the event). An EEG found no focal or epileptiform activity.

#### Anemia

Three Fampridine SR subjects had SAEs of anemia. Subject ACD-000085 was a 57 year old female who was hospitalized for anemia after one week of Fampridine SR treatment in this extension trial. In the previous controlled trial where this subject received Fampridine SR, her hemoglobin results were 12.3g/dL (screen), 11.7 g/dL (day 56), and 11.2 g/dL (day 119). This subject had screening tests for the extension trial and her hemoglobin was 7.2 g/dL (hematocrit 26.6%, no indices reported). She enrolled in the extension and 1 week later she had a hemoglobin of 5.9g.dL (hematocrit 20.6%) and was hospitalized and transfused 2 units of packed red blood cells. This event was presumed due to an upper GI bleed. The subject complained of upper GI pain that resolved with Tums, and admitted to frequent NSAID use and had been treated with steroids. She was treated with iron supplements and the event resolved. Subject ACD000162, a 50 year old female with a history of spinal cord injury and ulcerative colitis had an SAE of anemia that was attributed to her ulcerative colitis. Subject ACD-000403 was a 61 year old male with a spinal cord injury who complained of anorexia and nausea during treatment with Fampridine SR. The investigator noted that the subject's hemoglobin decreased from 14.1 g/dL at baseline to 12.7g/dL (hematocrit decreased from 45.8% to 36.5%). The subject's lab results included a normal haptoglobin and bilirubin and normal reticulocyte count. The subject had a normal ferritin, normal total iron binding



capacity, a decreased serum iron result and a decreased iron saturation, which are consistent with anemia of chronic disease. He denied vomiting, hematemesis, and bright red blood per rectum. The subject discontinued from the trial. The events resolved with omeprazole treatment.

#### Pancytopenia

Subject ACD-000628 had an SAE of pancytopenia. This subject was a 45 year old male with a spinal cord injury (T11-12). His baseline WBC count was 7.48 k/mm<sup>3</sup>, hemoglobin was 14.4 g/dL and platelet count was 202 k/mm<sup>3</sup>. After 2 months of Fampridine SR, the subject was seen for his last visit (trial closed by sponsor) and was found to have a WBC count of 3.45 k/mm<sup>3</sup> (normal 3.5-10.5k/mm<sup>3</sup>) and a hemoglobin of 12.8g/dL (nl 13-17.5g/dL) and a platelet count of 193 k/mm<sup>3</sup> (nl 140-370 k/mm<sup>3</sup>). The subject reported experiencing a GI illness with diarrhea just prior to these lab results. Fampridine SR was stopped and the subject was reported as having pancytopenia. Repeat labs 7 days later included a WBC count of 6.18 k/mm<sup>3</sup>, a hemoglobin of 14g/dL and a platelet count of 245k/mm<sup>3</sup>.

#### Pancreatitis

Subject ACD-000451 from trial 0296-003US was a 47 year old male with MS who was taking no other medications at the time he was diagnosed with pancreatitis. This subject presented with acute abdominal pain and was diagnosed with acute pancreatitis secondary to cholelithiasis. He underwent a laproscopic cholecystectomy. Acorda reported that the event resolved and that the subject discontinued from the trial.

#### SAEs in MS Subjects, Controlled and Uncontrolled Trials

In Table 11 (Summary of Clinical Safety, pp. 38-9) Acorda noted that 19.3% (177/917) of Fampridine SR MS trial subjects experienced one or more SAEs. The SAEs experienced by more than 3 MS subjects were multiple sclerosis relapse (4.1%, n=38), convulsion (1.4%, n=13), urinary tract infection (1.4%, n=13), cellulitis (1.2%, n=11), pneumonia (1.1%, n=10), and sepsis (0.8%, n=7). Three MS subjects experienced SAEs of complex partial seizures (0.3%).

#### SAEs in the Adequate and Well Controlled MS trials

Table 10 (Summary of Clinical Safety, p.35) summarized SAEs by treatment for the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204). SAEs were 3 times more frequent among Fampridine SR subjects (6.5%, 33/507) compared to placebo subjects (2.1%, 5/238) in these trials and the risk for all SAEs among Fampridine SR subjects appeared dose related. Multiple sclerosis relapse was the only SAE that occurred in more than 2 Fampridine SR subjects (fampridine n=7, 1.4%; placebo n=0).



#### SAEs in SCI Subjects, Controlled and Uncontrolled Trials

In SCI trials, 8.6% (51/593) of subjects experienced one or more SAEs. The SAEs reported by more than 3 SCI subjects were convulsion (1%, n=6), cellulitis (0.8%, n=5), and urinary tract infection (0.8%, n=5) (ISS, Table 87, pp.205).

#### SAEs in the Non-patient population (Healthy volunteers, renal deficiency)

One patient (0.3%, 1/382) from the non-patient population reported an SAE (visual hallucinations) (ISS, p.205).

#### SAEs in Non-pooled Trials

Two subjects from trials excluded from the integrated safety analysis experienced SAEs. Following 5 doses of 4-aminopyridine (12.5 mg q 6 hours), a female MS patient from a clinical pharmacology trial (1091-001US) experienced what was described as a tonic-clonic seizure lasting 30 seconds with loss of consciousness lasting 1 minute. Plasma levels in the hospital at an unknown time interval following the event were 104ng/mL. The trial report provided no additional details about this event. In a Guillain-Barre syndrome trial, a 77 year old male subject experienced 2 days of tachycardia (not further specified) after approximately 3 weeks of 4- aminopyridine treatment. The subject was hospitalized and the tachycardia resolved without treatment. The subject continued treatment with 4- aminopyridine throughout the event and completed the trial.

#### SAEs in the Safety Update

Acorda reported that 17 Fampridine SR patients experienced 28 SAEs during the period covered by the Safety Update. The newly reported SAEs were Multiple sclerosis relapse (n=3), syncope (n=2), intracranial hemorrhage (n=1), pyrexia (n=1), dehydration (n=1), renal mass (n=1), urinary tract infection (n=1), pulmonary embolism (n=1), fall (n=1), appendicitis perforated (n=1), post-operative wound infection (n=1), adenocarcinoma (n=1), depressed level of consciousness (n=1), septic shock (n=1), Escherichia infection (n=1), pancreatitis (n=1), cholelithiasis (n=1), peripheral vascular disorder (n=1), chest discomfort (n=1), myocardial infarction (n=1), abdominal pain upper (n=1), nausea (n=1), vomiting (n=1), bile duct stenosis (n=1), and suicide attempt (n=1). No new seizure SAEs were reported in the Safety Update.

### 7.3.3 Dropouts and/or Discontinuations

In the Fampridine SR MS clinical trial population, AE and withdrawal of consent were the most common reasons for discontinuing from a Fampridine SR clinical trial. The following table summarizes the reasons for discontinuation from MS Fampridine SR trials in the NDA database.



Reasons for Discontinuation from MS Fampridine SR trials in the NDA database.

Patient Accounting	Total Fampridine MS	Adequate and Well Controlled MS Trials		Open Label MS trials > 1 week
		Fampridine	Placebo	
Total exposed	1029	507	238	693
Completed	296 (29%)	475 (94%)	230 (97%)	24 (3%)
Ongoing	480 (47%)	0	0	484 (70%)
Discontinued	253 (25%)	32 (6%)	8 (3%)	185 (27%)
AE*	112	21	5	61
Non compliance	9	3	1	5
Withdrew consent	77	5	0	70
Lost to f/u	9	1	2	6
Other	49	2	0	44

\*Includes both TEAEs and non TEAEs leading to discontinuation (Acorda submission dated 8/14/09).

From ISS Tables 17, 17.2.1, and 17.2.2

TEAEs Leading to Discontinuation, MS and SCI Trials, Pooled

ISS table 27.1.1 reported that 221 (14.6%, 221/1510) Fampridine SR MS and SCI subjects experienced one or more TEAEs leading to discontinuation. The System Organ Class (SOC) groupings with the most TEAEs leading to discontinuation were Nervous system disorders (8.5%, 128/1510), Psychiatric disorders (4.2%, 63/1510), General disorders and administration site conditions (3.4%, 52/1510), Gastrointestinal disorders (2.5%, 38/1510), and Musculoskeletal and connective tissue disorders (1.9%, 28/1510). No other SOC grouping of TEAEs leading to discontinuation included >1% of subjects. In the table below, I identify those specific TEAEs leading to discontinuation that were reported for at least 3 subjects in MS and SCI trials.

Treatment Emergent Adverse Events Leading to Discontinuation of at Least 3 Fampridine SR subjects in MS and SCI Trials

AE Preferred Term	N (%)	AE Preferred Term	N (%)
Dizziness	38 (2.5%)	Vomiting	4 (0.3%)
Insomnia	22 (1.5%)	Chest discomfort	4 (0.3%)
Convulsion	19 (1.3%)	Muscular weakness	4 (0.3%)
Asthenia	19 (1.3%)	Burning sensation	4 (0.3%)
Nausea	17 (1.1%)	Hypoaesthesia	4 (0.3%)
Anxiety	17 (1.1%)	Memory impairment	4 (0.3%)
Paresthesia	15 (1.0%)	Multiple sclerosis relapse	4 (0.3%)
Headache	14 (0.9%)	Abnormal dreams	4 (0.3%)
Muscle spasticity	12 (0.8%)	Disorientation	4 (0.3%)
Tremor	12 (0.8%)	Dyspnea	4 (0.3%)
Muscle spasms	10 (0.7%)	Anorexia	3 (0.2%)



Difficulty in walking	9 (0.6%)	Back pain	3 (0.2%)
Fatigue	9 (0.6%)	Hypertonia	3 (0.2%)
Confusional state	9 (0.6%)	Vertigo	3 (0.2%)
Vision blurred	7 (0.5%)	Abdominal pain upper	3 (0.2%)
Urinary tract infection	6 (0.4%)	Irritability	3 (0.2%)
Constipation	6 (0.4%)	Pneumonia	3 (0.2%)
Pain in extremity	6 (0.4%)	Neuralgia	3 (0.2%)
Gait disturbance	5 (0.3%)	Sensory disturbance	3 (0.2%)
Disturbance in attention	5 (0.3%)	Urinary incontinence	3 (0.2%)
Trigeminal Neuralgia	5 (0.3%)	Depression	3 (0.2%)
Hyperhydrosis	5 (0.3%)		

Source: ISS Table 27.1.1

In addition to the TEAEs leading to discontinuation above, the following TEAEs led to discontinuation of one subject each: pancreatitis (described above with SAEs), hypersensitivity, rash macular, skin exfoliation, and toxic skin eruption. No subjects discontinued for hepatic failure, hepatitis, Stevens Johnson syndrome, Toxic epidermal necrolysis, angioedema, anaphylaxis, rhabdomyolysis, pancytopenia, or aplastic anemia.

Below I summarize information for select TEAEs leading to discontinuation for the pooled safety population.

#### Macular Rash

Subject MS-F202 EXT 19012, a 48 year old male discontinued from the trial for an AE of macular rash. After approximately 13 months of treatment with Fampridine SR in study MS-F202EXT, this subject developed a macular rash on his forehead. The narrative stated that approximately 8 months later he was treated with topical hydrocortisone. Apparently the rash persisted despite treatment for 3 months and he discontinued from the trial. The investigator rated the rash as mild in intensity.

#### Hypersensitivity

Subject SCI-F301 01702, a 33 year old male, discontinued from the trial for an AE of hypersensitivity. The narrative provided little useful information about this event, noting only that the subject experienced rib pain and "increased hypersensitivity" that was rated as moderate by the investigator. The event was reported as resolved on a follow up visit.

#### Skin exfoliation, Toxic skin eruption

Subject SCI-F301 03415, a 69 year old male, discontinued from the trial for an AE of skin exfoliation and toxic skin eruption. This subject started treated with Fampridine SR on 6/30/03. Fampridine was held for one dose on 7/17/03 for



elective urinary bladder surgery. On 8/25/03, the subject developed “toxic erythema” of the hands and trunk. On 8/27/03 he developed peeling skin on the hands. Fampridine SR was stopped and the subject was treated with corticosteroids. The event was resolved on 9/1/03.

#### TEAEs Leading to Discontinuation of MS Trial Subjects, Controlled and Uncontrolled Trials

ISS Table 27.2.1 listed TEAEs leading to discontinuation of Fampridine SR MS subjects from controlled and uncontrolled trials in the safety database. Eleven percent (102/917) of MS subjects had one or more TEAEs leading to discontinuation. The TEAEs leading to discontinuation of more than 3 MS subjects were convulsion (1.4%, n=13), balance disorder (0.9%, n=8), dizziness (0.8%, n=7), asthenia (0.7%, n=6), paresthesia (0.5%, n=5), trigeminal neuralgia (0.5%, n=5), headache (0.5%, n=5), confusional state (0.5%, n=5), multiple sclerosis relapse (0.4%, n=4), fatigue (0.4%, n=4), nausea (0.4%, n=4), and anxiety (0.4%, n=4). Three Fampridine SR MS subjects discontinued for TEAEs of complex partial seizures (0.3%).

#### TEAEs Leading to Discontinuation from Adequate and Well Controlled MS Trials

ISS Table 27.2.2 summarized AEs leading to discontinuation by treatment for the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204). In these trials, 3.4% (17/507) of Fampridine SR subjects had one or more TEAEs leading to discontinuation compared to 2.1% (5/238) of placebo subjects. The TEAEs leading to discontinuation of at least 2 Fampridine SR subjects and that led to discontinuation more frequently compared to placebo were headache (Fampridine SR 0.8%, 4/507; placebo 0/238), balance disorder (Fampridine SR 0.6%, 3/507; placebo 0/238), dizziness (Fampridine SR 0.6%, 3/507; placebo 0/238), and confusional state (Fampridine SR 0.4%, 2/507; placebo 0/238). One Fampridine SR (0.2%) and no placebo subjects discontinued for convulsion and no subjects discontinued for complex partial seizures.

#### TEAEs Leading to Discontinuation of SCI Subjects, Controlled and Uncontrolled Trials

In SCI trials, 20.1% (119/593) of Fampridine SR subjects had one or more TEAEs that led to discontinuation. The TEAEs leading to discontinuation of more than 3 SCI subjects were dizziness (5.1%, n=32), insomnia (3.4%, n=20), nausea (2.2%, n=13), asthenia (2.2%, n=13), anxiety (2.2%, n=13), muscle spasticity (1.9%, n=11), paresthesia (1.7%, n=10), tremor (1.7%, n=10), muscle spasms (1.5%, n=9), headache (1.5%, n=9), difficult walking (1.2%, n=7), balance disorder (1.2%, n=7), vision blurred (1%, n=6), fatigue (0.8%, n=5), urinary tract infection (0.8%, n=5), constipation (0.8%, n=5), vomiting (0.7%, n=4), convulsion (1%, n=6), pain in extremity (0.8%, n=5), disturbance in attention (0.8%, n=5), hyperhidrosis (0.8%, n=5), burning sensation (0.7%, n=4), muscular weakness (0.7%, n=4), memory impairment (0.7%, n=4), abnormal dreams (0.7%, n=4), confusional state (0.7%, n=4) (ISS, Table 27.3.1).



TEAEs Leading to Discontinuation for the Non-patient Population (Healthy volunteers, renal deficiency)

Four Fampridine SR subjects (1%, 4/382) had one or more TEAEs that led to discontinuation from the non-patient population. The TEAEs that led to discontinuation of at least 3 subjects were dizziness (0.8%, 3/382), and tremor (0.8%, 3/382) (ISS Table 27.4).

AEs Leading to Discontinuation in the Non-pooled Trials

Four subjects experienced AEs leading to discontinuation from trials excluded from the pooled safety analysis. A Guillain-Barre syndrome patient discontinued from trial CGBS Phase 2A for a “chronic demyelinating polyneuropathy”. Three Guillain-Barre syndrome patients discontinued from trial CGBS Phase 2B for tremor, cramping, weakness, dizziness, ataxia, and diabetic hypoglycemia; weakness, tremors, and postural hypotension; and dizziness

TEAEs leading to Discontinuation in the Safety Update

Acorda identified 4 Fampridine SR subjects who discontinued from ongoing MS open-label extension trials for TEAEs during the period covered by the Safety Update. The events leading to discontinuation were myocardial infarction, depressed level of consciousness, intracranial hemorrhage (also reported as a death), and trigeminal neuralgia.

#### 7.3.4 Significant Adverse Events

##### Seizures

Acorda explained that fampridine causes seizures, that this finding is consistent with the known pharmacology and toxicology of fampridine, and that the risk of seizure increases with fampridine  $C_{max}$  (Summary of Clinical Safety, p.39). One reason that Acorda gave for developing the Fampridine SR formulation was to reduce peak plasma levels associated with a given dose, presumably to reduce seizure risk. Acorda considered the seizure risk when designing Fampridine SR MS clinical trials. Potential study subjects were excluded if they reported a history of seizure, and MS study subjects with epileptiform activity on a screening EEG were excluded from clinical trials.

Acorda's presentations of seizure risk are based on the limited duration controlled trial data (9-15 weeks) and the longer duration, but uncontrolled, extension trial data. Acorda focuses their presentation on seizure risk in MS subjects exposed to the recommended Fampridine SR dose, 10mg bid, and also considers seizure risk in MS subjects exposed to higher Fampridine SR doses, MS subjects exposed to other fampridine formulations, and in SCI subjects (most of the SCI subjects were exposed to doses >10mg bid).

##### Seizure Risk in the General Population



Acorda cited an estimate of seizure prevalence in the general population of 0.5-1.0%. In addition, they cited annual epilepsy incidence estimates in the general population of 50/100,000 (Summary of Clinical Safety, p.41).

#### Seizure risk in MS patients

Despite evidence of an association between MS and seizure, precise, consistent quantitative risk estimates of this relationship are not available. Most of the available information about seizure risk among MS patients consists of prevalence estimates derived from cohorts. In a review of over 30 publications, Koch et al reported a range of seizure prevalence estimates in MS patients between 2-4%. Many of these publications did not distinguish between seizures that predated MS and those that arose after symptoms or diagnosis of MS.

Four publications reported epilepsy or seizure incidence or included incident cases of seizure and person time follow up data. Olafsson et al reported their experience in Iceland where 3 patients developed epilepsy (recurrent, 2 or more, unprovoked seizures >24 hours apart) after diagnosis of MS and one after developing symptoms of MS (but prior to MS diagnosis) during 2,771 person years of observation. These data yield an epilepsy incidence in MS patients of 140/100,000 PY (3-fold higher than their general population estimate). Nicoletti et al reported their experience from Catania, Italy where the age adjusted mean annual incidence of epilepsy (recurrent, 2 or more, unprovoked seizures >24 hours apart) among MS patients was 148/100,000 (4 cases among 170 MS patients). Eriksson et al reported their experience in Sweden where they found a yearly incidence of first seizure without identified cause among a cohort of 225 patients with probable or possible MS of 349/100,000. The authors also found that seizure incidence was increased among patients with progressive MS compared to those with relapsing remitting MS. Nyquist et al reported their experience in Olmstead County, MN where the incidence of seizure without identified cause after diagnosis of MS was 61/100,000 PY. The incidence of seizure without identified cause after development of symptoms of MS but prior to diagnosis was 80/100,000 PY. Interestingly, unprovoked seizure incidence in MS patients in this study was not different than the study's general population background unprovoked seizure incidence (61/100,000PY).

#### Preclinical data

Acorda explained that fampridine is a broad spectrum potassium channel blocker in the millimolar range of concentration and the plasma concentration with clinical use is <1 micromolar. At the plasma concentration achieved with clinical use, Acorda claims that fampridine is selective only for sensitive channels (i.e., in injured and demyelinated nerve fibers) (Summary of Clinical Safety, p.43).

#### In-vitro studies

Acorda reported that in-vitro brain slice experiments showed amygdala and hippocampus epileptiform discharges when perfused with solutions of fampridine at concentrations of 5 to 500 µM.



#### Animal studies

Acorda noted that a 2-week repeated dose study in rats found seizures at a dose of 10mg/kg/day given as a single oral dose but not at 3mg/kg/day or less. Acorda also reported that a fampridine dose of 12mg/kg/day was well tolerated when divided into 4 doses throughout the day (supporting seizure risk is related to Cmax rather than AUC).

In dogs exposed to fampridine, Acorda reported that a 2-week oral toxicity study resulted in seizures and death in 3 of 4 dogs assigned to a single 3mg/kg dose. In a 1-year repeated dose toxicity study in beagles, seizures were observed in those given 1.5 or 3mg/kg/day in 2 divided doses (mean plasma concentrations 117-287 and 130-399 ng/mL) but not in those given 0.75 mg/kg/day (plasma conc. 64.7-160 ng/mL).

#### Human data

##### MS Clinical Pharmacology Trials

Acorda reported that no seizures were observed in MS subjects in clinical pharmacology trials.

##### MS Clinical Trials

As previously noted, Acorda considered seizures occurring during clinical trials as events of special interest. In order to minimize the number of MS study subjects at increased risk of seizures from being exposed to Fampridine SR, Acorda excluded patients with a history of seizure and screened patients with EEGs prior to enrollment in MS randomized controlled trials. Furthermore, after completing a randomized controlled trial and prior to entering an open label extension, all MS subjects were again screened with EEGs. Acorda reported that subjects were excluded if they had “evidence of epileptiform activity” on screening EEG. Acorda did not provide in their protocols specific EEG criteria defining “evidence of epileptiform activity” and admitted that individual study sites excluded patients for a variety of EEG findings. Acorda did not analyze the specific EEG criteria used by study sites to exclude subjects (Response to reviewer questions dated 5/20/09).

In response to reviewer inquiry, Acorda provided two tables summarizing the numbers of study subjects excluded from Fampridine SR MS clinical trials for EEG findings. The following table identifies the number of subjects excluded from randomized controlled trials.

##### Number of Screened Subjects Excluded for EEG Abnormalities, MS Randomized Controlled Trials

	Study				
	MS-F201	MS-F202	MS-F203	MS-F204	Total
Number Screened	42	271	401	362	1076



Number (%) excluded	1 (2.4%)	11 (4.1%)	10 (2.5%)	15 (4.1%)	37 (3.4%)
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Source Acorda submission dated 5/20/09

The following table summarizes the number of subjects excluded from open label extension trials, stratified by treatment in the preceding randomized controlled trial.

Number of Screened Subjects Excluded for EEG Abnormalities, MS Extension Trials Overall and Stratified by Treatment in Preceding RCT

	Study Pair			Total
	MS-F202 MS-F202 EXT	MS-F203 MS-F203 EXT	MS-F204 MS-F204 EXT	
Number Screened	153	271	219	885
Number (%) excluded	4 (2.6%)	2 (0.7%)	5 (2.3%)	11 (1.2%)
Number (%) excluded that received fampridine in RCT	3/122 (2.5%)	0/202	1/108 (0.9%)*	5/432 (1.2%)
Number (%) excluded that received placebo in RCT	1/31 (3.2%)	2/69 (2.9%)	3/111 (2.7%)	6/211 (2.8%)

\*An additional patient from this study initially had an abnormal screening EEG, was subsequently re-screened and had a normal EEG and then was allowed to continue in the extension study.

None of the 12 patients from MS-F201 screened for the MS-F202EXT study were excluded for EEG screen abnormalities.

#### Randomized, Placebo-Controlled MS trials

Acorda pooled data from the following RCTs in MS patients: MS-F201, MS-F202, MS-F203, and MS-F204 (note this is different from prior analyses that presented data for adequate and well controlled trials and that did not include MS-F201). In these 4 trials, 532 subjects were randomized to fampridine and 249 to placebo. Five seizure AEs (0.9%) were observed in fampridine subjects and 1 (0.4%) in a placebo subject.

When Acorda presented risks by dose for these trials they included all subjects exposed to each dose so that subjects titrated to higher doses appear in more than one dose category. These trials had the following dose groups 10mg bid, 15mg bid, 20mg bid, 25mg bid, 30mg bid, 35mg bid, and 40mg bid. For the 10 mg bid dose group, Acorda included all subjects (N=532) in the denominator since all subjects were exposed to this dose (subjects randomized to higher doses were titrated through this dose on the way to their target dose, even though they received this dose briefly). The risk by dose that I present below use the number randomized to the dose as the denominator.



Given that trial MS-F201 was so differently designed than the other three randomized placebo controlled trials (MS-F201 included fewer subjects, and titrated subjects to higher fampridine doses) it is preferable to consider the results for MS-F201 separately. In MS-F201, 25 subjects were randomized to fampridine and 11 to placebo. The fampridine subjects started at 10mg bid and the fampridine dose was increased in weekly intervals to a target dose of 40mg bid. In this study, no placebo and 2 fampridine (8%) subjects experienced seizures. The fampridine subjects were receiving 30mg bid and 35 mg bid doses at the time of the seizures. I provide clinical details from the submitted information about these seizures in the following paragraphs.

#### 30mg bid

Subject #03002 from study MS-F201, a 55 woman with primary progressive MS (EDSS=3.5), experienced an episode of encephalopathy and a possible tonic seizure, which was observed by paramedics. The narrative reported that the subject experienced “tremulousness” without rhythmic jerking. An EEG found no focal or epileptiform activity. Three days before the event, at Study Visit 5, after a week of 25 mg b.i.d. treatment, her plasma fampridine concentration was 117.0 ng/mL. This case was complicated by the fact that the patient suddenly stopped taking clonazepam and began a new treatment with sumatriptan for migraine just prior to the event. The patient was experiencing hypokalemia and refractory migraine at the time. Other concomitant medications at the time of the event included Prozac and Excedrin.

#### 35mg bid

Subject #02006 from study MS-F201, a 61 year old woman with secondary progressive MS (EDSS=6.5), experienced a period of confusion, apnea, and possible seizure at a dose of 35 mg b.i.d. and was hospitalized for two days. In previous weeks of treatment, the patient’s plasma fampridine concentrations had been 44.4 ng/mL at 15 mg b.i.d., 61.6 ng/mL at 20 mg b.i.d., and 99.6 ng/mL at 25 mg b.i.d. At visit 6, three days prior to the event, and following a week of treatment at the 30 mg b.i.d. dose, the plasma concentration was below the limit of quantitation (<2ng/mL). This same patient experienced an episode of encephalopathy and possible seizure that was considered secondary to baclofen treatment 17 days after discontinuation of Fampridine SR. Other concomitant medications included estrogen, progesterone, amitriptyline, fosamax, and Fleets suppository.

The 3 adequate and well controlled trials were similarly designed, included treatment durations of 9-15 weeks, and exposed most Fampridine SR subjects to doses of 10 mg bid (Study MS-F202 exposed 50 subjects to 15mg bid and 57 subjects to 20mg bid).

The following table summarizes the seizure risk data for the 3 adequate and well controlled MS trials MS-F202, MS-F203, and MS-F204.



Seizure Risk Data for MS Trials MS-F202, MS-F203, and MS-F204

Study	Placebo	Total Fampridine	Fampridine 10mg BID	Fampridine 15mg BID	Fampridine 20mg BID
MS-F202	(0/47)	1.3% (2/159)	(0/52)	(0/50)	3.5% (2/57)
MS-F203	(0/72)	0.4% (1/228)	0.4% (1/228)	-	-
MS-F204	0.8% (1/119)	(0/120)	(0/120)	-	-
Total	0.4% (1/238)	0.6% (3/507)	0.3% (1/400)	(0/50)	3.5% (2/57)
	1.6/100 PY (1/62PY)	2.1/100 PY (3/142PY)	0.9/100 PY (1/108PY)	- (0/16 PY)	11.8/100 PY (2/17PY)

These pooled data demonstrate an increased seizure risk for all Fampridine SR subjects compared to placebo subjects. When risk is stratified by Fampridine SR dose, there is evidence of an increased seizure risk at 20mg bid, based on a small number of events and limited exposure.

I provide clinical details from the submitted information describing the seizures. Division neurologists Drs. Dunn and Illoh reviewed all available information about these events. They agreed that the events reported for the Fampridine SR subjects were likely seizures. They disagreed about whether the event reported for the placebo subject represented a seizure.

10mg bid

Subject #14003 from study MS-F203 was a 58 year old woman with secondary progressive MS (EDSS=6) assigned to 10 mg bid Fampridine SR. After 61 days on double blind treatment she experienced a severe case of sepsis, secondary to community acquired pneumonia. In the emergency room she experienced an apparent focal seizure, involving shaking of an extremity. It is not known when the patient may have taken the last dose of Fampridine SR prior to this event. Concomitant medications at the time of the event included oxybutinin, Prozac, oxycodone, calcium, Fosamax, Avonex, Tylenol, and Bactrim DS.

20mg bid

Subject #04006 from study MS-F202, was a 58 year old man with primary progressive MS (EDSS=6). He had been taking Fampridine SR for 33 days when he experienced a generalized seizure while riding on a bus, approximately 7.5 hours after taking his last dose of 20 mg Fampridine SR. He was taken to the emergency room and observed to have tongue lacerations. A CT scan was unremarkable. He was treated with methylprednisolone, fosphenytoin, and Dilantin and was discharged the following day. Five days earlier, at Study Visit 4, his plasma concentration of fampridine at approximately 6 hours post dose had been 35.5 ng/mL. Concomitant medications at the time of the event were baclofen and Viagra.



Subject #07019 from study MS-F202, a 47 year old woman with secondary progressive MS (EDSS=4), experienced a partial complex seizure after taking a double dose of 20 mg Fampridine SR (total 40 mg) to compensate for a previously missed dose. She was found by her father who reported that she was unresponsive with automatisms, and later was confused, tremulous, and diaphoretic. She did not recall the event and did not seek medical treatment. On the day of the overdose (Study Visit 7, 49 days on double blind treatment) the patient's plasma fampridine concentration at approximately 4.5 hours post dose was 79.0 ng/mL and she experienced a partial complex seizure of moderate severity 4 hours later. With reassurances of future compliance, the patient was allowed to continue in the trial but, ten days later, she again took two doses within a short period of time. She became confused for about an hour and was discontinued from the study at that point. An EEG performed 1 week later showed "bilaterally independent mild temporal slowing with some rare sharp waves, more prominent on the left than on the right, indicative of a tendency for partial seizures." Concomitant medications included Betaseron and Lexapro.

#### Placebo

Subject #028/408 from study MS-F204, a 65 year old female with secondary progressive MS, hypercholesterolemia, hypertriglyceridemia, osteopenia, osteoarthritis, and breast cancer, experienced an AE coded as complex partial seizures. After approximately 58 days on placebo the patient "watched an entire movie, and upon completion was not able to recall the title or details of the movie." The investigator felt that the patient possibly had a complex partial seizure. On the subsequent 2 days, the patient lost her balance and fell, with no significant injuries noted. Other symptoms noted around this time were increased paresthesia in the hands, increased fatigue, difficulty with short term memory, and worsening gait imbalance. An EEG performed 5 days after the event showed no evidence of epileptiform activity but did show mild intermittent bitemporal slowing more prominent on the left side. Her screening EEG showed mild intermittent left temporal slowing. Six days after the event the patient reported that her paresthesias, balance, and memory were improving. She had no further amnesic episodes. On follow up, 17 days after the event, the patient reported increased leg weakness, leg paresthesias, and increased paresthesias in her hands and was diagnosed with an MS exacerbation and treated with IV methylprednisolone.

#### Open label MS trials

In Table 13, Acorda reported seizure risk observed during MS open label trials. I summarize data from that table below.

Seizure Incidence and Dose at Time of Occurrence in Open-Label Extension Trials of Fampridine SR in MS through July 31, 2008



	MS- F202EXT >10mgbid*	MS- F202EXT 10mgbid	MS- F203EXT 10mgbid	MS- F204EXT 10mgbid	Total 10mgbid
Subjects exposed	175	177	269	214	660
Patient years	115	422	513	125	1060
Subjects with seizure AE	2	1	4 <sup>1,2</sup>	0	5
%	1.14%	0.56%	1.5%	0	0.76%
Incidence per 100 PY (95% CI)	1.7 (0.21- 6.28)	0.24 (0.01- 1.32)	0.78 (0.21- 2.00)	0	0.47 (0.15- 1.10)

\*Using the exposure datasets, I determined that the person time exposure in 202EXT at >10mg bid is almost entirely to 15mg bid, with <2PY exposure to 20mg bid.

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

2 One additional patient (#23015) experience seizure at 22 days following discontinuation from Study MS-F203EXT due to an MS relapse. This patient was not included here as the event is not likely associated with fampridine, 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.

bid = Twice daily; CI = Confidence interval; EXT = Extension; MS = Multiple sclerosis; SR = Sustained release.

Two of the open label trial subjects included above received placebo in their preceding RCTs (2/205) and the remainder received fampridine in the preceding RCT.

I summarize the seizure events in the following paragraphs.

#### 10mg bid

Subject #25016, a 60 year old female who received Fampridine SR in a preceding controlled trial, started open label Fampridine SR in study MS-F203EXT on 4/25/06. On (b) (6), she started tolterodine (8mg then 12 mg 12 hours later). Other concomitant medications were Diovan, Aricept, and Estradiol. On (b) (6), the subjects husband observed her, body rigid and convulsing, for approximately 3 minutes. The event occurred approximately 9 hours after her last dose of Fampridine SR. She was observed in an emergency department and Fampridine SR and tolterodine were stopped. The subject restarted tolterodine in (b) (6) and on (b) (6) experienced a grand mal seizure lasting approximately 10 seconds. Concomitant medications included Aricept and Diovan.

Subject #16001, a 46 year old female who received Fampridine SR in a preceding controlled trial, started open label Fampridine SR 10mg bid on 3/27/06. On (b) (6) the subject's daughter found her in the bathroom shaking, and the subject had vomited. EMTs witnessed the subject's seizure and administered valium 5mg iv which had no effect. In the ED, the subject was



observed to be unresponsive with eyes deviated to the left. The patient was able to move all 4 extremities, but was not able to follow commands. The subject had an initial glucose of 147 (no units) and SBP was in the 80's (increased to 114 with iv fluids). The subject was intubated and administered propofol. A head CT showed normal ventricles, no evidence of intra or extra axial mass, and no sign of an acute stroke or hemorrhage. She was started on Dilantin and fine tremors were noted. Propofol was increased. Seizure activity continued and additional Dilantin and Ativan were administered. The patient was given antibiotics and underwent an LP which showed clear, colorless CSF, glucose 74, protein 52, WBC count 2/mm<sup>3</sup> and 0 RBCs. Urine toxicology was negative for PCP, cocaine, amphetamines, cannabinoids, opiates, barbiturates, and methadone and positive for benzodiazepines. The subject was transferred to another hospital and was observed to be seizing despite continued propofol and Ativan. The patient was treated with Phenobarbital, the propofol infusion was increased and the Ativan infusion was continued. A repeat CT was negative and an EEG showed a burst suppression pattern that was invariant throughout the tracing. No evidence of electrographic status was seen. The bursts were not associated with visible musculoskeletal accompaniment (half of the EEG was performed with video). The subject was admitted to the ICU and her course was complicated by development of a left pneumothorax requiring chest tube placement. Repeat EEG documented "...some degree of healthy variability. In the initial part of the recording EEG features of a moderate encephalopathic 'process age encountered'. However, today the latter half of the recording architectural features of normal non-REM sleep were emerging which would appear to designate a moderate but potentially reversible encephalopathic process due to the preservation and emergence of such normal sleep architecture. Evidence of ongoing status epilepticus or even a seizure tendency is not noted in this recording". The patient required additional chest tubes and subsequently underwent a tracheostomy. The subject's mental status improved and she was transferred to a general care floor. A PEG was placed (aspiration shown on swallowing studies). The subject was discharged on (b) (6) with tracheostomy and PEG tube. Concomitant medications included Betaseron and baclofen.

Subject #35002, a 64 year old male who received Fampridine SR in a preceding controlled trial, started open label Fampridine SR 10mg bid on 4/26/06. On [REDACTED] the subject reported visual disturbances and noted that he was leaning to one side. He called for his wife and when she arrived she witnessed him shaking and unconscious. He was taken to an ER and was told that he had a seizure. He had been unconscious for approximately 45 minutes. The report for an EEG performed on [REDACTED] noted "...excessive fast activity, which may be related to medication effect; however, no suspect medications were listed for this patient. Further, the appearance of right temporal rhythmic theta and right temporal sharp waves are suspicious for a right temporal epileptogenic brain abnormality; however, because these waveforms occasionally have an appearance of



wickets, which is a normal variant, we recommend repeating a study with sleep deprivation.” A sleep deprived EEG was reportedly normal. The subject discontinued from the trial. Concomitant medications included Maxide, Lisinopril, and Valium.

Subject #21009, a 62 year old female who received Fampridine SR in a preceding controlled trial started open label Fampridine SR 10mg bid on 1/24/06. On (b) (6), while at a rehabilitation facility, recovering from a fall, a physician witnessed the subject experience a 90 second episode of generalized rigidity and rhythmic shaking. She was unresponsive during and for 10-15 minutes following the episode. She was given iv Dilantin and transferred to an acute care hospital. She complained of blurry vision, tinnitus, and garbled speech. A brain MRI showed no acute intracranial abnormalities or evidence of acute intracranial hemorrhage or ischemia. The subject discontinued from the trial. The subject continued Dilantin until 5/14/08. Concomitant medications included tizanidine, baclofen, buspirone, interferon beta 1b, oxazepam, and propranolol.

Subject #22031, a 48 year old female who received Fampridine SR in a preceding controlled trial, started treatment with open label Fampridine SR 10mg bid on 7/6/04. She was titrated to 15mg bid on 7/14/04 and remained on that dose until 3/30/05 when she was down titrated to 10 mg bid. On (b) (6) she experienced an episode where her eyes rolled back, her arm stiffened, and she could not swallow or spit out saliva from her mouth. This event was diagnosed as a partial complex seizure. She did not experience tongue biting or incontinence. She was taken to an ER and an EEG and MRI were reportedly unremarkable. Subsequently, she was seen by a neurologist and started on Keppra. She also experienced an episode of “shaking of the trunk”. The subject did not report these events to the study site until 8/16/07, at which time she was discontinued from the trial. The narrative noted that the subject reported 2 episodes of undiagnosed “convulsions” during sleep that occurred 1 and 2 years prior to this event. This subject was taking no other medications at the time of the event.

15mg bid

Subject #22024, a 59 year old female who received placebo in a preceding controlled trial, started open label Fampridine SR 10mg bid on 6/8/04. She was titrated up to a dose of 15mg bid on 6/14/04. On (b) (6) she experienced a seizure (not described) and was taken to an ER and admitted to a hospital. Her initial EEG showed mild, diffuse, encephalopathy with epileptic activity in the left hemisphere suggesting the possibility of a recent CVA. Repeat EEGs showed decline in epileptic potentials. MRI showed stable MS lesions and 2 foci of enhancement with volume loss in the left hemisphere. A repeat EEG approximately 6 weeks after the event showed no epileptiform abnormalities. The subject was initially treated with Dilantin and then switched to Keppra. She was discontinued from the trial and following discharge from the hospital was sent to



a rehabilitation facility. Concomitant medications were Reminyl, azathioprine, and baclofen.

Subject #22039, a 63 year old male who received placebo in a preceding controlled trial, started open label Fampridine SR 10mg bid on 8/5/04. He was titrated up to a dose of 15mg bid on 8/12/04. On (b) (6) he experienced a generalized motor seizure and was taken to an ER. He reported symptoms of gastroenteritis for a few days prior to the event. An EEG found mild to moderate diffuse encephalopathy. MRI was consistent with MS but did not show enhancing lesions. The subject was treated with carbamazepine and was sent home from the ER. He was discontinued from the study. Concomitant medications were lovastatin and baclofen.

#### Seizures in MS subjects exposed to other fampridine formulations

Six of 178 (3.3%) MS subjects exposed to other fampridine formulations experienced seizure AEs. All six events were classified as generalized seizures. One event occurred in a subject that had been treated for 22 months at a dose of 12.5mg bid (Subject #105, study 1293-001EXT). Three events occurred within the first 3 days of treatment, another at day 8 and another at day 26. The three cases with rapid onset of seizure occurred after relatively high doses of fampridine. In the first case (subject #107, Study 0293-001) the seizure occurred after two doses at 40 mg b.i.d. In the second case (patient #1091-001), the seizure occurred at two hours after the third dose of 12.5 mg q6h, and, in the third case, following two doses of 12.5 mg at 7 hours apart and an accidental overdose of 25 mg (2x12.5 mg) after another 9 hours (patient #210, Study 0494-001). Plasma samples were obtained from these three patients in the hospital and showed plasma concentration of fampridine of 202 ng/mL, 104 ng/mL, and 114 ng/mL respectively. These concentrations were greater than the maximum plasma concentration expected with the 10 mg bid dose of Fampridine-SR. The two remaining cases also occurred in Study 0494-001. Patient #261 experienced a seizure 8 days after initiation of treatment at 12.5 mg bid at approximately 10 hours following the last dose. Patient #414 experienced a seizure after 26 days of treatment at a dose of 17.5 mg bid and approximately 7 hours post dose. No fampridine plasma concentration measurements were obtained in these cases.

#### SCI Clinical Pharmacology Trials

There were no seizures in SCI CP trials

#### Double Blind Controlled SCI Trials

One Fampridine SR (0.27%, 1/372) and no placebo subjects (0/324) experienced a seizure during double blind controlled Fampridine SR SCI trials. The seizure occurred in a subject exposed to 40mg bid (4.3%, 1/23). No seizures were reported for subjects exposed to 17.5 mg bid (n=29), 20mg bid (n=66), 25mg bid (n=245). The seizure event is summarized below.



Subject #02C04, was a 67 year old male, randomized to Fampridine SR 40 mg bid in study SCI-F201. This subject experienced a 10-15 minute tonic-clonic seizure followed by a post-ictal period of several hours. The seizure occurred approximately 7 hours following his last scheduled dose of 40 mg Fampridine SR, a dose he had been taking for one week. He was treated with phenytoin and carbamazepine. A head CT showed no evidence of new focal injury, stroke, or hemorrhage. Blood chemistry test results were unremarkable. An EEG showed no evidence of seizure activity or seizure focus. This patient had experienced dizziness and nausea for some days prior, had discontinued the use of tizanidine the day before, and experienced hallucination the same day as the seizure. Concomitant medications included Zanaflex, baclofen, and Coumadin.

#### Open Label SCI Trials

Acorda reported that 5 SCI subjects (1.4%, 5/354) experienced seizures during open label Fampridine SR trials. One subject experienced a seizure while taking 25mg bid and the remaining 4 subjects were taking 30mg bid, 35mg bid, and 40mg bid (n=2). The subjects had been taking Fampridine SR in the extension study for 1-13 months prior to these events. I summarize these events below.

##### 30mg bid

Subject #06B02, a 50 year old male, started open label Fampridine SR 10mg bid on 11/12/02, was up titrated to 40mg bid on 12/24/02 and then down titrated to 30mg bid on 9/8/03. On (b) (6), his wife found him in the driveway of his home and noted that he was conscious but combative and confused. This lasted for 10 minutes. EMS restrained him and transported him to an ER. He was calm on arrival at the ER but could not recall the prior events. He had normal results for an EEG, head CT, cardiac enzymes, CBC, BNP, and brain MRI/MRA. He was discharged home on (b) (6) and was discontinued from the trial. The narrative noted that this subject was also taking bupropion and baclofen at the time of the event.

Subject #05Y12, a 41 year old male, started open label Fampridine SR 10mg bid on 8/21/02, and was up titrated to 30mg bid on (b) (6). Approximately 5 1/2 hours after his first 30mg dose (on (b) (6)), he experienced a seizure lasting 10 minutes which was associated with respiratory arrest that required rescue breathing. He was taken to an ER and a head CT and EEG were reportedly normal. The subject discontinued from the study. The narrative noted that this subject was also taking baclofen at the time of the event.

##### 35mg bid

Subject #03K06, a 46 year old female, started open label Fampridine SR 10mg bid on 6/25/02, was up titrated to 40mg bid and then down titrated to 35mg bid on 8/20/02. On (b) (6), she experienced a seizure lasting 10 minutes. She was taken to an ER and experienced a second seizure lasting 10 minutes. She was



treated with Ativan and Dilantin and admitted to the hospital. She had normal results for an EEG, thyroid profile, brain CT and brain MRI. She was discontinued from the trial and was treated for a UTI. The narrative noted that this subject was also taking baclofen at the time of the event.

40mg bid

Subject #12V10, a 53 year old female, started open label Fampridine SR 10mg bid on 8/26/03 and was titrated to 40mg bid on 11/18/03. On (b) (6), she had a seizure (not described). She was taken to an ER and treated with Ativan and Dilantin. She was discharged home on (b) (6) and continued on Dilantin. The narrative included no information about diagnostic workup for this event. The subject was discontinued from the trial. The narrative noted that this subject was also taking baclofen, diazepam, and gabapentin at the time of the event.

Subject #03W12, a 38 year old female, started open label Fampridine SR 10mg bid on 2/10/03 and was up titrated to 40mg bid on 3/24/03. On (b) (6), he experienced a seizure lasting 10 minutes. He was taken to an ER and experienced a second seizure lasting 5 minutes. An EEG, thyroid profile, and CT scan were reportedly normal. He was started on Keppra and was treated for a UTI. He was discontinued from the trial. The narrative noted that this subject was also taking baclofen and tizanadine at the time of the event.

#### Fampridine Plasma levels and Seizure risk

Acorda summarized available plasma level data collected during the development program. Acorda noted that study AN751-101 found a mean C<sub>max</sub> of 25.2ng/mL and an upper range of 44.7 ng/mL among 24 MS patients following a single 10mg dose. In the 2 pivotal trials, sparse sampling showed maximum mean plasma concentrations of 29.2 and 30.2 ng/mL. The highest recorded plasma fampridine concentrations in these 2 trials were 66.8 and 87.3 ng/mL. Among volunteer patients with severe renal deficiency, the mean C<sub>max</sub> following a single 10mg BID dose was 42.7ng/mL.

Among the 7 patients with seizures that also had fampridine plasma concentration data, the concentrations ranged from 104 to 475ng/mL. Acorda feels that this data supports that “a plasma fampridine concentration of approximately 100 ng/mL is likely to represent a threshold for increased risk of seizure in the absence of other significant risk factors.” (Summary of Clinical Safety, p.51). Acorda does concede that seizures have occurred in patients where plasma concentrations were likely in the normal therapeutic range and notes that it is not clear if fampridine contributed to the seizures in these cases or if there were other predisposing factors.

Acorda summarized seizure risk data from other medications approved in the US for the treatment of MS. Acorda presented data from package inserts, from publically available FDA clinical reviews, and from advisory committee briefing documents. Acorda acknowledged 2 difficulties in using such data for comparisons to fampridine including



the use of different inclusion exclusion criteria (ex. fampridine excluded MS patients with seizure history of epileptiform activity on EEG), and differences in study conduct (Acorda reported all seizures as SAEs).

Acorda noted that the incidence of convulsions in placebo treated subjects in Avonex, Betaseron, and Rebif trials ranged from 0 to 1.1/100PY while the incidence in the actively treated groups range from 0.2 to 2.7/100PY. In the Avonex pivotal trial, the incidence of seizures for Avonex was 1.4/100PY (n=4, 3 with no prior history of seizure) with no seizures in the placebo group. In the European Betaseron trial ME 93079 the incidence of seizure was 0.8/100 PY (n=8) for Betaseron and 0.6/100PY (n=6) for placebo. In the North American Betaseron trial in Secondary progressive MS the incidence of seizures for Betaseron was 0.4/100PY and for placebo was 0.2/100PY (only SAEs reported).

I read selected FDA clinical reviews for MS treatments and summarized findings with respect to seizure risk in the following table:

Drug	Review	Study size	Duration	Type	Risk
Rebif (IFN B-1a)	5/2/03	Rebif 339 Avonex 337	48 weeks	SAE	Rebif 0/339 Avonex 1/337
Rebif	2/9/99	PBO 187 Rebif 22 mcg 188 Rebif 44mcg 184	2 years	SAE	0 0 0
Avonex (IFN B-1a)	5/17/96	Avonex 158 PBO 143		AE	4/158 0/143
Avonex	5/23/03	Avonex (OL) 153	24 months	AE	Did not make >=2%

I also present labeling for these medications and summarize references to seizure risk below:

Avonex has the following Precautions statement in labeling:

Caution should be exercised when administering AVONEX<sup>®</sup> to patients with pre-existing seizure disorders. In the two placebo-controlled studies in multiple sclerosis, 4 patients receiving AVONEX<sup>®</sup> experienced seizures, while no seizures occurred in the placebo group. Three of these 4 patients had no prior history of seizure (see ADVERSE REACTIONS). It is not known whether these events were related to the effects of multiple sclerosis alone, to AVONEX<sup>®</sup>, or to a combination of both. The effect of AVONEX<sup>®</sup> administration on the medical management of patients with seizure disorder is unknown.

Seizure risk is described for patients in the Avonex Medication Guide.



Rebif has the following Precautions statement in labeling:

Caution should be exercised when administering Rebif to patients with pre-existing seizure disorders. Seizures have been associated with the use of beta interferons. A relationship between occurrence of seizures and the use of Rebif has not been established.

In the Rebif AE table that appears in labeling, seizure risk is summarized as follows: Convulsions PBO 2% (n=187), Rebif 22mcg 5% (n=189) Rebif 44mcg 4% (n=184)

The Medication Guide for Rebif does not mention seizure risk but instructs patients to tell their physician if they have epilepsy.

Copaxone does not have a Precautions statement in labeling for seizures. In premarketing studies (n=979) convulsion was reported as an infrequent AE (1/100-1/1000) for Copaxone. In Copaxone RCTs, seizure risk did not meet the criteria for inclusion in the AE table ( $\geq 2\%$  and greater on Copaxone compared to placebo; Copaxone n= 563 PBO n= 564).

Betaseron does not include a Precaution statement for seizure in its label. Seizure did not meet criteria for the Betaseron RCT AE table ( $\geq 2\%$  greater on Betaseron compared to placebo; Betaseron n=1115, PBO n=789). Convulsion is mentioned among post marketing events reported with Betaseron. The Betaseron Medication Guide does not mention seizure risk but instructs patients to tell their physician if they have epilepsy.

#### Discussion

Although there is no disagreement about the ability of fampridine to cause seizures, the relevant question is whether Fampridine SR increases seizure risk at the dose intended for the treatment of MS patients (10mg bid). Data from the controlled clinical trials at the 10mg bid dose did not suggest a difference in seizure risk compared to placebo but this comparison relies on only 400 Fampridine SR treated patients, 238 placebo patients and only 2 seizure events. In these same trials, at 20mg bid (only a doubling of the dose intended to be marketed), the seizure risk was 10-fold higher (based on 2 events in 57 subjects), a concerning finding suggesting a narrow therapeutic index. In the open label trials, the seizure risk in those treated with 10mg bid was similar to the risk seen in the Fampridine SR subjects treated with 10mg bid during controlled trials. The results from this open label population must be considered very carefully since this was a highly selected group of patients. These patients were screened by history and EEG prior to the RCT, those with exposure to Fampridine SR in the RCT (roughly 2/3 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.

Comparing the seizure risk in the Fampridine SR clinical trial population with background data or data from other MS drug development programs must also be



viewed with caution. The screening in the Fampridine SR trials and usual concerns about potentially important differences among the Fampridine SR population and the general MS background population or other drug development program populations make these comparisons problematic.

The current evidence suggests a dose-related risk of seizure with Fampridine SR, with limited data at the dose intended for treatment, and a suggestion of increasing risk just above therapeutic dose. If the risk benefit for Fampridine SR is favorable and the drug is approved, Fampridine SR should not be used in patients with seizure history and prospective patients should be screened with EEG prior to treatment, the conditions of use in the clinical trials. Fampridine SR labeling should include information about the potential for increased seizure risk at the intended dose, should strongly warn about not increasing the dose above the recommended dose and should urge caution in patients at risk for higher plasma exposures (ex. renal insufficiency). A Medication Guide should explain the risk for patients and include information about not increasing the dose.

#### Multiple Sclerosis Relapse

Acorda examined the risk for multiple sclerosis relapse among MS study subjects exposed to Fampridine SR. Acorda explained that relapses were initially coded to the COSTART term “aggravation reaction” and were to the MedDRA terms “multiple sclerosis” and “multiple sclerosis relapse” (Summary of Clinical Safety, p.54). Acorda also recognized the possibility that relapse events reported using the verbatim term “exacerbation” could be coded to the MedDRA term “condition aggravated” and found one subject where this was the case.

Results from the pooled analysis of AEs from the adequate and well controlled MS trials suggest an increased risk of multiple sclerosis relapse TEAEs among Fampridine SR subjects compared to placebo subjects and the risk among Fampridine SR subjects increased with increasing dose. The following table summarizes the MS relapse risk in the adequate and well controlled MS trials.

MS Relapse Risk in the Adequate and Well Controlled MS Trials

Event	Placebo (n=238)	Total Fampridine (n=507)	Fampridine 10mg bid (N=400)	Fampridine 15mg bid (n=50)	Fampridine 20mg bid (n=57)
MS Relapse	3.8% (n=9)	6.5% (n=33)	5.3% (n=21)	8% (n=4)	14% (n=8)
	14.5/100PY	23.1/100PY	19.2/100PY	24.9/100PY	46.4/100PY

From Table 22.2.2a

Given these results, Acorda examined when MS relapse AEs occurred during the study. In an analysis submitted on 5/28/09, Acorda provided the MS relapse risks and rates from the RCTs MS-F202, MS-F203, and MS-F204 and separately for the open label extensions for these same trials. For the RCTs, Acorda classified the MS relapse AEs



by the trial period (pre-treatment, double blind period, and post treatment follow up) that they occurred. I provide those results below.

MS Relapse Risks from RCTs by Trial Period and in Open Label Extensions

	Placebo Events/N (%)	Placebo Events/Patient years	Fampridine 10mg events/N (%)	Fampridine 10mg events/Patient years
RCTs MS-F202, MS-F203, and MS-F204				
Pre-treatment	0/238 (0)	0/100	6/400 (1.5%)	19.6/100
Double blind	8/238 (3.4%)	15.2/100	16/400 (4%)	17/100
Follow up	1/238 (0.4%)	11/100	6/400 (1.5%)	39.1/100
Open label extension trials MS-F202EXT, MS-F203, MS-F204				
	N/A	N/A	151/660 (22.8%)	14.2/100

According to table 22.2.2.b, in these RCTs, the MS relapse risk on active treatment for the 15mg bid group was 6% (3/50; 21.2/100PY) and for the 20mg bid group was 7% (4/57; 26.5/100PY).

This table suggests that the difference in MS relapse risk when comparing Fampridine SR and placebo in the RCT study data are driven by differences in the post treatment period, when subjects were not taking Fampridine SR. There appeared to be little difference in risk between Fampridine SR 10mg bid and placebo for the double blind periods of the RCTs. The MS relapse risk for the 15mg and 20mg bid groups was slightly higher, with a limited number of study subjects at these doses. The MS relapse risk during the open label trials was similar to the risk observed during the double blind period of the RCTs.

Acorda determined that a number of events occurred either during down titration (for those dosed above 10mg bid) or during the post treatment follow up period. After removing these cases from consideration, the MS relapse risks were as follows:

Study	Placebo	Total Fampridine	Fampridine 10mg BID	Fampridine 15mg BID	Fampridine 20mg BID
MS-F202	2.1% (1/47)	5.0% (8/159)	3.8% (2/52)	6% (3/50)	5.3% (3/57)
MS-F203	4.2% (3/72)	3.1% (7/228)	3.1% (7/228)	-	-
MS-F204	3.4% (4/119)	3.3% (4/120)	3.3% (4/120)	-	-
Total	3.4% (8/238)	3.7% (19/507)	3.3% (13/400)	6.0% (3/50)	5.3% (3/57)



Using the submitted AE data set I examined the cases of treatment emergent MS relapse in the adequate and well controlled MS trials. The commonly used verbatim terms for events coded to the MedDRA term “Multiple Sclerosis relapse” for Fampridine SR subjects were MS exacerbation (n=22), MS relapse or Relapse (n=7), MS worsening (n=2), MS exacerbation increased worsening tremors and increased leg weakness (n=1), unable to walk (MS exacerbation) (n=1), increased MS fatigue (n=1), worsening of MS symptoms (n=1) and MS relapse involving sensory system (n=1). For the placebo subjects, the verbatim terms coded to Multiple Sclerosis relapse were MS exacerbation (n=4), MS relapse (n=3), MS worsening (n=1), and Worsening of MS symptoms (n=1).

In the RCTs, of the 33 Fampridine SR subjects (36 events) with MS relapse, 6 had SAEs compared to none of the 9 placebo subjects. Of the 6 serious AEs in Fampridine SR subjects, 4 occurred during treatment and 2 after treatment completed (2 days and 4 days). Using investigator severity assessments, for Fampridine SR treated subjects 3 relapses were considered mild, 27 moderate, and 6 severe. For placebo relapses, 4 were mild and 4 were moderate.

Acorda felt the data did not indicate an increased risk of MS relapse with ongoing treatment. Acorda felt the overall incidence of MS relapse in their trials (14/100PY) was low. They also note that “There was a higher frequency of events categorized as MS relapse following discontinuation of treatment, some of which may derive from worsening of MS with respect to the on-treatment neurological condition.”

Given that the available data did not allow the Division to determine the nature of these events, it was not possible at this time to determine if these “relapses” represented a waning drug effect or new neurological deficits that would suggest actual relapse events as suggested by the AE terms. The Division asked the sponsor to return to study sites in order to collect additional information about the nature of these events.

In response to the Division’s request to better characterize AEs coded to the preferred term “MS relapse”, Acorda undertook additional exploratory efforts. In a submission dated 8/12/09, Acorda explained that they identified all events that could reasonably have been coded to “MS relapse”; reconstructed the clinical details of these events to the extent possible using Adverse Event pages, notations in Clinical and Subject Global Impression comments fields, Subject Summary Questionnaires, etc.; and made queries to investigational sites with respect to events in the post-treatment period, including requests for clarification from source documents regarding any additional verbatim descriptions of events. Acorda also collected and analyzed additional information on the occurrence of pre-treatment MS relapse events to the extent that it was available (MS-F203 and MS-F204 only).



Based on this re-characterization of events, Acorda presented the following tables summarizing risks for MS relapse by treatment in the MS adequate and well controlled trials:

**Table 1. Events of “Multiple Sclerosis Relapse” in the Adequate and Well-Controlled Studies MS-F202, MS-F203 and MS-F204 Fampridine-SR 10 mg b.i.d. vs. placebo in MS-F202, MS-F203 and MS-F204**

	Pre-treatment	During Treatment	Post-Treatment	Treatment Emergent	Uncontrolled Studies
<b>Fampridine-SR 10 mg b.i.d.</b>					
N	400	400	400	400	660
Approx. Patient-Years	23.1#	94.1*	15.4#	109.5	1213.2
Pts with MS Relapse	7	15	7	21	165
% Pts with MS Relapse	1.75%	3.75%	1.75%	5.25%	25%
Patients/100 pt-yrs	30.3	15.9	45.5	19.2	13.6
Events of MS-Relapse	7	15	7	22	250
Events/100 pt-yrs	30.3	15.9	45.5	20.1	20.6
<b>Placebo</b>					
N	238	238	238	238	
Approx. Patient-Years	13.7#	52.6*	9.2#	61.8#	
Pts with MS Relapse	1	9	1	9	
% Pts with MS Relapse	0.42%	3.78%	0.42%	3.78%	
Patients/100 pt-yrs	7.3	17.1	10.9	14.6	
Events of MS-Relapse	1	9	1	10	
Events/100 pt-yrs	7.3	17.1	10.9	16.2	

Pt-years calculated from ISS Table 22.2.2b

# Estimate of Pt-years from number of patients enrolled and duration of period per protocol

Fampridine-SR 15 and 20 mg b.i.d in MS-F202 and MS-F202 EXT

	Pre-treatment	During Treatment	Post-Treatment	Treatment Emergent	Uncontrolled Studies <sup>+</sup>
<b>Fampridine-SR 15 mg b.i.d.</b>					
N		50	50	50	175
# Approx. Patient-Years		13.5	2.9	16.4	108.1 <sup>@</sup>
Pts with MS Relapse		3	2	4	15
% Pts with MS Relapse		6%	4%	8%	8.6%
Patients/100 pt-yrs		22.2	69.3	24.5	13.9
Events of MS-Relapse		3	2	4	17
Events/100 pt-yrs		22.2	69.3	24.5	15.7



<b>Fampridine-SR 20 mg b.i.d.</b>					
N		57	57	57	10
# Approx. Patient-Years		15.3	3.3	18.6	1.54 <sup>@</sup>
Pts with MS Relapse		3	5	8	0
% Pts with MS Relapse		5.3%	8.8%	14%	0%
Patients/100 pt-yrs		19.5	152.1	42.9	0
Events of MS-Relapse		5	5	10	0
Events/100 pt-yrs		32.6	152.1	53.7	0

# Estimate of Pt-years from number of patients enrolled and duration of period per protocol

+ Extension data from MS-F202EXT Study Report, Table 10

@ Exposure data from Table 7.0 page 6 in ISS

Acorda notes that the incidence of MS relapse during double blind treatment is similar for Fampridine SR and placebo for all three of the studied doses (when using patients with an event/100PY) and that the incidence during double blind treatment is similar to the incidence seen during open label extension trials. Acorda also notes that there is an increased risk for MS relapse events in the post treatment period that is dose related.

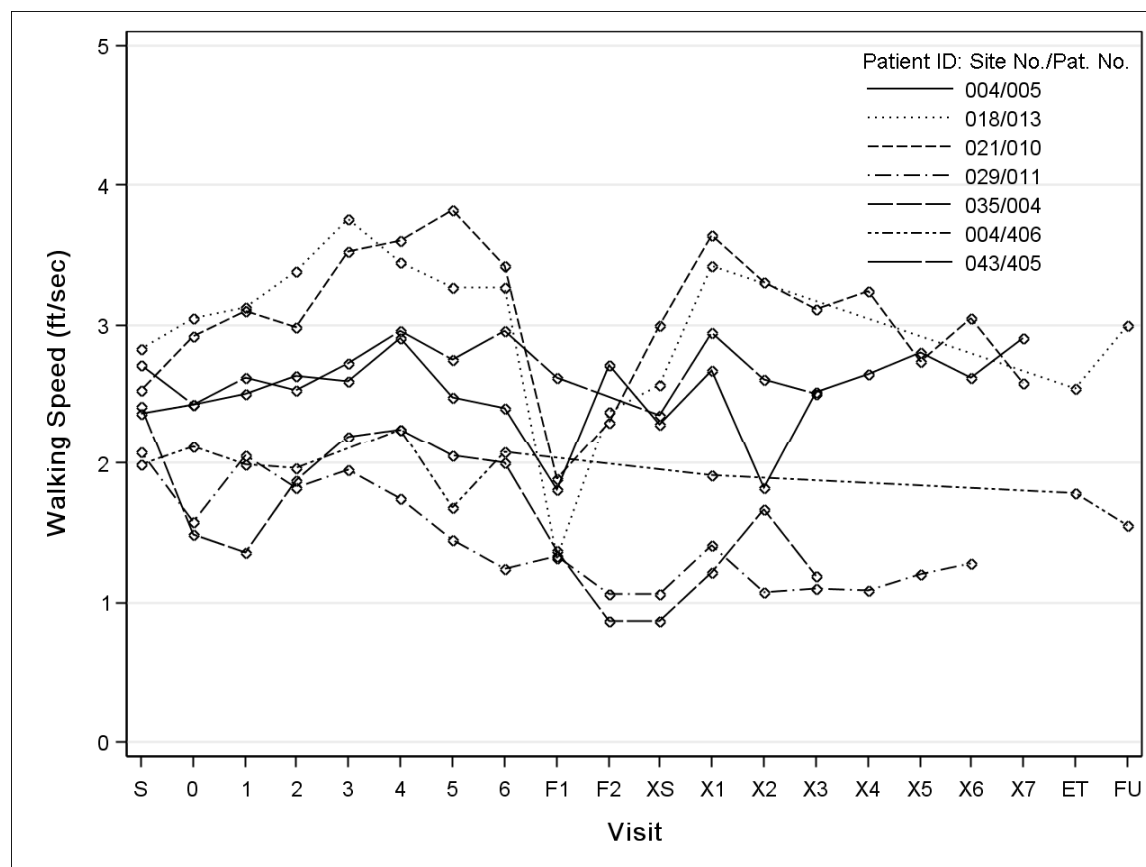
Acorda feels that these post-treatment events are due to “dose-related discontinuation effects that are transient and occur during the down-titration and post-treatment periods in a small proportion of patients.”

Acorda also commented that the short observation periods for pre-treatment and post-treatment demonstrated a higher incidence of relapse in the fampridine groups and a lower incidence in the placebo group when compared to the longer double blind period and that this finding reflects the “difficulty in estimating event rates from such short observation periods.”

Acorda reported that for the 7 Fampridine 10mg bid subjects that experienced post treatment MS relapse AEs, all 7 events occurred within 1-6 days after stopping treatment, that none of these events were SAEs and that all 7 subjects enrolled in open label extension trials (5 still participating) and only 1 of the 7 experienced another relapse during the extension trial.

Acorda provided the following graph of walking speed for the 7 Fampridine SR 10mg bid patients with post treatment MS relapse AEs, where F1 and F2 are the post-treatment visits and Xn are the open label extension visits.



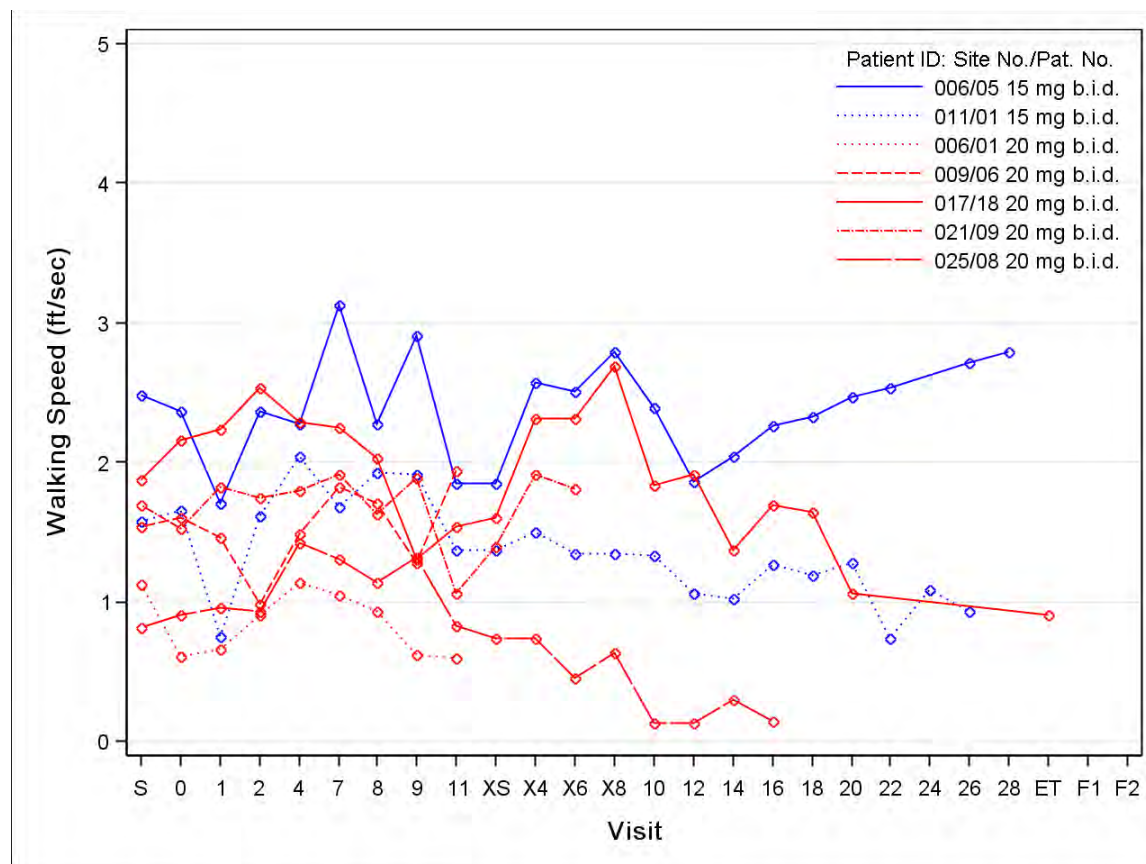


Acorda felt that the plots of walking times indicated that most patients experienced transient declines in walking speed after stopping treatment. Although not mentioned by Acorda, one might also appreciate that, after initial improvements in walking speed, the declines for most of these patients actually began at or prior to visit 5, during active treatment, but that the declines became more pronounced after stopping treatment.

Of the 7 Fampridine SR patients at doses above 10mg bid with MS relapses after discontinuation of treatment (2-15mg bid, 5-20mg bid) 3 events occurred during down titration and 4 events occurred after stopping active treatment (1-8 days). Two of these post treatment MS relapse events were SAEs. Five of the 7 patients that experienced post treatment MS relapse AEs continued Fampridine SR treatment in extension trials (4 still active, three have had additional MS relapse events).

Acorda provided the walking speed data for the Fampridine SR 15mg bid and 20mg bid patients that experienced post treatment MS relapse AEs. I provide that plot below.





In this graph, the follow up visit was visit 11 and Acorda noted that the interval between visit 11 and the screening visit for the extension study (XS) was approximately 9 months.

Acorda felt that these data support that these patients at 15mg bid and 20mg bid “experienced a decline in walking speed in the post-treatment period that could be observed at the two week follow up visit.”

Acorda examined the available clinical data regarding the MS relapse AEs and concluded that “There were no clear differences between events of MS relapse occurring in the post treatment period and those occurring at other times in the study.” Acorda admits that the verbatim terms for these events were not helpful.

Acorda compared demographic data for MS relapse patients and found no factors that distinguished subjects with post treatment MS relapse from the rest of the study population.

Acorda concludes that Fampridine SR treated patients and physicians should anticipate the possibility of worsening MS symptoms after discontinuing treatment. Acorda feels that this deterioration represents loss of therapeutic effect and that it is unlikely that



these events represent “true MS relapse in the sense of new or heightened inflammatory activity in the CNS.” Acorda points to the number of patients with post treatment MS relapse that continued into extension trials, many without additional MS relapse, as a reassuring factor.

#### FDA Review

Dr. Jody Green, a Division neurologist, reviewed the clinical data presented in the narratives that Acorda submitted for patients with MS relapse. Dr. Green felt that the narratives lacked objective description of signs that were present in these patients. Dr. Green was not able to determine whether these events represented MS relapse or decline in status following cessation of a drug that had been effective in these patients.

#### Discussion

As Acorda explained, in the adequate and well controlled MS trials, there was a dose dependent increased risk for MS relapse AEs in Fampridine SR subjects. The increased risk occurred during the post treatment phase of these trials. The post treatment phase was short in duration (only 2 weeks) meaning that this finding is based on very limited observation time. Looking at the placebo subjects, where one might not expect variability in risk by study phase, MS relapse risk was 7.3/100PY in the pre-treatment phase, 17.1/100 PY during the double blind phase, and 10.9/100PY during the post treatment phase. Also complicating this assessment is the suggestion of differences between the placebo and Fampridine SR groups based on the pre-treatment, baseline data. The MS relapse risk in the Fampridine SR group prior to initiating treatment was 4-fold higher (30.3/100PY) than the risk in the placebo group during the pre-treatment phase (7.3/100PY).

The reason for the observed difference in MS relapse risk between Fampridine SR subjects and placebo subjects is not clear. Acorda’s explanation, that the MS relapse AEs represent a waning therapeutic effect following discontinuation seems to be a reasonable explanation. Unfortunately the available data presented in the narratives for these events are not sufficient to allow differentiation between waning therapeutic effect and relapse of the MS disease process. In fact, in some cases, these events appeared to be true relapses to clinicians because the events resulted in hospitalization and treatment with steroids. Given the inherent complexity in diagnosing MS relapse, this finding might be expected.

The data from patients who experienced relapse during the post treatment phase and who continued in open label extension phases is reassuring. These data did not suggest continued uniform increased MS relapse risk among these patients. Furthermore, there did not appear to be increased MS relapse risk in the extension trial patients compared to the RCT patients.

Acorda suggests that patients and physicians should be counseled to expect the possibility of worsening MS symptoms after discontinuing treatment. Acorda did not



suggest how this might be accomplished. Labeling language and discussion in the Medication Guide could accomplish this goal.

#### Psychiatric AEs

When examining AE risks by Body system classification, Acorda noted an increased risk of Psychiatric AEs among Fampridine SR treated subjects compared to placebo subjects in the MS adequate and well controlled trials. This difference in risk was driven primarily by increases in risk among Fampridine SR subjects for anxiety and insomnia.

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 10mg bid, 2% (1/50) for Fampridine SR 15mg bid, and 3.5% (2/57) for Fampridine SR 20mg bid. 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. The anxiety risk for SCI patients receiving placebo was 1.3% (3/229) compared to 4.9% (12/247) for SCI patients receiving Fampridine SR 25mg bid and 30% (9/30) for SCI patients receiving Fampridine SR 40mg bid (ISS table 22.3.2a). In SCI adequate and well controlled trials one anxiety event was an SAE (Fampridine SR 25mg bid). In the SCI adequate and well controlled trials, one placebo patient (0.4%, 1/229) discontinued for anxiety compared to 2 Fampridine SR 25 mg bid patients (0.8%, 2/247) and 1 Fampridine SR 40mg bid patient (3.3%, 1/30).

In the adequate and well controlled MS trials, the risk for insomnia among placebo subjects was 3.8% (9/238) compared to 9.3% (37/400) for Fampridine SR 10mg bid, 18% (9/50) for Fampridine SR 15mg bid, and 12.3% (7/57) for Fampridine SR 20mg bid. None of these insomnia AEs were classified as SAEs and no subjects discontinued from these trials for insomnia. The finding of increased risk of insomnia AEs with Fampridine SR was replicated in the SCI adequate and well controlled trials. The insomnia risk for SCI patients receiving placebo was 4.8% (11/229) compared to 10.9% (27/247) for SCI patients receiving Fampridine SR 25mg bid and 33.3% (10/30) for SCI patients receiving Fampridine SR 40mg bid (ISS table 22.3.2a). In SCI adequate and well controlled trials no insomnia events were SAEs, and one placebo patient (0.4%, 1/229) discontinued for insomnia compared to 6 Fampridine SR 25 mg bid patients (2.4%, 6/247) and 2 Fampridine SR 40mg bid patient (6.7%, 2/30).

Acorda noted that there was no evidence of an increased risk of depression with Fampridine SR based on AE data from active treatment periods. During active treatment, there did not appear to be differences in the risk for depression when comparing Fampridine SR to placebo, but when examining all TEAEs (on drug and up to 2 weeks following discontinuation) the depression risk for placebo was 0.8% (2/238) compared to 1.3% (5/400) for Fampridine SR 10mg bid, 2% (1/50) for Fampridine SR 15mg bid, and 3.5% (2/57) for Fampridine SR 20mg bid. Four of the Fampridine SR depression AEs (1-10mgbid, 1-15mg bid, and 2-20mg bid subjects) occurred during the



14-day follow up period, after discontinuation of Fampridine SR. None of the depression AEs were SAEs or led to discontinuation from the adequate and well controlled MS trials. In the SCI adequate and well controlled trials, the risk for depression AEs was 3.1% (7/229) for placebo patients compared to 4.9% (12/247) for Fampridine SR 25mg bid patients and 0 (0/30) for Fampridine SR 40mg bid patients. Unlike the MS controlled trials, all of the depression AEs in SCI trials occurred during active treatment. While none of the depression AEs from the adequate and well controlled SCI trials were SAEs, 3 depression AEs led to discontinuation (all 3 Fampridine SR 25mg bid).

In addition to depression AEs, the NDA integrated safety database included one subject who committed suicide (MS-203 EXT 220011, described above with the deaths), one subject who attempted suicide (MS-F203 EXT, 34008) and three subjects who had AEs of suicidal ideation (MS-F203 EXT15001 SAE, SCI-F201 05T02, SCI-F201 EXT 05M11). The subject who attempted suicide (MS-F203 EXT, 34008) was a 46 year old female with a history of MS and depression. One month after being diagnosed with renal carcinoma she attempted suicide by ingesting 250 acetaminophen tablets and an unspecified number of aspirin tablets and Tylenol #3 tablets. She survived the event and discontinued from the study. The subject who had a suicidal ideation SAE (MS-F203 EXT15001) was a 50 year old female with a history of MS, depression, and suicidal ideation, who developed suicidal ideation requiring psychiatric evaluation. Contributing stressors included worsening MS, marital discord, family changes, and social isolation. Her citalopram dose was increased and she discontinued from the study.

In their Safety Update, Acorda reported 2 events of suicide attempt and 2 events of suicidal ideation. The first report of suicide attempt was an update of the event described above for subject MS-F203 EXT 34008 (update included the stop date for the event). The second report described a 56 year old male with MS, hypertension, elevated triglycerides, pulmonary embolism, UTI, and anxiety. He was taking multiple medications including bupropion, escitalopram and seroquel. He ingested alcohol and medications (not specified) in a suicide attempt. He survived this attempt and continued in the study. This subject subsequently committed suicide (slashed wrists and stabbed self in the abdomen) but this event was not included in the above list of deaths because it occurred after the Safety Update database lock date.

The 2 subjects with suicidal ideation AEs (MS-F203 EXT 19006, 35004) both had histories of depression that predated study participation and both continued in the study. Neither event was an SAE.

The clinical trial data support a causal relationship between anxiety and insomnia and Fampridine SR. These events occurred more frequently in Fampridine SR subjects than in placebo subjects and the risk appeared dose related. There was insufficient evidence to establish a relationship between Fampridine SR and depression AEs.



### Urinary Tract Infections

Acorda noted that urinary tract infection (UTI) AEs occurred commonly in the Fampridine SR NDA. The risk of UTI AEs among Fampridine SR subjects in controlled trials (both MS and SCI) exceeded the risk among placebo subjects. In MS adequate and well controlled trials, when considering AEs coded to the preferred terms UTI, cystitis, kidney infection, bacterial pyelonephritis, and Echerichia UTI, the risk among Fampridine SR subjects was 16.2% (82/507) compared to 10% (24/238) for placebo subjects. In SCI adequate and well controlled trials, the risk for those same AEs plus UTI enterococcal and urosepsis among Fampridine SR subjects was 28.9% (80/277) compared to 18.8% (43/229) for placebo subjects. Acorda noted that in the majority of cases, UTI AEs were diagnosed based on symptoms and that there was a lack of objective data (urinalysis results, urine culture results) supporting these diagnoses. Routinely collected UA data from adequate and well controlled MS trials showed that 25.1% (126/502) Fampridine SR subjects had leucocytes on UA compared to 30.9% (73/236) of placebo subjects. In SCI trials, 41% (83/202) of Fampridine SR subjects had positive leukocyte esterase results compared to 42% (78/187) of placebo subjects.

Despite the increased risk for UTI AEs among Fampridine SR subjects in adequate and well controlled trials, there were few UTIs that were SAEs and less consistent findings regarding difference in risk for UTI SAEs by treatment. In MS controlled trials, 4 Fampridine SR subjects experienced a UTI SAE (0.8%, pyelonephritis n=1, kidney infection n=1, and UTI n=2) compared to 1 (0.4%, UTI) placebo subject. In SCI trials, the risk for UTI SAEs was 0.7% for fampridine (2/277, UTI n=2) and 2.2% for placebo (5/229, UTI n=3, pyelonephritis n=1, urosepsis n=1).

Acorda postulated that Fampridine SR, which is excreted by the kidney and reaches high urinary concentrations, may produce sensory symptoms that are similar to the symptoms of UTI. They offered no empirical evidence to support this theory. In fact, when examining AEs from the Renal and Urinary Disorders body system grouping from the adequate and well controlled MS trials, except for urinary frequency (coded to pollakiuria) and urinary incontinence there is little evidence of a disparity of urinary symptoms when comparing fampridine subjects to placebo subjects. I provide that information in the following table.

### Treatment Emergent Renal and Urinary Disorder AEs from Adequate and Well Controlled MS trials

	Placebo (n=238)	All Fampridine (n=507)	Fampridine 10mg bid (n=400)	Fampridine 15mg bid (n=50)	Fampridine 20mg bid (n=57)
Renal and Urinary Disorders	5.9% (14)	7.3% (37)	6.8% (27)	6% (3)	12.3% (7)
Bladder discomfort	0.4% (1)	0	0	0	0
Bladder spasm	0	0.2% (1)	0.3% (1)	0	0
Dysuria	0.4% (1)	0.4% (2)	0.5% (2)	0	0
Hematuria	1.7% (4)	0.2% (1)	0.3% (1)	0	0
Leukocyturia	0.4% (1)	0.2% (1)	0.3% (1)	0	0



Micturition urgency	1.7% (4)	1% (5)	1% (4)	2% (1)	0
Nephrolithiasis	0	0.6% (3)	0.8% (3)	0	0
Nocturia	0.4% (1)	0.2% (1)	0.3% (1)	0	0
Pollakiuria	0.8% (2)	2.4% (12)	2% (8)	2% (1)	5.3% (3)
Polyuria	0	0.2% (1)	0.3 (1)	0	0
Pyuria	0	0.2% (1)	0.3% (1)	0	0
Renal disorder	0.4% (1)	0	0	0	0
Terminal dribbling	0	0.2% (1)	0.3% (1)	0	0
Urinary hesitation	0	0.2% (1)	0.3% (1)	0	0
Urinary incontinence	0	1.6% (8)	1.3% (5)	0	5.3% (3)
Urinary retention	0.4% (1)	0.6% (3)	0.3% (1)	2% (1)	1.8% (1)
Urine odor abnormal	0	0.4% (2)	0	0	3.5% (2)

Data From Table 22.2.2a

Similar findings were seen in the adequate and well controlled SCI trials (data not presented).

The AE data from the Fampridine SR clinical trials (both MS and SCI) suggested an increased risk for urinary tract infections in Fampridine SR patients compared to placebo patients. In many cases, these events were diagnosed based only on symptoms and UA and/or urine cultures were not performed. There did not appear to be consistent increases in risk among Fampridine SR subjects compared to placebo subjects for serious UTIs (elevated in MS patients but not in SCI patients). There is insufficient evidence to evaluate Acorda's hypothesis that these UTI events represent sensory symptoms rather than actual infections. Any future planned Fampridine SR trials should attempt to clarify the association between Fampridine and UTI, perhaps by questioning all study patients about urinary symptoms and collecting cultures and UAs in symptomatic patients.

#### Hepatic Injury Report

Although there were no reports of hepatic injury in the Fampridine SR NDA or Safety Update, and no signal for hepatic injury from lab data (see below), a published article described a case of hepatic injury in a patient treated with 4-aminopyridine.<sup>1</sup> The authors described a 60 year old female who developed malaise after 6 months of treatment with 4-aminopyridine (30mg in three daily doses) and 6 weeks after a course of intravenous steroids for MS. The patient was found to be slightly jaundiced and testing found a bilirubin of 33 umol/L, (1.9mg/dL), GGT 199 U/L, AST 359 U/L, and ALT 819 U/L (ALP not reported). These abnormalities were not present immediately following treatment with steroids. 4-aminopyridine was stopped. The report noted that the patient had negative results on serological tests (not specified). The patient's condition improved over the subsequent 3 months with no additional interventions.

<sup>1</sup> Polman CH, Bertelsmann FW, van Loenen AC, Koetsier JC. 4-Aminopyridine in the Treatment of Patients with Multiple Sclerosis. Arch Neurol. 1994;51:292-296.



The limited information provided about this case of hepatic injury does not allow for definitive determination about the role of 4-aminopyridine in this event. The transaminase data suggest hepatocyte injury in this patient, but the limited lab data does not allow one to determine if the patient's bilirubin exceeded 2.0mg/dL at any point. The summary of this case does not allow one to determine if other causes of liver injury were excluded. The authors did not describe which serologies were performed, if other testing was performed, or if the patient was taking any other medications. Given the lack of a signal for hepatic injury in the Fampridine SR NDA, and the lack of additional similar cases in the medical literature, it is premature to conclude that Fampridine SR causes hepatic injury. Acorda should closely follow and promptly report any liver injury cases reported for Fampridine SR.

### 7.3.5 Submission Specific Primary Safety Concerns

No additional submission specific primary safety concerns were identified during this review.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

AEs in MS and SCI Trials, Pooled

Acorda reported that 93.8% (1417/1510) of MS and SCI trial subjects exposed to Fampridine SR experienced one or more TEAEs (ISS Table 20.1.1). In the following table, I list the treatment emergent AEs that occurred in at least 2% of Fampridine SR subjects.

Treatment Emergent AEs  $\geq 2\%$  of Fampridine SR Subjects, MS and SCI Trials

<b>AE Preferred Term</b>	<b>% (n)</b>	<b>AE Preferred Term</b>	<b>% (n)</b>
Urinary tract infection	28.9% (436)	Excoriation	4.2% (63)
Dizziness	19.7% (298)	Pyrexia	4.1% (62)
Insomnia	19% (287)	Dyspepsia	4% (61)
Fall	18.1% (274)	Sinusitis	4% (60)
Headache	17.9% (270)	Influenza	3.9% (59)
Asthenia	15.5% (234)	Shoulder pain	3.9% (59)
Nausea	15.3% (231)	Pollakiuria*	3.6% (55)
Fatigue	13.2% (199)	Pharyngolaryngeal pain	3.2% (48)
Paresthesia	13% (196)	Stomach discomfort	3.1% (47)
Multiple sclerosis relapse	12.9% (195)	Micturition urgency	3.1% (47)
Muscle spasms	12.2% (184)	Cystitis	3% (46)



Upper resp tract inf	12% (181)	Myalgia	3% (45)
Muscle spasticity	11.3% (171)	Neck pain	2.9% (44)
Constipation	11% (166)	Skin laceration	2.9% (44)
Back pain	10.6% (160)	Hyperhidrosis	2.9% (44)
Pain in extremity	10.5% (159)	Decreased appetite	2.7% (41)
Arthralgia	9.4% (142)	Cough	2.7% (41)
Diarrhea	9% (136)	Gastroenteritis viral	2.6% (40)
Edema peripheral	8.5% (128)	Vision blurred	2.6% (39)
Nasopharyngitis	7.7% (117)	Abdominal pain upper	2.5% (38)
Contusion	7.2% (108)	Abdominal pain	2.5% (38)
Balance disorder	7% (106)	Muscle tightness	2.5% (37)
Anxiety	6.5% (98)	Dyspnea	2.5% (37)
Hypoaesthesia	6% (90)	Erythema	2.4% (36)
Depression	6% (90)	Cellulitis	2.3% (35)
Musculoskeletal stiffness	5.4% (81)	Joint swelling	2.3% (35)
Tremor	5.4% (81)	Vertigo	2.3% (34)
Urinary incontinence	5.1% (77)	Fecal incontinence	2.3% (34)
Vomiting	4.8% (73)	Bronchitis	2.2% (33)
Pain	4.4% (67)	Hypertension	2.2% (33)
Rash	4.4% (67)	Abnormal dreams	2.2% (33)
Burning sensation	4.4% (66)	Gait disturbance	2.1% (32)
Difficulty walking	4.3% (65)		

From ISS Table 22.1.1a

\*Urinary frequency

#### AEs in MS Subjects, Controlled and Uncontrolled Trials

The frequency of AEs in the MS trials (94.1%) was similar to the frequency observed for the pooled MS and SCI trials. The table below lists the AEs that occurred in at least 2% of MS subjects. This table includes many of the same AEs listed in the preceding table. The following AEs occurred in at least 2% of MS and SCI subjects but did not meet the 2% frequency criteria when considering only MS subjects: hyperhidrosis, abdominal pain, muscle tightness, abnormal dreams, muscle spasticity, fecal incontinence, and decreased appetite. The following AEs met the 2% frequency criteria for MS subjects but not for MS and SCI subjects combined: joint sprain, blood cholesterol increased, coordination abnormal, viral infection, blood CPK increased, pruritis, ecchymosis, fungal infection, migraine, hypercholesterolemia, and white blood cell count increased.



Treatment Emergent AEs in  $\geq 2\%$  of Fampridine SR Subjects, MS Trials

<b>AE Preferred Term</b>	<b>% (n)</b>	<b>AE Preferred Term</b>	<b>% (n)</b>
Urinary tract infection	27.5% (252)	Pyrexia	3.6% (33)
Fall	25.8% (237)	Skin laceration	3.6% (33)
Multiple sclerosis relapse	21.3% (195)	Shoulder pain	3.5% (32)
Asthenia	19.4% (178)	Myalgia	3.4% (31)
Insomnia	18.1% (166)	Pain	3.4% (31)
Headache	17.6% (161)	Pharyngolaryngeal pain	3.1% (28)
Dizziness	17.3% (159)	Cough	3.1% (28)
Fatigue	15.3% (140)	Gastroenteritis viral	3.1% (28)
Nausea	14.7% (135)	Burning sensation	2.9% (27)
Upper resp tract inf	13.4% (123)	Hypertension	2.9% (27)
Paresthesia	11.5% (105)	Vertigo	2.9% (27)
Back pain	11% (101)	Micturition urgency	2.8% (26)
Pain in extremity	10.7% (98)	Bronchitis	2.8% (26)
Arthralgia	10.7% (98)	Gait disturbance	2.8% (26)
Edema peripheral	9.7% (89)	Joint swelling	2.7% (25)
Balance disorder	9.6% (88)	Joint sprain	2.7% (25)
Contusion	9.1% (83)	Neck pain	2.6% (24)
Muscle spasms	8.3% (76)	Dyspnea	2.6% (24)
Nasopharyngitis	8.1% (74)	Cellulitis	2.6% (24)
Depression	7.3% (67)	Blood Cholesterol inc	2.5% (23)
Constipation	6.9% (63)	Coordination abnormal	2.5% (23)
Diarrhea	6.5% (60)	Viral infection	2.5% (23)
Hypoaesthesia	6.5% (60)	Blood CPK increased	2.4% (22)
Tremor	6.4% (59)	Pruritis	2.4% (22)
Difficulty walking	5.7% (52)	Vision blurred	2.4% (22)
Influenza	4.8% (44)	Stomach discomfort	2.3% (21)
Vomiting	4.6% (42)	Abdominal pain upper	2.3% (21)
Anxiety	4.5% (41)	Ecchymosis	2.2% (20)
Sinusitis	4.5% (41)	Fungal infection	2.2% (20)
Rash	4.5% (41)	Chest pain	2.1% (19)
Urinary incontinence	4.4% (40)	Erythema	2.1% (19)
Musculoskeletal stiffness	4.3% (39)	Migraine	2.1% (19)
Dyspepsia	3.8% (35)	Hypercholesterolemia	2% (18)
Pollakiuria	3.8% (35)	White blood cell count inc	2% (18)
Cystitis	3.8% (35)	Trigeminal neuralgia	2% (18)
Excoriation	3.7% (34)		



#### AEs from Adequate and Well Controlled MS Trials

ISS Table 22.2.2a summarized treatment emergent AEs for the adequate and well controlled MS trials (MS-F202, MS-F203, and MS-F204). In these trials, 86.4% (438/507) of Fampridine SR subjects experienced one or more AEs compared to 73.5% (175/238) of placebo subjects. The table below identified the AEs occurring in at least 1% of Fampridine SR subjects and that occurred more frequently compared to placebo. I highlighted those AEs that were at least 2 times more frequent among Fampridine SR subjects compared to placebo.

#### Treatment Emergent AEs Occurring in $\geq 1\%$ 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)
Urinary tract infection	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)
Multiple sclerosis 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)
Paresthesia	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)
Diarrhea	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
Dyspnea	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

From ISS Table 22.2.2a

#### AEs from Adequate and Well Controlled SCI Trials

ISS Table 22.3.2a summarized TEAEs for the adequate and well controlled SCI trials (SCI-F201, SCI-F301, and SCI-F302). In these trials, 90.6% (251/277) of Fampridine SR subjects experienced one or more AEs compared to 86.5% (198/229) of placebo subjects. The table below identifies the AEs occurring in at least 5% of Fampridine SR subjects and that occurred more frequently compared to placebo. I highlighted those AEs that were at least 2 times more frequent among fampridine subjects compared to placebo.

#### Treatment Emergent AEs in ≥5% of Fampridine SR Subjects and that Occurred More Frequently Compared to Placebo, Adequate and Well Controlled SCI Trials

AE Preferred term	Placebo (n=229)	Fampridine Total (n=277)	Fampridine 25mg bid (n=247)	Fampridine 40mg bid (n=30)
Subjects with 1 or more AEs	86.5% (198)	90.6% (251)	89.5% (247)	100% (30)
Urinary tract infection	16.6% (38)	26% (72)	25.5% (63)	30% (9)
Dizziness	2.6% (6)	15.9% (44)	13% (32)	40% (12)
Constipation	9.2% (21)	15.5% (43)	14.6% (36)	23.3% (7)



Headache	10% (23)	14.1% (39)	11.7% (29)	33.3% (10)
Muscle spasticity	12.2% (28)	13.7% (38)	10.5% (26)	40% (12)
Insomnia	4.8% (11)	13.4% (37)	10.9% (27)	33.3% (10)
Nausea	6.6% (15)	11.9% (33)	10.1% (25)	26.7% (8)
Paresthesia	3.9% (9)	11.6% (32)	10.1% (25)	23.3% (7)
Back pain	4.8% (11)	9.4% (26)	8.1% (20)	20% (6)
Fatigue	5.2% (12)	7.9% (22)	6.1% (15)	23.3% (7)
Anxiety	1.3% (3)	7.6% (21)	4.9% (12)	30% (9)
Pain in extremity	4.8% (11)	7.6% (21)	6.9% (17)	13.3% (4)
Asthenia	3.5% (8)	7.2% (20)	4.9% (12)	26.7% (8)
Musculoskeletal stiffness	4.8% (11)	6.1% (17)	4.9% (12)	16.7% (5)
Abdominal pain	0.9% (2)	5.4% (15)	4% (10)	16.7% (5)
Decreased appetite	1.3% (3)	5.1% (14)	3.6% (9)	16.7% (5)

From Table 22.3.2a

### Additional Analyses of Select Common AEs

#### Dizziness

Dizziness was commonly reported by subjects treated with Fampridine SR, was more common among Fampridine SR treated subjects than placebo subjects, and the risk for dizziness increased with dose. In MS adequate and well controlled trials, 48 Fampridine SR subjects experienced dizziness. The median time to onset of dizziness for these 48 subjects was 12 days (range 1 to 107 days). The median duration of dizziness for these subjects was 7 days (range 0-76 days). The majority of verbatim terms coded to the preferred term dizziness were “dizziness” and “lightheadedness”. The outcome for dizziness was reported as resolved for 43 subjects, not resolved for 4 subjects, and outcome was not provided for 1 subject. The vital sign data did not suggest meaningful Fampridine SR -related declines in blood pressure (see below) that would explain the increased risk of dizziness. In the adequate and well controlled MS trials, no subjects had AEs of blood pressure decreased and there did not appear to be a meaningful increase in risk for syncope among Fampridine SR subjects (0.4%, 2/507) compared to placebo (0/237).

I assessed the relationship between dizziness and other select AEs (contusion, balance disorder, difficulty walking, fall, fracture, and skin laceration) by comparing the percentage of MS patients from the adequate and well controlled trials with dizziness and a given AE, with the expected risk assuming that the events were independent (Risk of dizziness x Risk for studied AE).

For the examined events, the observed risk for co-occurrence in subjects of AEs exceeded the expected (presuming independence) for balance disorder and dizziness and fall and dizziness but after examining the individual cases, many of the events did not occur contemporaneously. In the adequate and well controlled trials, 8 fampridine patients (1.6%) experienced both dizziness and balance disorder compared to an expected risk of 0.6% (risk of dizziness 9.5% x risk of balance disorder 6.3%). An



examination of the data set for the 8 patients with dizziness and balance disorder demonstrated that the AEs were contemporaneous for only 4 of the 8 cases.

In the MS adequate and well controlled trials, 3.2% (n=16) of fampridine patients experienced both dizziness and fall compared to an expected risk of 1.5% (risk of dizziness 9.5% x risk of fall 15.6%). An examination of the data set for the 16 patients with dizziness and fall demonstrated that the AEs were contemporaneous for only 5 of the 16 cases.

#### Insomnia

Insomnia was commonly reported by subjects treated with Fampridine SR, was more common among Fampridine SR treated subjects than placebo subjects, and the risk for insomnia increased with dose. In MS adequate and well controlled trials, 53 Fampridine SR subjects experienced insomnia. The median time to onset of insomnia for these 53 subjects was 15 days (range 1 to 106 days). The median duration of insomnia for the 31 subjects with a day of resolution in the data set was 26 days (range 0-110 days).

#### Asthenia

Asthenia was commonly reported by subjects treated with Fampridine SR, was more common among Fampridine SR treated subjects than placebo subjects, and the risk for asthenia increased with Fampridine SR dose. In MS adequate and well controlled trials, 44 Fampridine SR subjects experienced asthenia. The median time to onset of asthenia for these 44 subjects was 44.5 days (range 1 to 121 days). The median duration of asthenia for the 26 subjects with a day of resolution in the data set was 14 days (range 0-43 days).

### 7.4.2 Laboratory Findings

#### Chemistry

##### Mean Change Results Adequate and Well Controlled MS Trials

ISS table 33.2.2 provided mean change from baseline chemistry results from the adequate and well controlled MS trials. The mean changes from baseline in these trials were generally similar for Fampridine SR and placebo subjects. Fampridine SR subjects experienced a larger mean increase in LDH compared to placebo subjects. The difference between Fampridine SR and placebo in mean change for LDH appeared to be driven by a large decline in one placebo subject (-1013). The median change from baseline for LDH was 3 for placebo and 1 for fampridine.

I summarize the mean change from baseline chemistry results below.

##### Chemistry Mean Change from Baseline to Days 43 through 119, Adequate and Well Controlled MS Trials

Analyte	Placebo (n=238)	Fampridine SR (n=507)
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Albumin (g/L)	-1.11 (n=230)	-1.39 (n=487)
Alkaline Phosphatase (U/L)	2.92 (n=233)	2.44 (n=491)
Blood Urea Nitrogen (mmol/L)	0.52 (n=233)	0.51 (n=491)
Calcium (mmol/L)	-0.01 (n=233)	-0.03 (n=491)
Cholesterol (mmol/L)	0.14 (n=233)	0.02 (n=491)
Triglycerides (mmol/L)	0.2 (n=233)	0.17 (n=491)
Creatine Kinase (μmol/L)	14.68 (n=233)	13.23 (n=489)
Creatinine (μmol/L)	2.28 (n=233)	3.67 (n=491)
Glucose (mmol/L)	0.17 (n=233)	0.04 (n=491)
Lactate dehydrogenase (U/L)	0.97 (n=233)	4.3 (n=489)
Phosphorus (mmol/L)	-0.09 (n=233)	-0.1 (n=488)
Potassium (mmol/L)	0.12 (n=233)	0.11 (0.38)
AST (U/L)	2.32 (233)	2.13 (n=490)
ALT (U/L)	4.48 (n=119)	3.6 (n=121)
Bilirubin (μmol/L)	0.52 (n=233)	0.63 (n=491)
Sodium (mmol/L)	-0.6 (n=233)	-0.65 (n=490)
Urate (mmol/L)	0.01 (n=233)	0.01 (n=491)
Protein (g/L)	-1.85 (n=233)	-2.41 (n=491)

#### Mean Change Results Adequate and Well Controlled SCI Trials

ISS table 33.3.2 summarized the mean change from baseline chemistry lab results. As with the MS trials, the mean changes from baseline were similar for Fampridine SR and placebo in the adequate and well controlled SCI trials. For LDH, Fampridine SR subjects experienced a mean increase from baseline at days 43-119 of 7.29 compared to 2.76 for placebo. The median increase in LDH for Fampridine SR subjects was 6 compared to 3 for placebo subjects.

#### Outlier Results Adequate and Well Controlled MS Trials

ISS table 42.2.2 identified the percentage of subjects with chemistry lab results that met clinically significant cutoff criteria. The chemistry outlier results were generally similar for Fampridine SR and placebo subjects. There was an almost 2 fold higher risk for phosphorus outliers for Fampridine SR subjects compared to placebo subjects. I summarize those results below.

#### Chemistry Outlier Results, Adequate and Well Controlled MS Trials

Analyte (outlier criteria)	Placebo (n=238)	Fampridine SR (n=507)
Albumin ( $\leq 25$ or $\geq 65$ g/L)	0/233	0/499
Alkaline Phosphatase ( $\geq 3 \times \text{ULN}$ )	0/236	0/503
BUN ( $\geq 10.7$ mmol/L)	1.7% (4/236)	1.4% (7/503)
Calcium ( $< 1.75$ or $> 3.0$ mmol/L)	0/236	0/503
Cholesterol ( $> 7.77$ mmol/L)	2.5% (6/236)	1.8% (9/503)



Creatine Phosphokinase ( $\geq 3 \times \text{ULN}$ )	1.7% (4/236)	0.6% (3/501)
Creatinine ( $\geq 176.8 \mu\text{mol/L}$ )	0/236	0.4% (2/503)
Glucose ( $< 2.775$ or $> 13.875 \text{mmol/L}$ )	0.8% (2/236)	1% (5/503)
Lactate dehydrogenase ( $\geq 3 \times \text{ULN}$ )	0/236	0/501
Phosphorus ( $< 0.646$ or $> 1.615 \text{mmol/L}$ )	2.5% (6/236)	4.6% (23/501)
Potassium ( $< 3.0$ or $> 5.0 \text{mmol/L}$ )	1.3% (3/236)	1.2% (6/501)
AST ( $> 3 \times \text{ULN}$ )	0/236	0/502
ALT ( $> 3 \times \text{ULN}$ )	0/121	0/123
Bilirubin ( $\geq 34.2 \mu\text{mol/L}$ )	0/236	0.4% (2/503)
Sodium ( $< 130$ or $> 150 \text{mmol/L}$ )	0/236	1.2% (6/502)

Using the submitted lab data sets, I determined that for phosphorus outliers, all 6 placebo subjects had high outlier results (2.5%, 6/238) and that 19 Fampridine SR subjects had high outliers (3.7%, 19/507) making this apparent disparity less concerning.

For the two Fampridine SR subjects with bilirubin elevations, the significant lab results (2.4mg/dL and 2.6mg/dL) represented declines from the baseline results for these subjects.

For the Fampridine SR subjects with sodium outlier results, 3 had elevations and 3 had declines.

#### Outlier Results Adequate and Well Controlled SCI Trials

ISS table 42.3.2 identified the percentage of subjects with chemistry lab results that were outside the normal range. The chemistry outlier results in the adequate and well controlled SCI trials were generally similar to those in the MS trials summarized above. As with the MS trials, there was a higher risk for sodium outlier results among Fampridine SR subjects (1.1%, 3/264) compared to placebo subjects (0/216). The finding in MS trials of an increased risk for phosphorus result outliers among Fampridine SR subjects was not replicated in the SCI trials where the outlier risk for Fampridine SR was 1.1% (3/264) and for placebo was 3.2% (7/216).

#### Additional Analyses

To look for evidence of Fampridine SR-related hepatotoxicity, I asked Acorda to identify and summarize all cases of liver injury as defined by ALT or AST  $> 3 \times \text{ULN}$  AND total bilirubin  $> 2 \times \text{ULN}$ . Acorda reported that no cases in their database met those criteria. For the adequate and well controlled MS trials, no subjects with normal ALT at baseline had an on treatment ALT  $> 3 \times \text{ULN}$ , with normal AST at baseline had an on treatment AST  $> 3 \times \text{ULN}$ , or with normal bilirubin at baseline had on treatment bilirubin  $> 1.5 \times \text{ULN}$ .



In the SCI adequate and well controlled trials, one Fampridine SR subject (ACD-002580) with a normal AST at baseline had an AST result on treatment that was >3xULN (result was <5x ULN). One Fampridine SR subject (ACD-000583) with a normal bilirubin at baseline had an on treatment bilirubin >1.5xULN (result was <2xULN) (Response to reviewer questions 3/13/09).

## Hematology

### Mean Change Results Adequate and Well Controlled MS Trials

ISS table 34.2.2 provided mean change from baseline hematology results from the adequate and well controlled MS trials. The mean changes from baseline in these trials were generally similar for Fampridine SR and placebo. I summarize results from that table below.

### Hematology Mean Change from Baseline to Days 43 through 119, Adequate and Well Controlled MS Trials

Analyte	Placebo (n=238)	Fampridine SR (n=507)
Basophils (10 <sup>9</sup> /L)	0.01 (n=231)	0.01 (n=486)
Eosinophils (10 <sup>9</sup> /L)	0.02 (n=231)	0.03 (n=486)
Hematocrit (%)	-1.17 (n=231)	-1.49 (n=487)
Hemoglobin (g/L)	-2.3 (n=231)	-2.97 (n=488)
Lymphocytes (10 <sup>9</sup> /L)	-0.14 (n=231)	0.02 (n=485)
Monocytes (10 <sup>9</sup> /L)	0.05 (n=231)	0.05 (n=486)
Neutrophils (10 <sup>9</sup> /L)	-0.47 (n=231)	-0.46 (n=486)
Platelets (10 <sup>9</sup> /L)	5.95 (n=231)	6.55 (n=487)
Leukocytes (10 <sup>9</sup> /L)	-0.15 (n=231)	-0.13 (n=488)

### Mean Change Results Adequate and Well Controlled SCI Trials

ISS table 34.3.2 summarized the mean change from baseline hematology lab results. As with the MS trials, the mean changes from baseline in the adequate and well controlled SCI trials were similar for Fampridine SR and placebo. In the SCI trials, for lab results between days 43 and 119, Fampridine SR subjects experienced a slight mean increase in platelet count (4.66) compared to a slight decline (-1.79) for placebo subjects.

### Outlier Results Adequate and Well Controlled MS Trials

ISS table 43.2.2 identified the percentage of subjects with hematology lab results that met clinically significant outlier cutoff criteria. The hematology outlier results were generally similar for Fampridine SR and placebo subjects. Fampridine SR subjects did have a higher risk for low hemoglobin outlier results compared to placebo. I summarize those results below.



#### Hematology Outlier Results, Adequate and Well Controlled MS Trials

Analyte (outlier criteria)	Placebo (n=238)	Fampridine SR (n=507)
Basophils $\geq 0.4$ )	0/234	0.4% (2/500)
Eosinophils ( $\geq 0.7$ )	0.9% (2/234)	0.8% (4/500)
Hematocrit ( $\leq 37\%$ males, $\leq 32\%$ females)	2.1% (5/234)	2.4% (12/500)
Hemoglobin ( $\leq 115$ males, $\leq 95$ females)	0.4% (1/234)	1.2% (6/501)
Lymphocytes ( $\leq 0.5$ or $\geq 4.5$ ))	2.1% (5/234)	3.8% (19/499)
Monocytes ( $\geq 1.5$ )	0.4% (1/234)	0.4% (2/500)
Neutrophils ( $\leq 1.0$ )	0.9% (2/234)	0.2% (1/500)
Platelets ( $\leq 75$ or $\geq 700$ k/mm <sup>3</sup> )	(0/234)	0.4% (2/500)
Leukocytes ( $\leq 2.8$ or $\geq 16$ k/mm <sup>3</sup> )	3.0% (7/234)	3.2% (16/501)

#### Outlier Results Adequate and Well Controlled SCI Trials

ISS table 43.3.2 identified the percentage of subjects with hematology lab results that were outside the normal range. The hematology outlier results in the adequate and well controlled SCI trials were generally similar to those in the MS trials summarized above. The finding in MS trials of an increased risk for low hemoglobin result outliers among Fampridine SR subjects was not replicated in the SCI trials where the low hemoglobin outlier risk for placebo was 2.8% (6/212) and for Fampridine SR was 0.8% (2/257).

#### Urinalysis

##### Adequate and Well Controlled MS Trials

ISS table 44.2.2 provided urinalysis results from the adequate and well controlled MS trials. There were no meaningful differences in risk for urinalysis test results when comparing Fampridine SR and placebo subjects. Despite the increased risk of UTI among Fampridine SR study subjects, they did not appear to have an increase in urinary leukocytes results. Acorda reported that 25.1% (126/502) Fampridine SR subjects had leukocytes on UA compared to 30.9% (73/236) of placebo subjects.

##### Adequate and Well Controlled SCI Trials

ISS table 44.3.2 provided outlier urinalysis results from the adequate and well controlled SCI trials. There were no meaningful differences in outlier risk for urinalysis test results when comparing Fampridine SR and placebo subjects. As with the MS study results, UA results from SCI subjects did not support AE data suggesting an increased risk of UTI with Fampridine SR. Acorda reported that 41% (83/202) of Fampridine SR subjects had positive leukocyte esterase results compared to 42% (78/187) of placebo subjects.



### 7.4.3 Vital Signs

#### Mean Change Results Adequate and Well Controlled MS Trials

ISS table 45.2.2 summarized the mean change from baseline vital sign results from the adequate and well controlled MS trials. There did not appear to be notable mean change vital sign differences between Fampridine SR and placebo in these trials. I provide those results below

#### Vital Sign Change from Baseline to Days 43 through 70, Adequate and Well Controlled MS Trials

Analyte	Placebo (n=238)	Fampridine (n=507)
Diastolic BP (mmHg)	0.06 (n=226)	-0.61 (n=462)
Diastolic BP upright-supine (mmHg)	0.83 (n=109)	-0.41 (n=341)
Systolic BP (mmHg)	0.95 (n=226)	-0.68 (n=463)
Systolic BP upright-supine (mmHg)	0.29 (n=109)	-0.33 (n=342)
Temperature (C)	0.21 (n=226)	0.04 (n=461)
Weight (kg)*	-0.05 (n=237)	-0.35 (n=504)

\*Uses Final Assessment data

#### Mean Change Results Adequate and Well Controlled SCI Trials

ISS table 45.3.2 summarized the mean change from baseline vital sign results from the adequate and well controlled SCI trials. There did not appear to be notable mean change vital sign differences between Fampridine SR and placebo in these trials.

#### Outlier Vital Sign Results Adequate and Well Controlled MS Trials

ISS table 47.2.2 identified the percentage of subjects with vital sign results that met clinically significant outlier cutoff criteria during the adequate and well controlled MS trials. Fampridine SR subjects had a slightly higher risk for low SBP outliers (<90mm Hg and decrease  $\geq 20$ mmHg) compared to placebo (fampridine 4.5%, 23/507; placebo 2.5%, 6/238). The risk for low SBP outlier by fampridine dose was 3.3% (13/400) for 10mg bid; 12% (6/50) for 15mg bid; and 7% (4/57) for 20mg bid. The risks for the remaining vital sign outliers were similar for Fampridine SR and placebo.

#### Outlier Vital Sign Results Adequate and Well Controlled SCI Trials

ISS table 47.3.2 identified the percentage of subjects with vital sign results that met clinically significant outlier cutoff criteria during the adequate and well controlled SCI trials. The risks for vital sign outliers were similar for Fampridine SR and placebo. In these trials, the risk for low SBP outliers among placebo subjects was 16.4% (37/226) was slightly higher when compared to fampridine subjects (14.8%, 41/277).



#### 7.4.4 Electrocardiograms (ECGs)

##### Mean Change Results Adequate and Well Controlled MS Trials

ECGs were performed in the MS adequate and well controlled trials at screening, during study treatment and following treatment. Acorda summarized ECG results from the Adequate and Well Controlled MS Trials in ISS table 48.2.2. For the mean change analyses, I focused on the change from screen to days 43-119, an on-treatment period that included the greatest number of study participants. In the table below, I summarize these results. There did not appear to meaningful differences when comparing Fampridine SR and placebo subjects in these trials.

##### ECG Mean Change from Screening to Days 43 through 119, Adequate and Well Controlled MS Trials

ECG Parameter	Placebo (n=238)	Fampridine SR (n=507)
Heart rate (beats per minute)	-1.6 (n=234)	-1.16 (n=492)
PR interval (msec)	3.21 (233)	2.51 (492)
QRS interval (msec)	2.43 (234)	2.34 (492)
QT Interval (msec)	2.15 (234)	3.10 (492)
QTcF (msec)	3.10 (234)	4.06 (492)

From ISS table 48.2.2

##### Mean Change Results Adequate and Well Controlled SCI Trials

Acorda summarized ECG results from the Adequate and Well Controlled SCI Trials in ISS table 48.3.2. The reported mean changes from these trials were generally small and similar for Fampridine SR and placebo subjects.

##### Outlier ECG Results Adequate and Well Controlled MS Trials

ISS table 50.2.2 identified the percentage of subjects with ECG results that met clinically significant outlier cutoff criteria during the adequate and well controlled MS trials. The risks for the ECG outliers were similar for Fampridine SR and placebo. I summarize that data below.

##### ECG Outlier Results, Adequate and Well Controlled MS Trials

ECG Parameter	Outlier criteria	Placebo (n=238)	Fampridine SR (n=507)
Heart rate	<50 bpm and >25% change from baseline	0/236	0.2% (1/505)
PR	>=200 msec and >25% change from baseline	0/235	1/505
QRS	>=100 msec and >25% change from baseline	1.7% (4/236)	1% (5/505)
QTc	>=450 msec	3.4% (8/236)	2% (10/505)
QT	>=450 msec	2.5% (6/236)	2.8% (14/505)



QTc	>=500 msec	0.4% (1/236)	0/505
QT	>=500 msec	0.4% (1/236)	0/505

From ISS table 50.2.2

#### Outlier ECG Results Adequate and Well Controlled SCI Trials

ISS table 50.3.1 identified the percentage of subjects with ECG results that met clinically significant outlier cutoff criteria during the adequate and well controlled SCI trials. The risks for ECG outliers were similar for Fampridine SR and placebo.

#### QTc Increases from Baseline Adequate and Well Controlled MS Trials

In the adequate and well controlled MS trials, 3.8% (9/236) of placebo subjects experienced an increase in QTc from baseline of >30-≤60 msec compared to 4.6% (23/505) Fampridine SR subjects. In these same trials, 0.4% (1/236) of placebo subjects experienced an increase in QTc of >60 msec compared to no (0/505) Fampridine SR subjects (ISS table 51.2.2).

#### QTc Increases from Baseline Adequate and Well Controlled SCI Trials

In the adequate and well controlled SCI trials, 5.9% (13/221) of placebo subjects experienced an increase in QTc from baseline of >30-≤60 msec compared to 10.4% (28/270) Fampridine SR subjects. In these same trials, 1.8% (4/221) of placebo subjects experienced an increase in QTc of >60 msec compared to 3% (8/270) Fampridine SR subjects (ISS table 51.3.2).

### 7.4.5 Special Safety Studies/Clinical Trials

#### Thorough QT Trial

As part of the development program, Acorda conducted a thorough QT trial to examine the effect of Fampridine SR on cardiac repolarization. The thorough QT trial was reviewed by CDER's Interdisciplinary Review Team in a memo dated 12/04/08. The review team found no significant QT prolongation with either the 10mg or the 30mg Fampridine SR dose. The team found that "The largest upper bounds of the 2-sided 90% CI for the mean difference between Fampridine SR (10 mg and 30 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance." The team reported that assay sensitivity was established in this study by detection of QT prolongation with moxifloxacin.

### 7.5 Other Safety Explorations



### 7.5.1 Dose Dependency for Adverse Events

In proposed labeling for Fampridine SR, Acorda recommends only the 10mg bid dose for MS patients. Because patients will only be treated with one dose, information about dose dependency for AEs has limited utility for prescribers. Assessment of dose dependency may provide supplemental evidence of causal relationships between Fampridine SR and AEs.

The adequate and well controlled clinical trials for MS included Fampridine SR doses of 10mg bid, 15mg bid, and 20mg bid. Acorda reported evidence of a dose response for AEs leading to discontinuation from MS controlled trials. Acorda noted that 8.8% (5/57) of subjects randomized to Fampridine SR 20mg bid discontinued for AEs compared to 2.8% (11/400) randomized to 10mg bid, 2% (1/50) randomized to 15mg bid and 2% (5/238) randomized to placebo. This dose relationship was especially evident for Nervous System Disorder AEs leading to discontinuation where 8.8% (5/57) of MS subjects randomized to Fampridine SR 20mg bid discontinued for Nervous System Disorder AEs compared to 2% (1/50) randomized to 15mg bid, 1.3% (5/400) randomized to 10mg bid and 0.8% (2/238) randomized to placebo (ISS Table 27.2.2).

In the following table I identify those common Fampridine SR -related AEs ( $\geq 2\%$  of fampridine MS subjects and more common than placebo) that also showed evidence of a dose response (risk higher among the 15mg bid and 20mg bid dose groups compared to the 10mg bid dose group).

Common Fampridine SR -related AEs ( $\geq 2\%$  of Fampridine SR MS subjects and More Frequent than Placebo) that Showed Evidence of a Dose Response

AE Preferred term	Placebo (n=238)	Fampridine SR Total (n=507)	Fampridine SR10mg bid (n=400)	Fampridine SR15mg bid (n=50)	Fampridine SR 20mg bid (n=57)
Subjects with 1 or more AEs	73.5% (175)	86.4% (438)	84.8% (339)	94% (47)	91.2% (52)
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)
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)
Multiple sclerosis 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)
Paresthesia	3.4% (8)	5.7% (29)	4.8% (19)	6% (3)	12.3% (7)
Muscle spasms	3.4% (8)	4.1% (21)	3.8% (15)	6% (3)	5.3% (3)
Constipation	2.1% (5)	3.7% (19)	3.5% (14)	4% (2)	5.3% (3)
Pharyngolaryngeal pain	0.8% (2)	2.6% (13)	2.3% (9)	4% (2)	3.5% (2)



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)

From ISS Table 22.2.2a

AEs leading to discontinuation also displayed a dose response in the SCI adequate and well controlled trials. The adequate and well controlled SCI trials included Fampridine SR doses of 25mg bid and 40 mg bid. In these trials, 33.3% (10/30) of 40mg bid subjects discontinued for AEs compared to 15.4% (38/247) of 25mg bid subjects and 3.5% (8/229) of placebo subjects. Dose response for body system AEs leading to discontinuation was seen with Gastrointestinal disorders (40mg bid 13.3%, 20mg bid 3.2%, placebo 0.4%), General disorders (40mg bid 20%, 20mg bid 4%, placebo 0.9%), Nervous system disorders (40mg bid 33.3%, 20mg bid 9.3%, placebo 1.3%), and Psychiatric disorders (40mg bid 20%, 20mg bid 4.9%, placebo 0.4%) (ISS table 27.3.2).

In the following table I identify those common Fampridine SR -related AEs ( $\geq 5\%$  of fampridine SCI subjects and more common than placebo) that also showed evidence of a dose response (risk higher among the 40mg bid dose group compared to the 25mg bid dose group).

Common Fampridine SR AEs ( $\geq 5\%$  of Fampridine SR SCI subjects and More Frequent than Placebo) with Evidence of Dose Response

AE Preferred term	Placebo (n=229)	Fampridine Total (n=277)	Fampridine 25mg bid (n=247)	Fampridine 40mg bid (n=30)
Subjects with 1 or more AEs	86.5% (198)	90.6% (251)	89.5% (247)	100% (30)
Urinary tract infection	16.6% (38)	26% (72)	25.5% (63)	30% (9)
Dizziness	2.6% (6)	15.9% (44)	13% (32)	40% (12)
Constipation	9.2% (21)	15.5% (43)	14.6% (36)	23.3% (7)
Headache	10% (23)	14.1% (39)	11.7% (29)	33.3% (10)
Muscle spasticity	12.2% (28)	13.7% (38)	10.5% (26)	40% (12)
Insomnia	4.8% (11)	13.4% (37)	10.9% (27)	33.3% (10)
Nausea	6.6% (15)	11.9% (33)	10.1% (25)	26.7% (8)
Paresthesia	3.9% (9)	11.6% (32)	10.1% (25)	23.3% (7)
Back pain	4.8% (11)	9.4% (26)	8.1% (20)	20% (6)
Fatigue	5.2% (12)	7.9% (22)	6.1% (15)	23.3% (7)
Anxiety	1.3% (3)	7.6% (21)	4.9% (12)	30% (9)
Pain in extremity	4.8% (11)	7.6% (21)	6.9% (17)	13.3% (4)
Asthenia	3.5% (8)	7.2% (20)	4.9% (12)	26.7% (8)
Musculoskeletal stiffness	4.8% (11)	6.1% (17)	4.9% (12)	16.7% (5)
Abdominal pain	0.9% (2)	5.4% (15)	4% (10)	16.7% (5)
Decreased appetite	1.3% (3)	5.1% (14)	3.6% (9)	16.7% (5)

From Table 22.3.2a



## 7.5.2 Time Dependency for Adverse Events

Examination of time dependency for select AEs is included above in section 7.4.1.

## 7.5.3 Drug-Demographic Interactions

Acorda analyzed TEAE data from adequate and well controlled MS trials for evidence of demographic interactions. Using all TEAEs, Acorda provided AE risks stratified by treatment and by the following demographic factors: sex, age ( $\leq 45$  years, 46- $< 65$  years, and  $> 65$  years), and race (Caucasian, non-Caucasian). From these data I calculated relative risks. I provide the results of this analysis below. For sex and age, there did not appear to be important differences in risk for all AEs. 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.

TEAE Risk from Adequate and Well Controlled MS Trials Stratified by Demographic Factors

Demographic factors	Percent (number) with any TEAE		Relative Risk
Sex	Fampridine (n=507)	Placebo (n=238)	
Male	80.4% (123)	68.1% (64)	1.2
Female	89.0% (315)	77.1% (111)	1.2
Age			
$\leq 45$	87.1% (101)	70.8% (46)	1.2
46- $< 65$	86.6% (316)	76.1% (118)	1.1
$> 65$	80.8% (21)	61.1% (11)	1.3
Race			
Caucasian	86.4% (406)	76.9% (166)	1.1
Non-Caucasian	86.5% (32)	40.9% (9)	2.1

From Table 18, Summary of Clinical Safety, p.66.

In addition to the demographic analysis using all TEAEs summarized above, Acorda also provided tables (32.2.2.1, 32.2.2.2, and 32.2.2.3) that stratified each individual TEAEs by sex, age, and race. I used these tables to look for demographic interactions, focusing on 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.

### Sex

The relative risk for insomnia was higher for females (RR 2.9; Fampridine SR 12.1%, placebo 4.2%) than males (RR 2.0; Fampridine SR 6.5%, placebo 3.2%). Females also had a higher relative risk for balance disorder TEAEs (RR 5.4; Fampridine SR 7.6%, placebo 1.4%) compared to males (RR 3.0; fampridine 3.3%, placebo 1.1%). For the



remaining TEAEs occurring in at least 5% of Fampridine SR subjects and at least twice as commonly compared to placebo, the RR for males and females were similar.

#### Age

The oldest age group (>65 years) included only 26 Fampridine SR subjects and 18 placebo subjects, offering insufficient information to support firm conclusions about TEAE risks in this age group. 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%). For the remaining TEAEs occurring in at least 5% of Fampridine SR subjects and at least twice as commonly compared to placebo, the RR for subjects aged <45 years and subjects 45->=65 years were similar.

#### Race

Most subjects (470 of 507 Fampridine SR and 216 of 238 placebo subjects) in the adequate and well controlled MS trials were Caucasian, limiting the ability to detect differences in relative risk for TEAEs when stratified by race.

### 7.5.4 Drug-Disease Interactions

Acorda looked for evidence of drug-disease interaction among MS patients with and without abnormal renal function. Acorda considered patients with a creatinine clearance  $\leq 80 \text{ ml/min}^2$  as having abnormal renal function (Response to Reviewer questions 7/14/09). For all TEAEs, the relative risk for subjects with abnormal renal function (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. I provide those data below.

#### TEAE Risk Stratified by Renal Function

AE	Normal Renal Function		RR	Abnormal Renal Function		RR
	Fampridine N=409	Placebo N=199		Fampridine N=98	Placebo N=39	
Nausea	7.1% (29)	2.5% (5)	2.8	10.2% (10)	2.6% (1)	3.9
Balance disorder	4.2% (17)	1.5% (3)	2.8	15.3% (15)	0	-

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<sup>2</sup> Estimated creatinine clearance (in mL/minute) was calculated using the Cockcroft/Gault formulae:  
(140-Age)\*Weight / (72 \* Serum Creatinine) for males;  
(140-Age) \* Weight \* 0.85 / (72 \* Serum Creatinine) for females



Dizziness	8.8% (36)	5% (10)	1.8	12.2% (12)	0	-
Insomnia	9% (37)	4% (8)	2.3	16.3% (16)	2.6% (1)	6.3

Data from ISS table 32.2.2.4

### 7.5.5 Drug-Drug Interactions

Using 3 broad categories of concomitant medications, Acorda looked for evidence of drug-drug interactions among MS patients. Acorda classified subjects as to whether they were taking immune modulators, antispasticity medications, or antidepressants. For the 3 classes of concomitant medications studied, there did not appear to be important differences in relative risks for all TEAEs when comparing subjects taking the medications to those not taking the medication (Data from Summary of Clinical Safety, Table 18, pp.66-7).

For those TEAEs occurring 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, the relative risks comparing Fampridine SR and placebo subjects for those taking immune modulators were either similar to or lower than the relative risks for those not taking immune modulators, suggesting no interaction for these events (Data from ISS table 32.2.2.5).

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%)(Data from ISS table 32.2.2.6).

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%) (Data from ISS table 32.2.2.7)



## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Acorda did not include in their NDA submission a review of human cancer diagnoses in the Fampridine SR development program, so I requested a listing of all malignancies diagnosed during Fampridine SR clinical trials. The listing provided by Acorda included the diagnoses that were present in the AE dataset, captured under the body system category “Neoplasms benign, malignant, and unspecified (incl cysts and polyps)”. Therefore, I relied on the AE dataset and relevant ISS tables to review cancers diagnosed during the Fampridine SR clinical trials.

In the integrated safety database, the risk for “Neoplasms benign, malignant, and unspecified (incl cysts and polyps)” body system category TEAEs was 2.1% (45/2115). The malignant neoplasms that occurred in more than one subject were basal cell cancer (n=10), squamous cell cancer (n=5), breast cancer (n=3), and prostate cancer (n=2) (ISS Table 22.0).

In the adequate and well controlled MS trials, there were 3 AEs under the “Neoplasms benign, malignant, and unspecified (incl cysts and polyps)” body system category. All three events (breast cancer, lentigo, and leiomyoma) occurred in Fampridine SR subjects (ISS Table 22.2.2a). In the adequate and well controlled SCI trials, there were 2 TEAEs under the “Neoplasms benign, malignant, and unspecified (incl cysts and polyps)” body system category. Both events (lip and or oral cavity cancer, lipoma) occurred in Fampridine SR subjects (ISS Table 22.3.2a).

The clinical trial database did not suggest a relationship between Fampridine SR and cancer diagnoses. Due to the relatively short duration of exposure and follow up, the Fampridine SR safety database is not expected to support a robust assessment of human carcinogenicity.

### 7.6.2 Human Reproduction and Pregnancy Data

Acorda did not identify any human pregnancy concerns in their submission. They report that adequate and well controlled trials in pregnant women have not been performed. A search of the AE data set identified one Fampridine SR subject (MS-F203EXT, 03004) with a pregnancy. This 35 year old female had her first dose of study medication in this trial on 2/8/06. On 4/14/07 she stopped Fampridine SR due to pregnancy. On 4/25/07 she had an ultrasound that estimated the gestational age at 7 weeks and 3 days. The patient delivered a full term female on 11/27/07. No birth defects were noted.



Acorda reported that the safety of Fampridine SR in infants of breast feeding women is not known.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Acorda did not study the use of Fampridine SR in pediatric subjects.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

#### Overdose

Acorda identified 2 patients in clinical trials that took doses of Fampridine SR that were either higher or more frequent than prescribed. I summarize those events below.

Subject #07019 from study MS-F202, a 47 year old woman with secondary progressive MS (EDSS=4), experienced a partial complex seizure after taking a double dose of 20 mg Fampridine-SR (total 40 mg) to compensate for a previously missed dose. She was found by her father who reported that she was unresponsive with automatisms, and later was confused, tremulous, and diaphoretic. She did not recall the event and did not seek medical treatment. On the day of the overdose (Study Visit 7, 49 days on double blind treatment) the patient's plasma fampridine concentration at approximately 4.5 hours post dose was 79.0 ng/mL and she experienced a partial complex seizure of moderate severity 4 hours later. With reassurances of future compliance, the patient was allowed to continue in the trial but, ten days later, she again took two doses within a short period of time. She became confused for about an hour and was discontinued from the study at that point. An EEG performed 1 week later showed "bilaterally independent mild temporal slowing with some rare sharp waves, more prominent on the left than on the right, indicative of a tendency for partial seizures." Concomitant medications included betaseron and lexapro.

Subject #10 from trial SCI-F301, a 36 year old male spinal cord injury patient experienced an adverse event of accidental study drug overdose. This event was associated with AEs of confusion, disorientation, and sweating. None of these AEs were considered SAEs. The subject recovered on the same date that the overdose was reported. This overdose resulted from the patient mistakenly taking two 25mg tablets at the same time (Response to Reviewer Questions 7/14/09).

In addition to the Fampridine SR clinical trial data, Acorda summarized overdose reports for 4-aminopyridine that they identified from the medical literature (ISS, pp. 367-9). The highest identified 4-aminopyridine overdose came from a report by Smeets and Kunst which described a 22 year old who ingested 2 to 4 grams of 4-aminopyridine (not clear



over what period of time). The patient's serum level was 355µg/L (represents approximately 7 times the therapeutic level, time following ingestion not reported). Reported symptoms included seizures, vomiting, agitation, tachypnea, diaphoresis, incontinence, hypertension (160/104 mmHg), transient right bundle branch block, PVCs, and accelerated idioventricular rhythm. He was treated with gastric lavage, activated charcoal, diazepam, iv fluids, clonazepam, lidocaine, phenytoin, and nitroprusside and recovered in 2 days.

A case series by Burton et al reported on 4 MS patients who ingested 4-aminopyridine doses approximately 10 times higher than expected (due to improper compounding). The authors reported that these patients experienced unusual sensory and behavioral symptoms, and status epilepticus. Three patients recovered but continued to have increased neurological disability when examined 1 year after the event. The fourth patient died following a prolonged hospitalization.

Other symptoms reported in patients who ingested overdoses of 4-aminopyridine include tremulousness, dystonia, choreoathetoid-type movements, fixed stare, facial paralysis, delirium, slurred speech, disorientation, and hypothermia.

In a publication by Badruddin, Menon, and Reder, the authors suggested that 4-aminopyridine toxicity mimics autoimmune-mediated limbic encephalitis. The authors described a 22 year old male with MS who ingested 30 10mg tablets of 4-aminopyridine. The patient initially experienced hypertension (209/108mm Hg) and runs of supraventricular tachycardia. An EEG showed diffuse polyspike and spike-wave discharges that normalized over time (the patient did not experience seizures). An echocardiogram demonstrated hypokinesia with an EF of 24%. MRI showed bilateral medial temporal lobe hyperintensity on T2 and fluid attenuated inversion recovery that did not enhance with gadolinium. CSF had normal cell count, protein, and glucose, but contained oligoclonal bands. Five days after overdose, the patient was awake but had minimal awareness of the examiner and did not speak and his strength was described as 1/5. His CPK peaked at 494U/L. His speech was described as hypophonic and neuropsychiatric evaluation found memory loss. His EF improved to 57% and an endomyocardial biopsy on day 12 did not find inflammation, fibrosis, or toxic inclusion. Nerve conduction velocities were normal, EMG was consistent with myopathy, and muscle biopsy showed mild focal endomysial inflammation with normal blood vessels and architecture. The patient's speech and language and ambulation improved over time. An MRI at 4 months after the overdose no longer showed signal abnormalities. At one year, the patient continued to have difficulty with short term memory and learning new tasks. The authors felt that the cognitive deficits, abulia, and temporal lobe lesions in this patient were similar to the findings in patients with HSV or paraneoplastic limbic encephalitis. The authors explained that in limbic encephalitis, antibodies bind potassium channels of peripheral and central neurons. The authors suggested that blockade by 4-aminopyridine of Kv1.1 and other Kv1 subtypes in the hippocampus and limbic circuit was likely and could explain the amnesia, bradykinesia and impaired visual



learning seen in their overdose patient. The authors felt that the cardiac dysfunction, EMG abnormalities, and skeletal muscle findings were due to a reversible toxic myopathy.<sup>3</sup>

#### Drug Abuse Potential

Acorda reports that there are no indications of abuse potential with Fampridine SR. Acorda notes that preclinical studies indicate that Fampridine SR specifically binds potassium channels and not other receptors or channels and that aside from toxicological effects at higher doses animal studies did not find behavioral effects. In healthy human subjects, fampridine produced dizziness, nausea, and insomnia but did not produce stimulant or depressant effects on mood. In the development program trials, no reports of euphoric mood were seen in the 993 MS and SCI controlled trial patients or the 1029 MS patients overall. Acorda did note that there were 3 reports of euphoric mood among 704 uncontrolled trial SCI patients and 2 reports in non patient safety population (n=382). Acorda also found few cases of hallucination (4/1029 MS patients, 5/704 SCI patients, 1/384 non patient population). Lastly, Acorda reports that the overdose reports are mostly accidental. Acorda noted that there are a few literature reports of attempted abuse of fampridine, but these were one-time events, based on uninformed exploratory behavior, that produced acute negative side effects and did not lead to repeated attempts (response to Reviewer Questions 7/14/09).

#### Withdrawal

In Fampridine SR trials, investigators recorded AEs that occurred following discontinuation of study medication, allowing for an assessment of withdrawal effects. ISS table 22.1.1c summarized the TEAEs occurring after cessation of trial medication for all MS and SCI trials. The TEAEs reported by at least 1% of MS and SCI patients following discontinuation of Fampridine SR were urinary tract infection (2.6%, 40/1510), fall (2.2%, 33/1510), asthenia (1.6%, 24/1510), fatigue (1.6%, 24/1510), muscle spasticity (1.2%, 18/1510), muscle spasms (1.1%, 16/1510), and MS relapse (1.1%, 16/1510).

In table 22.2.2c, Acorda summarized TEAEs occurring after stopping study medication for the adequate and well controlled MS trials. The post treatment TEAEs that occurred in at least 1% of Fampridine SR subjects and more frequently when compared to placebo were urinary tract infection (Fampridine SR 3.2%, 16/507, placebo 0.8%, 2/238), MS relapse (Fampridine SR 2.2%, 11/507, placebo 0.4%, 1/238), asthenia (Fampridine SR 2.2%, 11/507, placebo 0.4%, 1/238), fatigue (Fampridine SR 2%, 10/507, placebo 0), balance disorder (Fampridine SR 1.4%, 7/507, placebo 0), difficulty in walking (Fampridine SR 1.2%, 6/507, placebo 0), muscle spasticity (Fampridine SR 1%, 5/507, placebo 0.8%, 2/238), cystitis (Fampridine SR 1%, 5/507, placebo 0), and upper respiratory tract infection (Fampridine SR 1%, 5/507, placebo 0.8%, 2/238).

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3 Badruddin A, Menon RS, Reder AT. 4-Aminopyridine Toxicity Mimics Autoimmune-Mediated Limbic Encephalitis, *Neurology* 2009;72;1100-1101.



In table 22.3.2c, Acorda summarized AEs occurring after stopping study medication for the adequate and well controlled SCI trials. The post treatment TEAEs that occurred in at least 1% of Fampridine SR subjects and more frequently when compared to placebo were constipation (Fampridine SR 1.8%, 5/277, placebo 0.9%, 2/229), fatigue (Fampridine SR 1.4%, 4/277, placebo 0), oedema peripheral (Fampridine SR 1.1%, 3/277, placebo 0.4%, 1/229), urinary tract infection (Fampridine SR 2.9%, 8/277, placebo 1.3%, 3/229), muscle spasms (Fampridine SR 2.2%, 6/277, placebo 1.7%, 4/229), musculoskeletal stiffness (Fampridine SR 1.4%, 4/277, placebo 0.9%, 2/229), somnolence (Fampridine SR 1.1%, 3/277, placebo 0), anxiety (Fampridine SR 1.1%, 3/277, placebo 0.4%, 1/229), and decubitus ulcer (Fampridine SR 1.1%, 3/277, placebo 0).

The AE data set included one study subject with an AE of drug withdrawal. This 53 year old male spinal cord injury patient participating in study SCI F201EXT experienced “excess sweating –assoc. withdrawal symptom”. This event was classified as severe but was not an SAE. The recorded outcome of this event was “resolved”.

## **7.7 Additional Submissions / Safety Issues**

There were no data from submissions other than those noted above.

## **8 Postmarket Experience**

Fampridine is not approved for use and therefore there are no available post marketing data.





U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoeconomics and Statistical Science  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 22,250

**Drug Name:** Fampridine-SR Tablets

**Indication(s):** Multiple Sclerosis

**Applicant:** Acorda Therapeutics

**Date(s):** Document Date: January 30, 2009  
PDUFA Date: July 30, 2009

**Review Priority:** Priority Review

**Biometrics Division:** Division I

**Statistical Reviewer:** Sharon Yan

**Concurring Reviewers:** Kun Jin, Team Leader  
James Hung, Division Director

**Medical Division:** Division of Neurological Drug Products

**Clinical Team:** Kachikwu Illoh, M.D., Clinical Reviewer  
Billy Dunn, M.D., Clinical Team Leader  
Eric Bastings, M.D., Deputy Director

**Project Manager:** James Reese

**Keywords:**

Link to DBII key Words:

[http://cdernet/ob\\_apps/ob/edocs/eDocs\\_Main\\_Single.cfm?id=189](http://cdernet/ob_apps/ob/edocs/eDocs_Main_Single.cfm?id=189)



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# **1. EXECUTIVE SUMMARY**

## **1.1 Conclusions and Recommendations**

Fampridine-SR is proposed as a treatment for patients with multiple sclerosis (MS) for improvement of walking ability. The primary efficacy variable for both pivotal studies F203 and F204 was response rate, which was based on timed 25-foot walking test. In both studies response rate for Fampridine-SR group was statistically significantly higher than the response rate for placebo group. Statistical significance is also achieved in the 3-step test that comprised the primary analysis for Study F203.

## **1.2 Brief Overview of Clinical Studies**

Fampridine-SR is proposed as a treatment for patients with multiple sclerosis (MS) for improvement of walking ability. The clinical development program for Fampridine-SR consists of 3 clinical studies MS-F202, MS-F203, and MS-F204, in which MS-F203 and MS-F204 are pivotal studies and are covered in this review.

The two pivotal Phase 3 studies (MS-F203 and MS-F204) are parallel group, randomized, double-blind study comparing Fampridine-SR 10 mg b.i.d. with placebo. The primary efficacy variable was Timed-Walk Response, defined as consistent improvement in walking speed based on the T25FW (T25FW Responder Analysis) where at least three of the four on-treatment efficacy visits had walking speeds faster than the fastest walking speed achieved among five off-treatment visits (i.e. the four pre-treatment visits and the post-treatment visit two weeks after drug withdrawal). The 12- item Multiple Sclerosis Walking Scale and the Subject Global Impression and Clinician Global Impression were used to validate the clinical meaningfulness of the Timed-Walk response criterion. The duration of the double-blind period was 14 weeks for F-203 and 8 weeks for F-204.

## **1.3 Statistical Issues and Findings**

In Study F203, 301 subjects were randomized and 283 completed the study. A significantly greater proportion of patients taking Fampridine-SR had a consistent improvement in walking speed, the study's primary outcome, compared to patients taking placebo (34.8% vs. 8.3%) as measured by the Timed 25-Foot Walk ( $p < 0.001$ ). In addition, the effect was maintained throughout the 14-week treatment period ( $p < 0.001$ ) and there was a statistically significant improvement in the 12-Item MS Walking Scale (MSWS-12) for walking responders vs. non-responders ( $p < 0.001$ ). Thus, all three components of the pre-specified primary endpoint were achieved.



In MS-F204, a total of 239 patients with MS were randomized and 227 completed this study. 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 ( $p < 0.001$ ).

The primary efficacy endpoint, the responder status based on timed 25-foot walking test, was not a conventional or validated endpoint. In order to validate this endpoint, a 3-step analysis was defined and statistical significance needed to be achieved. Although both studies have achieved statistical significance in all 3 steps, the reviewer has doubts about the validation of the primary endpoint of response status.

## **2. INTRODUCTION**

### **2.1 Overview**

Fampridine-SR is proposed as a treatment for patients with multiple sclerosis (MS) for improvement of walking ability. The clinical development program for Fampridine-SR included 2 pivotal studies, MS-F203 and MS-F204.

The two pivotal Phase 3 studies (MS-F203 and MS-F204) are parallel group, randomized, double-blind study comparing Fampridine-SR 10 mg b.i.d. with placebo. The primary efficacy variable was Timed-Walk Response, defined as consistent improvement in walking speed based on the T25FW (T25FW Responder Analysis) where at least three of the four on-treatment efficacy visits had walking speeds faster than the fastest walking speed achieved among five off-treatment visits (i.e. the four pre-treatment visits and the post-treatment visit two weeks after drug withdrawal). The 12- item Multiple Sclerosis Walking Scale and the Subject Global Impression and Clinician Global Impression were used to validate the clinical meaningfulness of the Timed-Walk response criterion. The duration of the double-blind period was 14 weeks for F-203 and 8 weeks for F-204.

Both studies were conducted in centers in US and Canada. A total of 301 subjects were randomized in F203, and 239 subjects were randomized in F204.

### **2.2 Data Sources**

All document reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for the submission is listed below:

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### **3. STATISTICAL EVALUATION**

#### **3.1 Evaluation of Efficacy**

##### **3.1.1 Study F203**

###### **3.1.1.1 Description of the Study**

The objectives of this study were to assess the safety and efficacy of Fampridine-SR in patients diagnosed with MS. The study was to evaluate the efficacy of Fampridine-SR in walking speed, as measured by the Timed 25 Foot Walk and performed in a response analysis, to determine numbers of patients who showed a consistent improvement while on drug.

This was a Phase 3, 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.

A total of 240 patients from approximately 30 centers in the U.S. and Canada were to be randomized to one of two treatment groups, 10 mg b.i.d. Fampridine-SR or placebo, in a ratio of 3:1 (three patients in the active treatment group to every one patient in the placebo treatment group).

Upon meeting the eligibility criteria through assessments at Visit -1, subjects returned to clinic after one week for assessments at Visit 0, which represented the beginning of a single-blind two-week placebo run-in period. Subjects returned for another assessment at Visit 1 after one week. Immediately following the placebo run-in, patients were randomized at Visit 2 to one of two treatment arms (Fampridine-SR or placebo) to begin 14 weeks of treatment.

Visit 6 marked the end of the 14-week randomized treatment period. At this visit, patients began a four-week follow-up period during which no study medication was to be taken. Patients returned to the clinic after two weeks and after 4 weeks for follow-up assessments at Visit 7 and Visit 8.



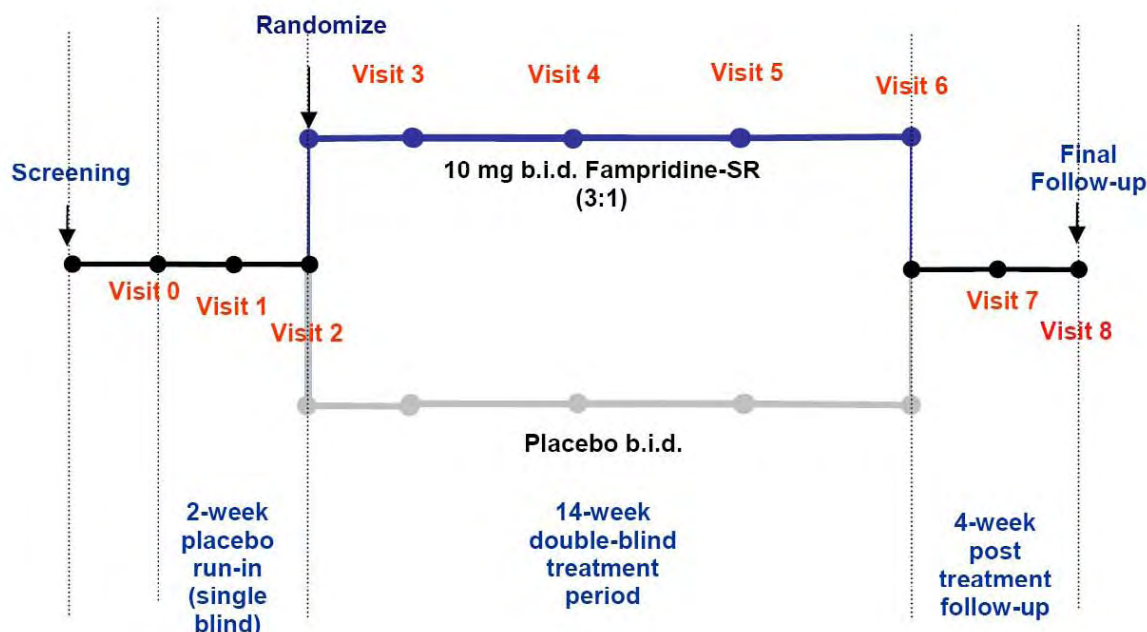


Figure 1 General Scheme of the Overall Study Design (Source: Figure 1 of Sponsor’s Study Report)

### 3.1.1.2 Efficacy Evaluation

#### Background

In Acorda’s previous phase II study MS-F202, the primary efficacy analysis of the percent change from baseline in average walking speed on the T25FW failed to show treatment effect of Fampridine. In a post hoc analysis, a response criterion was defined based on consistently faster walking speeds while on drug than when not on drug. This criterion was met by 36.7% of patients in the combined Fampridine-SR group versus 8.5% of the patients in the placebo group.

This responder variable was applied prospectively in the current study as the first step in a three stage, stepwise analysis that defines the primary endpoint.

#### The Primary Efficacy Variable

The primary efficacy variable was responder status, based on consistency of response in walking speed on the Timed 25 Foot Walk. A three stage, stepwise analysis based on this variable was to be used to establish a positive outcome on the primary endpoint and to define a successful trial.

The first step was to show a significantly greater proportion of responders in the Fampridine-SR group as compared to the placebo group. The second step was to provide validation of the clinical meaningfulness of this primary efficacy variable by testing whether the responders register a significant improvement in MSWS-12 score, when compared to non-responders,



regardless of treatment group. The third step was to confirm maintenance of effect by testing whether those patients who responded to Fampridine-SR would still register a significant improvement in walking speed relative to placebo-treated patients at the last observed double-blind visit ( i.e., the change from baseline in walking speed at the double-blind endpoint).

### **Responder Criteria and Data Handling**

At each study visit, there were to be two trials of the Timed 25-Foot walk. Time is recorded in seconds using a stopwatch. The walking speed for a particular study visit was to be derived by calculating the average of the walking speeds for Trial 1 and Trial 2 of that visit. If either trial was missed, then the walking speed for that visit was to be the walking speed from the completed trial. If both trials were missed, the walking speed for the visit was to be considered slower than the maximum speed recorded during the non-double-blind period.

A responder was defined as a patient 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). The last follow-up visit (Visit 8) was to be primarily a safety visit and was not to be used as part of the responder criterion. Patients with fewer than three on-treatment walking speed measurements were to be categorized as non-responders.

The MSWS-12 is a 12-question questionnaire that asks patients to rate limitations of their mobility due to MS during the preceding two weeks on a 5-point scale (from 1= not at all to 5 = extremely). For a visit in which at least 50% of the component questions were answered but at least one was not, scores from unanswered component questions were to be imputed using the respondent-specific mean score. For a visit in which at least 50% of the component questions were not answered, the MSWS-12 score was to be considered missing. For a particular visit the MSWS-12 Score was to be calculated by summing the 12 components and transforming to a scale with a range of 0 to 100.

### **Analysis of Efficacy Variables**

The principal analysis of efficacy was to be based on the ITT population. The intent-to-treat (ITT) population was to consist of all randomized patients to whom double-blind study medication was dispensed and who had at least one efficacy (Timed 25 Foot Walk and MSWS-12) evaluation during the treatment period.

For this study to be considered a positive study, all three of the conditions listed below must have been met in the following stepwise order:

1. Fampridine-SR had to be statistically superior to placebo with respect to the primary efficacy variable – the proportion of responders
2. The responders had to be statistically superior to the non-responders with respect to the average change from baseline in the MSWS-12 (i.e., it had to be demonstrated that primary efficacy variable was clinically meaningful)



3. Fampridine-SR responders had to be statistically superior to the placebo group with respect to the endpoint change from baseline (i.e., it had to be demonstrated that among patients who respond to Fampridine-SR, the response was maintained).

The overall significance level of the above was to be no greater than 0.05.

### **Step 1: Responder Analysis**

Treatment differences in the proportion of responders between Fampridine-SR-treated and placebo-treated groups were to be analyzed by the Cochran-Mantel-Haenszel (CMH) test, controlling for center.

A sensitivity analysis of the responder criterion was to be performed to determine whether missing data on the follow-up visit might have affect the overall outcome. A modified responder was defined in the same manner with the following restriction: any patient treated with Fampridine-SR who was considered a responder for the primary analysis but who was missing the first post-treatment visit (Visit 7) was to be considered a non-responder for the purpose of the sensitivity analysis. This restriction was not to be applied to placebo patients. That is, if a placebo patient was a responder for the primary analysis, the patient would still be a modified responder for the sensitivity analysis, regardless of whether or not the patient missed the first post-treatment visit (Visit 7).

### **Step 2: Validation Procedure**

Validation of the clinical meaningfulness of the responder variable (based on consistently improved double-blind walking speeds) was to be performed by testing whether responders perceive improvement in their walking disability, as registered by the MSWS-12 score, when compared to non-responders. The average change from baseline in the MSWS-12 score over the double-blind treatment period was to be analyzed with respect to responder status (responders vs. non-responders) by an analysis of variance model, with effects for responder status and center.

### **Step 3: Change from Baseline in Walking Speed**

For the walking speed endpoint change from baseline, differences between the three responder analysis groups (placebo, Fampridine-SR non-responders, and Fampridine-SR responders) were to be analyzed by t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis group and center. The primary efficacy comparison of interest is the Fampridine-SR responders versus placebo.

For walking speed only, the endpoint in walking speed was to be derived based on the last observed (non-missing) double-blind visit walking speed.

If assumptions of normality were grossly violated, nonparametric analysis via the CMH test controlling for center, using the row mean score statistic and standardized midranks (i.e., in SAS, scores=modridit) were to be employed.



## **Analysis for Secondary Efficacy Variables**

A number of secondary efficacy variables were proposed. In order to maintain the overall alpha level less than or equal to 0.05, a prospectively defined stepwise procedure was to be performed for the secondary variables. If statistical significance was not achieved at a particular step, no subsequent step would be eligible to be declared statistical significant. Provided that the primary endpoint was achieved, eligibility for the secondary objective variables was to be determined in the following stepwise order:

1. the Fampridine-SR responders must be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the double-blind period;
2. the Fampridine-SR non-responders must 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 must 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 must be validated by demonstrating patients who have consistent improvements significantly perceive this improvement (via the average SGI score during the double-blind) versus those who do not;
5. the Fampridine-SR responders must be statistically superior to the placebo group with respect to the average change from baseline in Ashworth score during the double-blind period;
6. the Fampridine-SR non-responders must be statistically superior to the placebo group with respect to the average change from baseline in Ashworth score during the double-blind period.

For the endpoint change from baseline and each of the secondary objective variables, differences between the three responder analysis groups (placebo, Fampridine-SR non-responders, and Fampridine-SR responders) were to be analyzed by t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis group and center.

If assumptions of normality were grossly violated, nonparametric analysis via the CMH test controlling for center, using the row mean score statistic and standardized midranks (i.e., in SAS, scores=modridit) were to be employed.

### **3.1.1.3 Study Population Results**

A total of 301 subjects were randomized: 72 to the placebo group and 229 to the Fampridine-SR group. One subject was “unable to digest the study medication” during the placebo run-in period and was excluded from the safety population. The subject was randomized to Fampridine group, but did not take any double-blind medication. A total of 18 subjects discontinued study prematurely. Among the 17 subjects discontinued from the study in Fampridine group, 11 were due to AEs, 4 withdrew consent, and 2 due to other reasons. One placebo-treated subject discontinued due to lost of follow-up. A total of 5 subjects, all randomized to Fampridine



(including one subject who did not take any double-blind medication), discontinued study prior to completing any of the scheduled double-blind walking speed and MSWS-12 assessments, and therefore were excluded from the ITT patient population. The primary efficacy analysis was based on the ITT population which was comprised of 296 patients (72 patients randomized to placebo and 224 to Fampridine-SR).

The safety population consisted of 68.3% females and 31.7% males. There were more males in the placebo group than in the Fampridine group (40.3% vs. 28.9%). The majority of the patients were Caucasian (92.7%). The mean age of the patients were 51.4 years (range: 26-70 years). Most of the patients (53.3%) had a diagnosis type of secondary progressive followed by relapsing remitting (27.7%), primary progressive (15.0%) and progressive-relapsing (4.0%). The mean duration of disease was 13.3 years (range: 0.4- 41.7 years), while the mean Expanded Disability Status Scale (EDSS) score at screening was 5.8 (range: 2.5-7.0).

#### **3.1.1.4 Efficacy Results**

The efficacy results presented in this section represents the analyses performed by the sponsor and confirmed by the reviewer. Additional analyses performed by the reviewer are noted where they are presented.

##### **3.1.1.4.1 Analysis of Primary Efficacy Variable**

The first step of the primary analysis is to compare the response rate between the placebo group and the Fampridine group. A total of 78 (34.82%) of the 224 Fampridine-treated subjects and 6 (8.33%) of the 72 placebo-treated subjects were responders. The treatment difference is statistically significant with a p-value of <.0001.

A prospectively planned sensitivity analysis was performed. In this analysis, a Fampridine responders who missed first post-treatment visit (Visit 7) was re-categorized as non-responders. Responder status for the placebo-treated subjects was not changed. Two such Fampridine-treated subjects had their status changed from responders to non-responders, resulting in 76 responders in the Fampridine group compared to 6 responders in the placebo group. The treatment difference in this modified responder analysis is still statistically significant with a p-value of <.0001.

To validate the clinical meaningfulness of the responder variable, the 84 responders (78 in the Fampridine-SR group and 6 in the placebo group) were compared against the 212 non-responders (146 in the Fampridine-SR group and 66 in the placebo group) on the average change from baseline in MSWS-12 to determine if patients with consistently improved walking speeds could perceive benefit relative to those patients who did not. The mean reduction from baseline in average MSWS-12 over the double-blind period was 6.84 among the responders, compared to an increase of 0.05 among the non-responders. The difference is statistically significant with a p-value of 0.0002.



The last step of the primary analysis is to compare between the Fampridine responders and placebo patients in the maintenance of walking speed evaluated by change from baseline to endpoint. The mean changes in walking speed from baseline to the end of the double-blind were 0.10 ft/sec, 0.17 ft/sec, and 0.52 ft/sec for the placebo group, Fampridine non-responder group and Fampridine responder group, respectively. The treatment difference between Fampridine responder group and the placebo group was statistically significant with a p-value of < .001. The treatment difference between Fampridine non-responder group and placebo group is not significant (p=0.483) and the treatment difference between Fampridine responder group and Fampridine non-responder group is statistically significant (p < .001).

By achieving the statistical significance in the above 3 steps, the study has achieved statistical significance in the primary efficacy analysis.

Additional analyses are performed by the reviewer in order to shed some light in interpreting the complex of the study results.

In addition to the comparisons between Fampridine responders and placebo group in the change from baseline in 25-foot walking speed, Fampridine group and placebo group are also compared to assess the treatment difference without regarding to responder status. From Visit 2 to Visit 6, the mean walking speed for Fampridine group increased by 0.21 ft/sec, representing 1.05 second improvement for the 25-foot walk, compared to an increase for placebo group of 0.05 ft/sec, representing 0.27 second improvement in time. The difference is statistically significant with a p-value of 0.0342.

**Table 1 Mean Change from Visit 2 to End of Treatment Period in Walking Speed by Treatment Group - F203 (Source: Reviewer's Analysis)**

<b>Mean (SD) in Walking Speed (ft/sec)</b>	<b>Placebo N=71</b>	<b>Fampridine N=222</b>
Visit 2	2.11 (.79)	2.13 (.84)
Visit 6 (LOCF)	2.16 (.81)	2.34 (1.05)
<b>Change</b>	.05 (.45)	.21 (.56)
<b>Difference in Time (sec)</b>	.27	1.05
Nominal p-value		.0342

Mean walking speed at each visit by treatment group and response status are calculated and presented in the following table.



**Table 2 Average Walking Speed (ft/sec) by Visit and Response Status (Observed Cases) (Source: Reviewer's Analysis)**

	Pre-Treatment Visit				Double-blind Treatment				Follow-up
	Visit -1	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
<b>Placebo</b>									2.19
N	72	72	72	71	72	71	70	70	
Mean	2.02	2.03	2.09	2.12	2.11	2.23	2.20	2.17	64
									2.19
# Non-resp	66	66	66	65	66	65	64	64	
Mean	2.04	2.03	2.09	2.11	2.09	2.20	2.17	2.14	6
									2.23
#Resp	6	6	6	6	6	6	6	6	
Mean	1.82	2.06	2.09	2.18	2.32	2.60	2.52	2.58	
<b>Fampridine</b>									2.05
N	224	222	221	222	223	218	214	213	
Mean	2.00	2.00	2.07	2.14	2.34	2.34	2.35	2.37	141
									2.04
# Non-resp	146	145	145	144	146	140	137	136	
Mean	2.01	1.96	2.06	2.10	2.22	2.20	2.20	2.23	76
									2.07
#Resp	78	77	76	78	77	78	77	77	
Mean	1.98	2.08	2.10	2.21	2.57	2.59	2.61	2.60	
<b>Non Resp</b>									
N	212	211	211	209	212	205	201	200	205
Mean	2.02	1.98	2.07	2.11	2.18	2.20	2.19	2.20	2.08
<b>Responder</b>									
N	84	83	82	84	83	84	83	83	82
Mean	1.97	2.08	2.10	2.21	2.55	2.59	2.61	2.60	2.08

The average walking speed was comparable between the two treatment groups during the pre-treatment visits. The average speed was below 2.05 ft/sec before placebo run-in period (Visits -1 and 0), and went up slightly to above 2.10 ft/sec after the placebo run-in period. By the end of the double-blind treatment period, the walking speed can be summarized as follows:

1. Subjects improved their walking speed during the pre-treatment period and double-blind treatment period regardless of treatment group or responder status.
2. At Visit 2 assessment (the last visit before randomization), the mean walking speed for placebo group was 2.12 ft/sec, represented 11.79 seconds used in the 25 feet walking test. The mean walking speed for Fampridine group at the visit was 2.14 ft/sec, represented 11.68 seconds for the test. At the Visit 6 (the end of the treatment visit), the mean walking speed of 2.17 ft/sec for placebo-treated patients represented a time of 11.52 seconds on the 25-feet walking test and the mean walking speed of 2.37 ft/sec for Fampridine-treated patients represented a time of 10.55 seconds on the same test. The treatment difference in walking speed represented a difference of about 1 second in time spent on the walking test.
3. The walking speed achieved during the double-blind period was generally maintained through the end of the double-period.
4. There was little treatment difference among the non-responders, and there was little treatment difference among the responder at the end of the double-blind treatment period. When combining the treatment groups, the responders improved walking speed quite significantly from the beginning of the treatment group, and maintained so through the end of the treatment period.



5. At the end of the double-blind treatment period, the walking speed between the non-responders and responders represented a difference of 1.75 seconds in time spent on the 25-feet walking test. For the placebo-treated patients, non-responders spent 1.99 seconds more than the responders. The difference for Fampridine-treated patients was 1.60 seconds.

Analysis of MSWS-12 scores is also performed. The mean change from baseline to Visit 6 in MSWS-12 scores was -1.56 for Fampridine group and 3.59 for placebo group. The difference yielded a nominal p-value of 0.0633. Means of MSWS-12 scores are also calculated by treatment group and response status. The MSWS-12 score ranges 0 to 100 with 100 indicating extreme illness.

**Table 3 Mean MSWS-12 Scores by Treatment Group and Response Status (Observed Cases) (Source: Reviewer's Analysis)**

	Pre-treatment		Double-blind				Follow-up
	Visit 0	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
<b>Placebo</b>							
N	72	72	72	70	70	70	71
Mean	69.93	67.03	67.61	67.56	68.44	72.05	73.42
# Non-resp	66	66	66	64	64	64	65
Mean	70.67	67.85	68.45	69.08	70.17	74.12	75.00
# Resp	6	6	6	6	5	6	6
Mean	61.81	57.99	58.33	51.39	50.00	50.00	56.25
<b>Fampridine</b>							
N	222	223	222	219	215	213	220
Mean	72.31	68.98	66.57	68.11	68.85	69.28	75.89
# Non-resp	145	146	144	141	137	136	143
Mean	71.50	69.56	67.43	71.09	71.06	72.11	74.81
# Resp	77	77	78	78	78	77	77
Mean	73.84	67.86	64.98	62.71	64.96	64.29	77.90
<b>Non-resp</b>							
N	211	212	210	205	201	200	208
Msws	71.24	69.03	67.75	70.46	70.78	72.75	74.87
<b>Responder</b>							
N	83	83	84	84	84	83	83
Msws	72.97	67.15	64.51	61.90	63.89	63.25	76.33

Overall, placebo group had an average of about 2 points increase and Fampridine group had an average of about 3 points reduction in MSWS-12 scores from Visit 0 to Visit 6. There was little change in MSWS-12 scores among the non-responders while the responders had an average of 9.7 point decrease. However, most of the 9.7 points decrease among the responders occurred from Visit 0 to Visit 2 during the pre-treatment period. Breaking down to the treatment, placebo responders had 3.82 points decrease during the pre-treatment period and 7.99 points decrease



during the treatment period. Fampridine responders had 5.98 points decrease during the pre-treatment period and 3.57 points decrease during the treatment period.

### 3.1.1.4.2 Analysis of Secondary Efficacy Variables

Average change from baseline in LEMMT and Ashworth scores were analyzed. In this analysis, the average change was obtained by averaging all double-blind available scores minus the average of all pre-treatment scores. The following table presents the results from comparisons between treatment groups and between responder groups in LEMMT and Ashworth scores. The nominal p-values were obtained from comparisons of each group versus placebo group.

**Table 4 Average Change from Baseline in LEMMT and Ashworth Scores - F203 (Source: Reviewer's Analysis)**

Study F203	Placebo	Fampridine	Fampridine	
			Responders	Non-Responders
<b>LEMMT</b>				
Mean (SD)	0.04 (.22)	0.13 (.21)	0.18 (.19)	0.11 (.21)
Nominal p-value		.0029	.0002	.0207
<b>Ashworth</b>				
Mean (SD)	-0.07 (.28)	-0.16 (.34)	-0.13 (0.36)	-0.17 (.33)
Nominal p-value		.0210	.0899	.0240

For the Ashworth scores, Fampridine non-responders had larger improvement than Fampridine responders in average. Based on the closed testing procedure, statistical significance for LEMMT has been reached in the comparisons of Fampridine versus placebo, Fampridine responders versus placebo, and Fampridine non-responders versus placebo.

## 3.1.2 Study F204

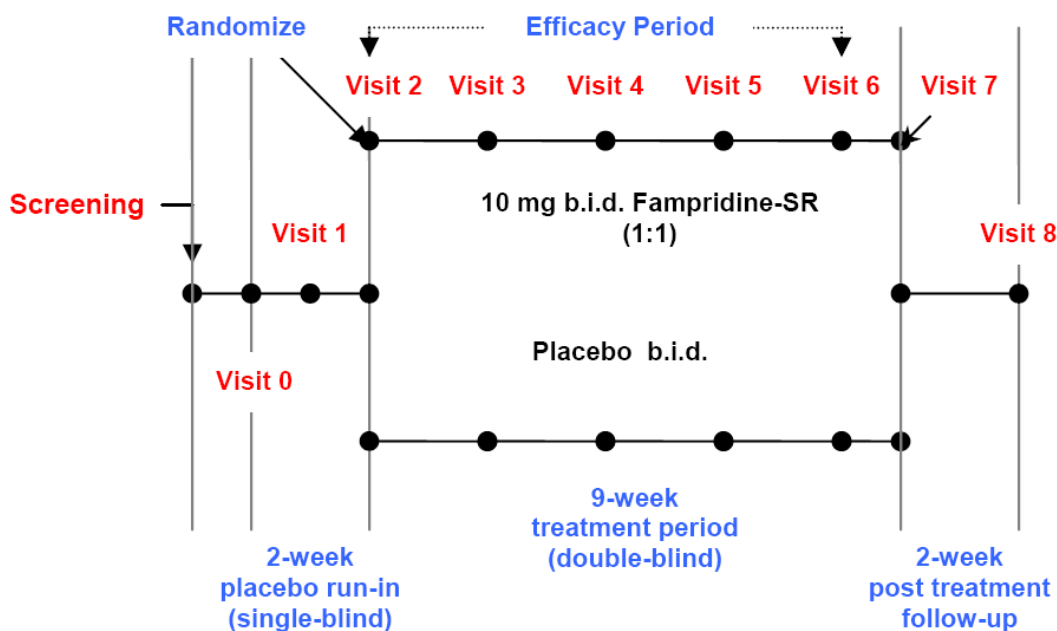
### 3.1.2.1 Description of the Study

The primary efficacy objective was to assess whether the proportion of patients who experienced consistent improvements in walking speed while on drug would be greater in the Fampridine-SR-treated group compared to the placebo-treated group. This “response to drug” criterion was considered validated as a clinically meaningful measure in study F203.

The design of this study is the similar to that of F203 except that the double-blind treatment period is shorter. This was a Phase 3, multi-center, double-blind, placebo-controlled, parallel group, 14-week study (one week post screening, two weeks of single-blind placebo run-in, nine weeks of double-blind treatment, and two weeks of no-treatment follow-up). The treatment



group comparisons with respect to efficacy were based on the first eight weeks of double-blind treatment; end of dosing interval activity (pharmacokinetics and pharmacodynamics of drug) was evaluated at the end of the final week of double-blind treatment. Approximately 200 patients were to be randomized in a ratio of 1:1 to one of two treatment groups, 10 mg b.i.d. Fampridine-SR or placebo. The following figure displays the general scheme.



**Figure 2 General Scheme of the Overall Study Design – F204 (Source: Figure 1 of Sponsor’s Study Report)**

The target population consisted of patients diagnosed with clinically definite MS. Patients were to be enrolled at approximately 35 investigational centers in the U.S. and Canada, with each site enrolling approximately 6 patients until a minimum of 200 patients had been randomized.

### 3.1.2.2 Efficacy Evaluation

#### The Primary Efficacy Variable

The primary goal of this study is to confirm the efficacy results obtained in study F-203. The primary efficacy variable is responder status defined similarly as in F-203. However, this efficacy variable is considered validated by study F-203, and thus the validation and maintenance of the walking speed are not part of the primary analysis in this study. However, to be consistent with study MS-F203, the additional measurements (Ashworth assessment of spasticity, MSWS-12, SGI, and CGI) collected in Study F-203 were also assessed in the MS-F204 study.



The primary efficacy variable was responder status, based on consistency of response in walking speed on the Timed 25 Foot Walk.

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 pre-treatment visits (Screening Visit, Visits 0, 1 and 2) and the post-treatment visit (Visit 8). 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. As such, this visit (Visit 7) was not part of the responder criterion.

For the calculation of the patient's responder status, if a walking speed for an eligible double-blind visit (Visits 3 through 6) was missing, the walking speed for that double-blind visit was considered slower than the maximum walking speed during the non-double-blind period. Patients with walking speeds at fewer than three of the eligible double-blind treatment visits therefore were automatically categorized as Non-responders.

### **Secondary Efficacy Variable**

The secondary efficacy variable was the average change from baseline in LEMMT during the eight-week, double-blind treatment period.

### **Analysis of Efficacy Variables**

Treatment differences between fampridine-treated and placebo-treated groups in the proportion of Timed Walk Responders were analyzed by the Cochran-Mantel-Haenszel (CMH) test, controlling for center.

A sensitivity analysis of the responder criterion was to be performed on the modified responder variable. A modified responder variable was defined in the same manner as a Responder with the following restriction: Any patient treated with Fampridine-SR who was considered a Responder for the primary analysis but who was missing the post-treatment visit (Visit 8) was considered a Non-responder for the modified responder variable. This restriction was not to be applied to placebo patients. That is, if a placebo patient was a Responder for the primary analysis, the patient was also a modified Responder for the sensitivity analysis, regardless of whether or not the patient missed the post-treatment visit (Visit 8).

With respect to the secondary efficacy variable (average change from baseline LEMMT score), it was hypothesized that in addition to patients who experienced a consistent improvement in walking speed with treatment, Fampridine-SR may also have benefits for patients who did not experience a consistent improvement in walking speed. In order to maintain the overall alpha level less than or equal to 0.05, a prospectively defined, stepwise procedure was to be performed for the secondary efficacy variable. If statistical significance was not achieved at the first step, the second step would not be eligible to be declared statistical significant. Provided that there was a statistically significant difference between the two treatments on the primary endpoint, eligibility for the secondary variable was to be determined in the following stepwise order:



1. the Fampridine-SR Timed Walk Responders had to be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the eight-week double-blind period;
2. the Fampridine-SR Timed Walk Non-responders had to be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the eight-week double-blind period.

Differences in the average change from baseline in LEMMT between the three walking speed responder analysis groups (placebo, fampridine Timed Walk Non-responders, and fampridine Timed Walk Responders) were analyzed by t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis group and center. The normality assumption was assessed via the Shapiro-Wilk test. Should the normality assumption be grossly violated, nonparametric analysis via the CMH test, controlling for center: using the row mean score statistic and standardized midranks (i.e., in SAS, scores=modridit) was to be employed to analyze each of the three pairwise responder group comparisons.

### **3.1.2.3 Population Results**

A total of 239 patients were randomized into the study at 39 centers in the U.S. and Canada: 119 were assigned to placebo and 120 to 10 mg b.i.d. Fampridine-SR. All 239 patients took at least one dose of investigational drug and were included in the safety population. A total of 12 patients, 5 in the placebo group and 7 in the Fampridine group, discontinued study prematurely. Two patients, one for each treatment group, discontinued from the study prior to completing any scheduled assessments and were excluded from the (modified) ITT population, which included 237 patients (118 placebo/119 Fampridine-SR).

The safety population consisted of 67.8% females and 32.2% males. There were more males in the placebo group than in the Fampridine group (37.8% vs. 26.7%). The majority of the patients were White (91.2%). The mean age of the patients were 51.7 years (range: 24-73 years). Almost half of the patients (49.4%) had a diagnosis type of secondary progressive followed by relapsing remitting (34.7%), primary progressive (13.0%) and progressive-relapsing (2.9%). The mean duration of disease was 13.76 years (range: 0.1-45.6 years). The mean EDSS score at baseline was 5.55 for the placebo group and 5.83 for the Fampridine group, and more patients in the Fampridine group than in the placebo group (94 versus 83) had baseline EDSS scores in the 8 to 10 range, resulting in a significant difference with a p-value of 0.024.

### **3.1.2.4 Efficacy Results**

#### **3.1.2.4.1 Analysis of Primary Efficacy Variable**

The primary efficacy variable was responder status. There were 51 (42.9%) timed walk responders and 68 non-responders in the Fampridine group compared to 11 (9.3%) responders



and 107 non-responders in the placebo group. This difference is statistically significant with a p-value of <.001.

No Fampridine responders had missed post-treatment visit 8. Therefore, the prospectively planned sensitivity analysis is identical to the primary analysis.

In order to exam the consistency and robustness of the efficacy results, the reviewer performed same analyses of validation and endpoint as in F-203.

Among the 175 non-responders, the average MSWS-12 score over the double-blind treatment period increased by 0.85, compared to a decrease of 6.04 among the responders. This difference is statistically significant ( $p < .001$ ). (Most sites enrolled a small number of patients, and the variation is large in this analysis.)

In the endpoint analysis, mean change in walking speed from baseline to Visit 6 (the end of Week 8) reduced by 1.87 ft/sec, 8.57 ft/sec, and 2.85 ft/sec for the placebo group, Fampridine responder group, and Fampridine non-responder group, respectively. The difference in the walking speed between Fampridine responder group and the placebo group is statistically significant ( $p < .01$ ). The difference between Fampridine responders and Fampridine non-responders is also statistically significant ( $p < .05$ ).

Thus, the study has achieved statistical significance in the same 3-step analysis defined in F-203.

In addition to the comparisons by responder group, comparison by treatment groups in the walking speed at the end of the treatment period was also performed. Note that in the above analysis of maintenance of efficacy in walking speed, baseline was defined as the average of all pre-treatment values. Because of large difference in walking speed during the pre-treatment period (see Table 6), the following table used Visit 2 (the last visit before double-blind treatment) value as baseline. At the end of the double-blind treatment period, the change from Visit 2 in walking speed was 0.11 for the placebo group and 0.22 for the Fampridine group. The difference in speed translates to a time improvement of 0.50 second for the placebo group and 1.02 second for the Fampridine group. The nominal p-value for the treatment difference is 0.0425.

**Table 5 Mean Change from Visit 2 to End of Treatment in Walking Speed by Treatment Group – F204**  
(Source: Reviewer's Analysis)

<b>Mean (SD) in Walking Speed (ft/sec)</b>	<b>Placebo N=118</b>	<b>Fampridine N=117</b>
Visit 2	2.28 (.73)	2.22 (.80)
Visit 6 (LOCF)	2.39 (.84)	2.44 (.93)
<b>Change</b>	.11 (.40)	.22 (.43)
<b>Difference in Time (sec)</b>	.50	1.02
Nominal p-value		.0425

The following table presents the average walking speed by treatment group and responder status at each visit using observed cases.



**Table 6 Average Walking Speed (ft/sec) by Visit and Response Status (Observed Cases) - F204 (Source: Reviewer's Analysis)**

	Pre-Treatment Visit				Double-blind Treatment				Follow-up
	Visit -1	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
<b>Placebo</b>									
N	118	118	117	117	116	114	113	113	116
Mean	2.11	2.16	2.26	2.28	2.36	2.36	2.41	2.40	2.38
# Non-resp	107	107	106	106	105	103	102	102	106
Mean	2.11	2.16	2.26	2.28	2.33	2.31	2.38	2.36	2.38
#Resp	11	11	11	11	11	11	11	11	10
Mean	2.09	2.16	2.28	2.25	2.69	2.77	2.74	2.76	2.36
<b>Fampridine</b>									
N	119	119	119	118	116	116	114	113	116
Mean	2.05	2.06	2.15	2.21	2.39	2.45	2.41	2.44	2.21
# Non-resp	68	68	68	67	66	65	63	62	64
Mean	2.06	2.04	2.09	2.14	2.20	2.27	2.20	2.21	2.19
#Resp	51	51	51	51	50	51	51	51	51
Mean	2.05	2.09	2.21	2.30	2.63	2.68	2.67	2.73	2.25
<b>Non Resp</b>									
N	175	175	174	173	171	168	165	164	170
Mean	2.09	2.12	2.19	2.23	2.28	2.30	2.31	2.30	2.31
<b>Responder</b>									
N	62	62	62	62	61	62	62	62	61
Mean	2.06	2.10	2.23	2.29	2.64	2.70	2.68	2.73	2.27

The data above can be summarized as follows:

1. Subjects improved their walking speed during the pre-treatment period regardless of treatment group or responder status.
2. At the Visit 2 assessment (the last visit before randomization), the mean walking speed for placebo group was 2.28 ft/sec, represented 10.96 seconds to complete the 25 feet walking test. The mean walking speed for Fampridine group was 2.21 ft/sec, represented 11.31 seconds for the test. At the Visit 6 (end of treatment visit), the mean walking speed of 2.40 ft/sec for placebo-treated subjects represented 10.42 seconds for the 25-feet walking, an improvement of about a half second. The mean walking speed of 2.44 ft/sec for Fampridine-treated subjects represented 10.25 seconds for the same test at the Visit 6, an improvement of about 1 second.
3. The walking speed achieved during the double-blind period is generally maintained through the end of the double-period.
4. The non-responders had little changes from Visit 2 through the end of the treatment period while responders improved walking speed quite significantly, and maintained so through the end of the treatment period.
5. At the end of the treatment period, non-responders used 10.87 seconds to complete the 25 feet walking test, and responders used 9.16 seconds for the same test. The difference in time spent was 1.71 seconds. Breaking down the treatment group, the difference in time between the responders and non-responder among placebo-treated subjects was 1.54 seconds, and the same difference for the Fampridine-treated subjects was 2.15 seconds.



The above findings are consistent to the findings from Study F203.

Analysis of MSWS-12 scores is also performed. The mean change from baseline to Visit 6 in MSWS-12 scores was -2.70 for Fampridine group and 0.94 for placebo group. The difference yielded a nominal p-value of 0.0249. Means of MSWS-12 scores are also calculated by treatment group and response status. The MSWS-12 score ranges 0 to 100 with 100 indicating extreme illness.

**Table 7 Mean MSWS-12 Score by Visit and Response Status (Observes Cases) - F204 (Source: Reviewer's Analysis)**

	Pre-treatment		Double-blind				Follow-up
	Visit 0	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
<b>Placebo</b>							
N	118	117	117	116	116	113	116
Mean	67.79	67.53	68.33	68.37	68.62	68.38	70.85
# Non-resp	107	106	106	105	105	102	106
Mean	66.90	66.72	68.16	68.05	68.47	67.85	70.52
# Resp	11	11	11	11	11	11	10
Mean	76.45	75.38	69.97	71.40	70.08	73.30	74.38
<b>Fampridine</b>							
N	118	119	118	118	116	114	116
Mean	75.59	73.27	70.63	71.03	72.09	70.23	76.24
# Non-resp	67	68	68	67	65	63	66
Mean	75.68	74.94	74.93	74.97	76.43	73.91	76.99
# Resp	51	51	50	51	51	51	50
Mean	73.16	71.04	64.78	65.85	66.56	65.69	75.25
<b>Non-resp</b>							
N	174	174	174	172	170	165	172
Msws	70.28	69.93	70.81	70.75	71.52	70.16	73.00
<b>Responder</b>							
N	62	62	61	62	62	62	60
Msws	73.74	71.81	65.72	66.83	67.18	67.04	75.10

### 3.1.2.4.2 Analysis of Secondary Efficacy Variables

Average change from baseline in LEMMT scores was analyzed. In this analysis, the average change was obtained by averaging all double-blind available scores minus the average of all pre-treatment scores. The following table presents the results from comparisons between treatment groups and between responder groups in LEMMT scores. The nominal p-values were obtained from comparisons of each group versus placebo group.

**Table 8 Average Change of LEMMT and Ashworth Scores - F204 (Source: Reviewer's Analysis)**

			<b>Fampridine</b>
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<b>Study F204</b>	<b>Placebo</b>	<b>Fampridine</b>	<b>Responders</b>	<b>Non-Responders</b>
<b>LEMMT</b>				
Mean (SD)	0.04 (.25)	0.09 (.22)	0.14 (.21)	0.05 (.22)
Nominal p-value		.1059	.0278	.5998

Based on the closed testing procedure, statistical significance for LEMMT has been reached in the comparisons of Fampridine responders versus placebo. Statistical significance in the comparison of Fampridine versus placebo and Fampridine non-responders versus placebo were not reached based on the order of the testing.

### 3.2 Evaluation of Safety

Please refer to Clinical Review by Dr. Illoh for evaluation of safety.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

Response rate and mean walking speed are summarized by gender and age group and presented in Table 9 for Study F203 and in Table 10 for Study F204. No gender or age discrepancies were found in response rate. The mean walking speed is similar between males and females and between older age group and younger age group.

**Table 9 Response Rate and Change from Baseline in Walking Speed by Gender and Age - F203 (Source: Reviewer's Analysis)**

<b>Study F-203</b>	<b>Placebo</b>	<b>Fampridine</b>
<b>Responder</b>		
<b>Gender</b>		
Male		
N	29	66
# (%) of Responders	3 (10.34%)	19 (28.79%)
Female		
N	43	158
# (%) of Responders	3 (6.98%)	59 (37.34%)
<b>Age</b>		
≤ 50 (years)		
N	36	97
# (%) of Responders	4 (11.11%)	36 (37.11%)
> 50 years		
N	36	127
# (%) of Responders	2 (5.56%)	42 (33.07%)
<b>Change in Walking Speed</b>		
<b>Gender</b>		
Male		
N	29	66



Mean (SD)	0.10 (.26)	0.29 (.40)
Female		
N	43	158
Mean (SD)	0.10 (.32)	0.28 (.39)
<b>Age</b>		
≤ 50 years		
N	36	97
Mean (SD)	0.11 (.36)	0.29 (.45)
> 50 years		
N	36	127
Mean (SD)	0.08 (.22)	0.28 (.35)

**Table 10 Response Rate and Change from Baseline in Walking Speed by Gender and Age - F204 (Source: Reviewer's Analysis)**

<b>Study F-204</b>	<b>Placebo</b>	<b>Fampridine</b>
<b>Responder</b>		
<b>Gender</b>		
Male		
N	44	31
# (%) of Responders	2 (4.55%)	13 (41.94%)
Female		
N	74	88
# (%) of Responders	9 (12.16%)	38 (43.18%)
<b>Age</b>		
≤ 50 (years)		
N	55	44
# (%) of Responders	4 (7.27%)	16 (36.36%)
> 50 years		
N	63	75
# (%) of Responders	7 (11.11%)	35 (46.67%)
<b>Change in Walking Speed</b>		
<b>Gender</b>		
Male		
N	44	31
Mean (SD)	0.20 (.31)	0.38 (.38)
Female		
N	74	88
Mean (SD)	0.15 (.38)	0.26 (.33)
<b>Age</b>		
≤ 50 years		
N	55	44
Mean (SD)	0.17 (.34)	0.28 (.38)
> 50 years		
N	63	75
Mean (SD)	0.16 (.38)	0.29 (.33)

## 4.2 Other Special/Subgroup Populations

In order to exam the efficacy of Fampridine in sub-type of MS, mean walking speed is summarized by sub-type MS in the following table. Analysis of responder status is not



performed due to the small number of responders in the placebo group. Because of the large difference in walking speed during the pre-treatment period, subject's Visit 2 walking speed is used as baseline.

**Table 11 Mean Walking Speed by MS Type (Source: Reviewer's Analysis)**

	Placebo	Fampridine	Fampridine	
			Responders	Non-Responders
<b>Study F203</b>				
Primary Progressive				
N	14	30	12	18
Mean (SD)	-0.04 (.41)	0.14 (.47)	0.26 (.51)	0.06 (.43)
Progressive Relapsing				
N	2	10	4	6
Mean	-0.32 (.09)	0.32 (.28)	0.49 (.24)	0.21 (.26)
Relapsing Remitting				
N	21	61	15	46
Mean	0.08 (.59)	0.32 (.76)	0.60 (1.16)	0.23 (.57)
Secondary Progressive				
N	34	121	47	74
Mean	0.09 (.38)	0.16 (.48)	0.37 (.43)	0.04 (.46)
<b>Study F204</b>				
Primary Progressive				
N	19	10	5	5
Mean	0.17 (.30)	0.24 (.46)	0.45 (.53)	0.03 (.29)
Progressive Relapsing				
N	2	5	2	3
Mean	-0.16 (.49)	0.25 (.53)	0.64 (.75)	-0.01 (.18)
Relapsng Remitting				
N	40	42	16	26
Mean	0.05 (.39)	0.17 (.49)	0.42 (.39)	0.02 (.49)
Secondary Progressive				
N	56	61	28	33
Mean	0.14 (.43)	0.24 (.38)	0.41 (.37)	0.09 (.34)



## Clinical Pharmacology/Biopharmaceutics Review

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PRODUCT (Generic Name):	Fampridine (4-Aminopyridine)
NDA:	22-250
SUBMISSION DATE	4/22/2009
PRODUCT (Brand Name):	Amaya <sup>TM</sup>
DOSAGE FORM:	Extended Release Tablet
DOSAGE STRENGTH:	10 mg
INDICATION:	Treatment of patients with multiple sclerosis for the improvement of walking ability
NDA TYPE:	505 (b)(i)
SPONSOR:	Acorda Therapeutics, Inc.
OCP REVIEWER:	Jagan Mohan Parepally, Ph.D.
OCP TEAM LEADER:	Angela Men, M.D, Ph.D.
PM REVIEWER	Joo-Yeon Lee, Ph.D
PM TEAM LEADER	Yaning Wang, Ph.D.
OCP DIVISION:	DCP-1, HFD-860
OND DIVISION:	Division of Neurology Drug Products, HFD-120

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**Note to Advisory Committee Members: this document only includes the Clinical Pharmacology/Biopharmaceutics Executive Summary, and the Pharmacometrics review.**



## 1.0 EXECUTIVE SUMMARY

The sponsor is seeking approval of Amaya™ (fampridine) as a treatment to improve walking ability in patients with multiple sclerosis (MS). Fampridine or 4-aminopyridine is a potassium channel blocker. Fampridine was primarily used as a research tool, in characterizing subtypes of potassium channel in laboratory. Fampridine has an orphan drug status in United States. 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.

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 b.i.d.

Significant exposure-response (the percent change from the baseline at the end of double blind phase in walking speed (ft/sec)) relationship was identified with placebo included in the exposure-response analysis. The relationship looked flat without placebo within the observed exposure range. At 10 mg bid 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 should be studied if the current safety profile including seizure incidence at 10 mg bid is not acceptable.

The dose has to be reduced to 7.5 mg b.i.d in patients with mild and moderate impairment based on exposure-response relationship of fampridine. Caution should be taken in prescribing 7.5 mg b.i.d fampridine in patients with moderate renal impairment. Renal function in moderately impaired patients should be closely monitored since higher exposure of fampridine may lead to CNS adverse events. Fampridine is not recommended in patients with severe renal impairment.

## 1.1 OVERALL SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

### Background:

Clinical pharmacology program included 20 clinical studies. To support the efficacy for multiple sclerosis of fampridine as a treatment to improve walking ability in patients with multiple sclerosis, this NDA contains results from 2 adequate and well-controlled trials



(MS-F203 and MS-F204), one placebo-controlled, dose-ranging study (MS-F202), one early stage placebo controlled dose ranging study (MS-F201) and three long term open-label extension studies (MSF202EXT, MS-F203EXT and MS-F204EXT). To support the safety of fampridine data from clinical studies in spinal chord injury patients was also included along with the data from healthy subjects and multiple sclerosis patients. In addition, 5 in vitro studies were conducted to characterize the fampridine metabolism, plasma protein-binding, to identify the potential drug-drug interactions involving inhibition and induction, and to investigate the potential for involvement of transporters (P-gp). Important clinical pharmacology findings are summarized below.

### **General Pharmacokinetic Properties:**

- The plasma C<sub>max</sub> 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 q12h as a tablet in the fasted state and further confirmed with fampridine SR 12.5 tablet following multiple-dose.
- The steady-state concentrations of fampridine in plasma are achieved within 4 days of q12h dosing. This is consistent with its apparent elimination half-life in plasma of approximately 5-6 h.

### **Absorption:**

- Fampridine is rapidly and almost completely absorbed from gastrointestinal tract following oral administration.
- Relative bioavailability was 96% when compared to an aqueous oral solution. The sustained release tablet delays absorption of fampridine relative to the solution formulation characterized by lower C<sub>max</sub> concentration and delayed T<sub>max</sub>, with no effect on the extent of absorption.
- Food had relatively small impact on C<sub>max</sub> and AUC (a slight increase of approximately 17% and approximately 5%, respectively) under fed conditions. T<sub>max</sub> values were delayed by approximately 2 hours. Since fampridine is indicated for chronic dosing, the delay in T<sub>max</sub> is not considered clinically significant. The results justify administration of fampridine-SR tablets with or without regard to food.

### **Distribution**

- 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 (5, 50, and 500 ng/mL) and pH (7.2-7.6). Fampridine was largely unbound and had a high free drug fraction at all three concentrations tested.



### Metabolism and Elimination

- Fampridine is not extensively metabolized and mainly eliminated as unchanged drug in urine.
- The 2 major metabolites 3-hydroxy-4-aminopyridine and 3-hydroxy-4-aminopyridine sulfate were identified, both were inactive.
- 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.
- Radiolabeled 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 feces. 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.
- 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).

### Relative Bioavailability and Bioequivalence

- The relative bioavailability of fampridine-SR 10 mg dose used in the pivotal Phase 3 studies MS-F203 and MS-F204 as compared to a 10 mg buffered aqueous oral solution (0.83 mg/mL) was assessed under fasting conditions. Fampridine-SR tablets, 25 mg were studied in the third arm. The peak concentrations following administration as a sustained release tablet were approximately 40% of those achieved with the oral solution and occur approximately 3.5 hours postdose. The plasma elimination half-life was prolonged, from 3.2 hours for the oral solution versus 5.4 to 5.5 hours on average for the sustained release tablets. The two sustained release tablets were bioequivalent.
- 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 (manufactured by Elan) by alternate manufacturer (Patheon Pharmaceuticals).



Single dose administration of 10 mg Fampridine-SR test formulation manufactured by Patheon Pharmaceutical (P10) was bioequivalent to reference formulation manufactured by Elan Pharmaceuticals (E10). The 90% CI of C<sub>max</sub> and AUC<sub>0-inf</sub> fell within 80-125% acceptance criteria for BE.

### **Intrinsic Factors:**

Body mass index and subject status (healthy volunteers vs. MS patients) did not appear to effect pharmacokinetics of fampridine according to population PK analysis.

Renal impairment: single-dose administration of fampridine-SR in subjects with normal renal function, mild, moderate or severe renal impairment.

The mean C<sub>max</sub> and AUC(0-inf) 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<sub>max</sub> and AUC(0-inf) 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 CL<sub>r</sub> of fampridine showed significant relationship ( $p < 0.0001$  for CL/F and  $p = 0.0001$  for CL<sub>r</sub>) with creatinine clearance.

**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).

**Gender:** 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.

**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.



**Extrinsic Factors:****Drug-Drug Interaction with Baclofen**

The study of single-dose 15 mg fampridine-SR coadministered with 10 mg Lioresal® (baclofen) in 12 healthy male volunteers did not show PK interaction. The geometric mean ratios for the plasma C<sub>max</sub> and AUC<sub>0-∞</sub> values ranged from 97.6-100.7% for fampridine, with and without concomitant administration of 15 mg fampridine, with 90%CI falling into 80-125%. These results were confirmed by population PK analysis of coadministration of fampridine-SR 10 mg tablet with baclofen showing no effect on PK parameters.

**Drug-Drug Interaction with Beta-Interferon**

The impact of 7.5 mg q8h of fampridine immediate release formulation coadministered with 8 million units of interferon beta-1b Betaseron® (baclofen) in 3 male and 6 female MS patients showed that fampridine kinetics were comparable following administration of fampridine alone (steady state C<sub>max</sub> of 56.7 ng/mL and AUC<sub>0-8</sub> of 216.0 ng·hr/mL) or following co-administration of interferon beta (steady state C<sub>max</sub> of 50.1 ng/mL and AUC<sub>0-8</sub> of 207.2 ng·hr/mL). No pharmacokinetic drug-drug interaction of interferon beta-1b 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.

**Effect of Fampridine on PK of Coadministered Drugs**

- 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. Which 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 upto 25 µM.
- In vitro studies indicated that fampridine is neither a substrate of the P-gp (MDR1-MDCK, MDCK cells), nor an inhibitor of digoxin (Caco-2 cells) transport activity.

**Population PK analysis: Effect of Concomitant Medications**

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, bactrim, amoxicillin, and trimethoprim) and diuretics (including HCTs and potassium sparing drugs).

### **Population Exposure-Response Relationship (Efficacy and Safety)**

Yes, there is a significant exposure (AUC ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ ))-response (the percent change from the baseline at the end of double blind phase in walking speed (ft/sec)) relationship when the placebo group was included in the analysis (reviewer's analysis). However, the relationship is flat without placebo within the observed exposure range.

A phase II study (MS-F202) and two phase III studies (MS-F203, MS-F204) were included in the sponsor's exposure-response analyses for both efficacy and safety.

"Timed Walk Responder" was the primary efficacy endpoint, which was 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 posttreatment visit. Based on the primary endpoint, fampridine showed superior effectiveness (37.3% 10 mg bid vs. 8.9% placebo for pooled data) in the efficacy analysis and the sponsor's exposure-response analysis also predicted similar results. However, a patient who may have no drug effect at the last visit of double blind treatment phase could be declared as a responder by definition of "timed walk responder". In addition, it is not possible to evaluate how much improvement a patient achieved in actual walking speed by the primary endpoint.

Hence, the reviewer performed the independent analysis using the percent change in walking speed from the baseline at the end of double blind phase as an endpoint. Figure 4 (in appendix 4.2) presents the results from pooled data analysis. First the linear model was applied to the pooled data and linear regression showed the statistically significant relationship between AUC ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ ) and the endpoint (p-value=0.015). The same model was fitted to the data after excluding placebo data and results are shown in the right panel (see Figure 4 in appendix 4.2). The flat relationship without placebo suggests that the response reached the plateau at 10 mg bid and a lower dose may be as efficacious as 10 mg bid. This observation is supported by the similar responder rate at each dose group.

The safety of 10mg bid was evaluated using the probability of having at least one CNS-related AE as an endpoint. The sponsor claimed that CNS-related AE incidence was flat up to an AUC of 200  $\mu\text{g}\cdot\text{hr}/\text{mL}$  and 10 mg bid should be safe based on the model prediction.

In order to further evaluate the safety of 10 mg bid compared to placebo, the reviewer focused on the patients who were assigned to 10 mg bid or placebo. As observed in the sponsor's analysis, the incidence rate appeared to be similar to placebo up to the AUC of 200  $\mu\text{g}\cdot\text{hr}/\text{mL}$  and showed increasing trend for the range of AUC > 200  $\mu\text{g}\cdot\text{hr}/\text{mL}$  with a relatively flat but higher rate within 220  $\mu\text{g}\cdot\text{hr}/\text{mL}$  and 350  $\mu\text{g}\cdot\text{hr}/\text{mL}$ .



Overall, fampridine seems to show the effectiveness based on both primary endpoint (responder analysis) and the reviewer's endpoint (percent change from the baseline in walking speed (ft/sec)). However, the exposure-response relationship is flat within the studied exposure range and for most of the exposure range under 10 mg bid, the incidence rate of CNS-related AE is higher than that for the placebo group. Hence, a lower dose than 10 mg bid should be studied if the current safety profile including seizure incidence at 10 mg bid is not acceptable.

## **2.0 REVIEWER'S ANALYSIS (PHARMACOMETRICS)**

### **2.1 Introduction**

The sponsor evaluated the effectiveness of fampridine based on the primary endpoint, timed walk responder. However, a patient who may have no drug effect at the last visit of double blind treatment phase could be declared as a responder by the definition of "timed walk responder". In addition, it is not possible to see how much improvement a patient achieved in actual walking speed by the current endpoint.

Hence, it would be worthwhile to explore the exposure-response relationship based on the actual continuous scale such as the percent change in walking speed from the baseline at the end of double blind phase.

Also the sponsor claimed that CNS related AE incidence did not show increasing trend between placebo and 10mg bid. However, the reviewer observed meaningful difference in CNS related to AE between placebo and 10mg bid (12% .vs. 30%) in one of pivotal study (MS-F204) so the safety of 10mg bid was further examined by the reviewer.

### **2.2 Objectives**

The reviewer aims to re-evaluate the exposure-response relationship focusing on

- Whether or not there exists exposure-response relationship using a different efficacy endpoint, the percent change from the baseline in walking speed (ft/sec) at the end of double blind phase.
- Whether or not the sponsor's claim that there is little difference in CNS-related AE incidence between placebo and 10mg bid can be confirmed.
- Whether or not the proposed dose of 10mg bid is appropriate, based on the observation on E-R relationship for both efficacy and safety



## 2.3 Methods

The percent change from the baseline at the end of double blind phase in walking speed (ft/sec) was used as the primary efficacy endpoint in the reviewer's exposure-efficacy analysis.

The relationship between CNS-related AE incidence and exposure at the dose of 10mg bid was re-examined based on the subset of the patients who were assigned to the 10mg bid and placebo treatment arms only.

### 2.3.1 Data Sets

Data sets used are summarized in Table 1.

**Table 1. Analysis Data Sets**

Study Number	Name	Link to EDR
MS-F202, MS-F203, MS-F204	pddata.csv	

### 2.3.2 Software

SAS 9.2 was used for the analysis.

### 2.3.3 Model Results

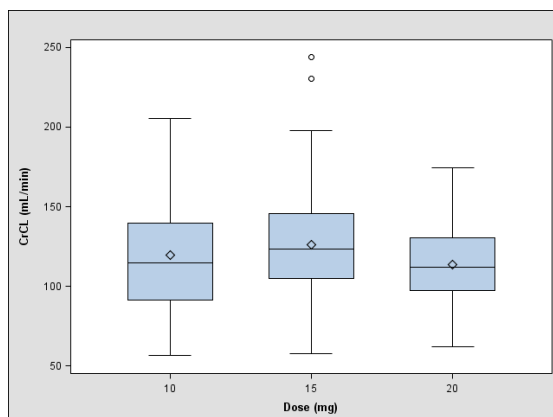
First, the reviewer summarized the baseline population characteristics (Table 2) to explore whether there exists any difference between studies. Most demographics are comparable across studies while CrCL in study MS-F202 appears to be slightly higher than that in MS-F203 and MS-F204. Also notice that there is slightly unbalanced CrCL (mL/min) distribution shown between dose groups (Figure 1).

**Table 2. Baseline population characteristics.**

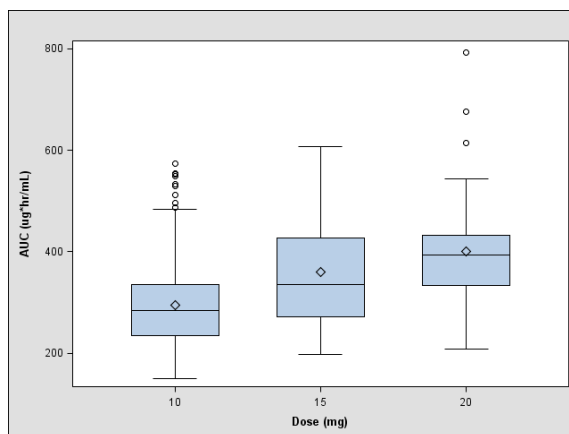
	MS-F202	MS-F203	MS-F204
Age (yrs)	49.9±8.6	51.5±8.7	51.7±9.6
Weight (kg)	74.7±17.2	75.0±18.8	71.4±21.4
CrCL (mL/min)	120.0±32.8	108.5±33.4	101.3±38.4
BMI	26.4±5.9	26.3±5.9	24.4±7.9
Sex (Female/male)	103/55	158/66	86/31
Race (White/black/Asian/other)	145/8/1/4	208/9/3/4	111/2/0/4



**Figure 1. The distribution of individual CrCL (mL/min) at each dose for the study of MS-F202.**



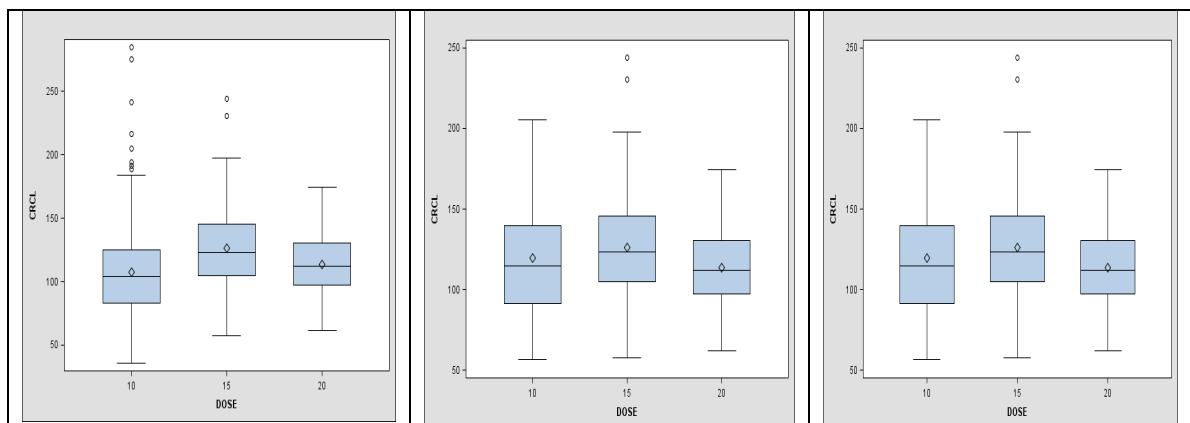
**Figure 2. The distribution of AUC (ug\*hr/mL) at each dose group.**



**Figure 3** shows the percent change from the baseline in walking speed at each dose group within each study. A dose of 10mg bid showed slightly higher response than placebo across all studies but the doses of 15mg and 20mg bid did not give any additional benefit.

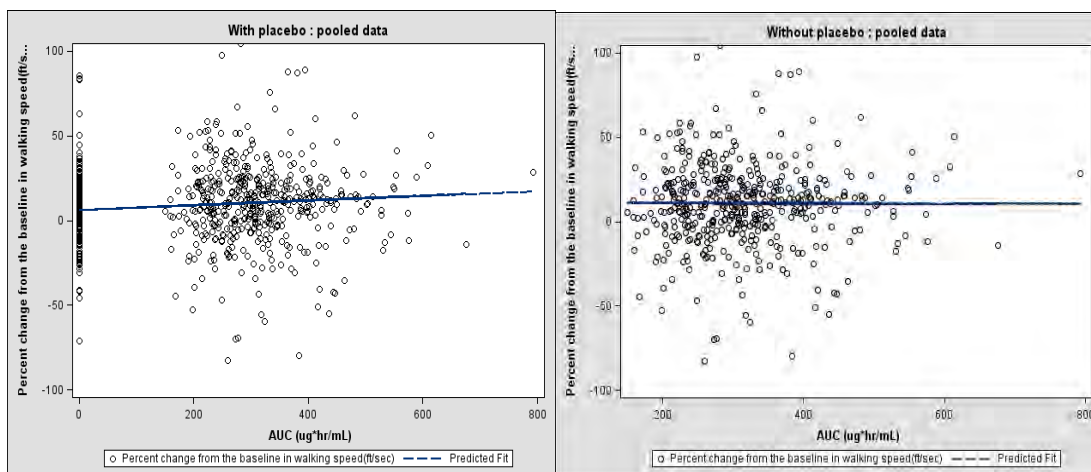
**Figure 3. The percent change from the baseline in walking speed by dose group and study.**





Linear regression analysis was conducted for the pooled data to explore the relationship between exposure (AUC (ug·hr/mL)) and the percent change from the baseline in walking speed. Figure 4 presents the results from pooled data analysis. When the patients who were assigned to placebo were included, it showed the statistically significant relationship between AUC (ug·hr/mL) and the percent change from the baseline in walking speed (p-value=0.015). The same model was fitted to the data after excluding placebo data and results are shown in the right panel in the Figure 4. The flat relationship without placebo suggests that the response reached the plateau at 10mg bid and a lower dose may be as efficacious as 10 mg bid. This observation is supported by the similar responder rate at each dose group.

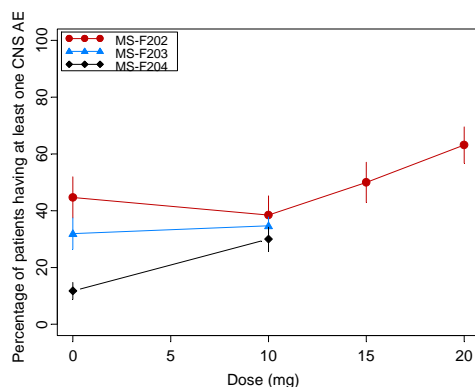
**Figure 4. The pooled data analysis : the relationship between AUC (ug·hr/mL) and the percent change from the baseline in walking speed (ft/sec) with placebo (left panel, p-value=0.015) and without placebo (right panel, p-value=0.935).**





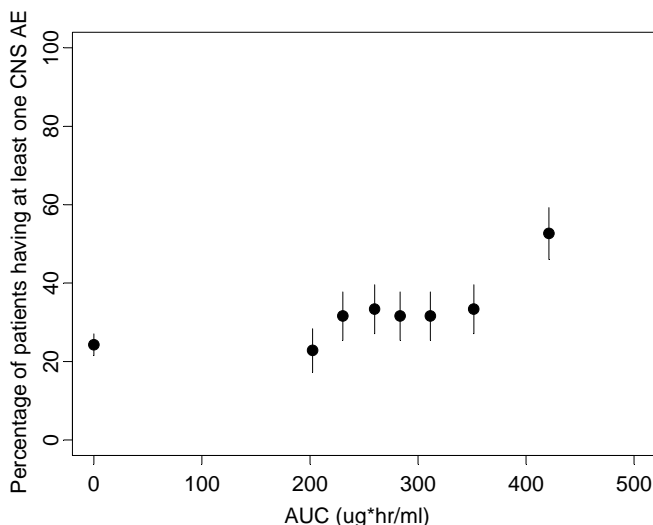
The safety of 10mg bid was evaluated using the probability of having at least one CNS-related AE as an endpoint. The sponsor claimed that CNS-related AE incidence was flat up to an AUC of 200 ug-hr/mL and 10mg bid should be safe based on the model prediction. Figure 5 shows CNS-related AE at each dose within each study. It is noticeable that the CNS-related AE incidence for placebo group is highly variable across studies (11%, 32% and 45% for the studies of MS-F204, MS-F203 and MS-F202, respectively). It is apparent that there is an increasing trend between placebo and 10mg bid in study MS-F204, although the incidence rate for placebo group is also lowest in this study.

**Figure 5. The dose-CNS-related AE relationship for each study.**



In order to further evaluate the safety of 10mg bid compared to placebo, the reviewer focused on the patients who were assigned to 10 mg bid or placebo. Figure 6 shows the observed CNS-related AE incidence at the octile of AUC at the dose of 10mg bid and placebo. As observed in the sponsor's analysis, the incidence rate appears to be similar to placebo up to the AUC of 200 ug-hr/mL and shows an increasing trend for the range of AUC > 200 ug-hr/mL with a relatively flat but higher rate within 220 ug-hr/mL and 350 ug-hr/mL.

**Figure 6. The probability of having at least one CNS related AE by AUC at the dose of 10mg bid from the observed data. Each dot represents the proportion of having at least one CNS related AE at each octile of AUC and vertical bars indicate one standard error ( $\pm$ SE).**





Overall, fampridine-SR seems to show the effectiveness based on both primary endpoint (responder analysis) and the percent change from the baseline in walking speed (ft/sec). However, the exposure-response relationship is flat within the studied exposure range and for most of the exposure range under 10 mg bid, the incidence rate of CNS-related AE is higher than that for the placebo group. Hence, a lower dose than 10 mg bid should be studied if the current safety profile including seizure incidence at 10 mg bid is not acceptable.