CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 20, 2010
From	Eric Bastings, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22250
Applicant	Acorda
Date of Submission	4/22/2009
PDUFA Goal Date	1/22/2010
Proprietary Name / Established (USAN) names	Fampridine Sustained Release
Dosage forms / Strength	Sustained Release 10 mg tablets
Proposed Indication(s)	Treatment of patients with multiple sclerosis for the improvement of walking ability
Recommended:	Approval

1. Introduction

Acorda submitted a new drug application (NDA) to support the marketing of fampridine Sustained Release 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. As discussed below, a risk of confusion of the established name "fampridine" with the name "famotidine" was identified during the review cycle, and the division asked Acorda to propose a new name. The division accepted as an alternate established name "dalfampridine". In this document however, I will use the name "fampridine", as it is the established name used in the various FDA reviews.

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 discussed at greater length below, the proposed primary efficacy endpoint is novel, and has no precedent in regulatory use. 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. For this product, benefit must be considered against a widely acknowledged safety signal for 4-aminopyridine, and other pyridine compounds: seizures.

The review team consisted off:

- CMC, by Dr. Lyudmila Soldatova (supervisor Dr. Ramesh Sood)
- Non clinical, by Dr. Richard Houghtling (supervisor Dr. Lois Freed)
- Clinical safety, by Dr. Gerald Boehm (team leader Dr. Sally Yasuda)
- Clinical efficacy, by Dr. Kachi Illoh
- 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)
- Controlled Substance Staff (Dr. Chad Reissig and Dr. Lori Love)
- Maternal Health Team (Jeanine Best and Dr. Karen Feibus)
- Carton and Container labeling review, by Mr. Todd Bridges (supervisor Dr. Denise Toyer)
- Tradename review, by Ms. Laurie Kelley (supervisor Ms. Carol Holquist)
- REMS and Communication plan review, by Kate Henrich, Suzanne Robottom and Amy Toscano

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 Cmax 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 weeks 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. 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 ≥ 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 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.

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/Device

Dr. Soldatova recommends approval from a CMC standpoint. Based on the drug product stability data, Dr. Soldatova recommends a shelf-live of 36 months for fampridine tablets packaged in 60-count, 60 cc HDPE round bottles, and physician samples packaged in 14-count in 30 cc HDPE round bottles. Dr. Soldatova also notes that the recommendation for drug substance manufacturing facility (b) (4) under DMF (b) (4) from the Office of Compliance is "acceptable".

4. Nonclinical Pharmacology/Toxicology

As discussed by Dr. Lois Freed, Supervisory Pharmacologist, and by Dr. Richard Houghtling, Acorda has conducted a full battery of nonclinical studies.

Dr. Houghtling noted as non clinical deficiencies an inadequate assessment of the potential of fampridine to affect embryo-fetal development toxicity in rat, and an insufficient evaluation of two impurities, (b) (4) (a potentially genotoxic impurity), and (b) (4)

Dr. Freed essentially agrees that fampridine should be further assessed for potential adverse effects on embryofetal development in the rat, but believes that additional evaluation may be conducted post-approval, particularly since fampridine has been adequately assessed in an embryofetal development study in rabbit.

Regarding impurities, Dr. Freed discusses in her memorandum the various interactions between the review team and Acorda during the review cycle, and notes that of (b) (4) potentially genotoxic impurities originally identified by the CMC team, only the (b) (4) impurity contains an additional structural alert (the (b) (4) for which the genotoxic potential still needs to be addressed. Dr. Freed proposes that Acorda may either test the (b) (4) impurity directly in in vitro genetic toxicology studies, or demonstrate that the (b) (4) is a metabolite in either rat or mouse at sufficiently high levels at the doses used in the carcinogenicity studies.

Dr. Freed also believes that the (b) (4) impurity needs to be tested for the potential to adversely affect embryofetal development. Dr. Freed emphasizes that this study should test

both the impurity and a high dose of fampridine, as the evaluation of the effect of fampridine on embryofetal development in the rat was somewhat deficient.

Dr Freed notes that Dr. Houghtling has recommended that the NDA not be approved until nonclinical studies are conducted to address the genotoxic potential of (b) (4) to qualify the (b) (4) impurity, and to further characterize the potential for fampridine to adverse affect embryofetal development. Considering the unmet medical need for this new indication, Dr. Freed has no objection to approval of the NDA based on the available nonclinical data, with the nonclinical deficiencies discussed to be addressed post-approval. I agree. These studies will constitute post-marketing requirements.

5. Clinical Pharmacology/Biopharmaceutics

Absorption, Distribution, Metabolism and Elimination
Fampridine is rapidly and almost completely absorbed from gastrointestinal tract following oral administration. The sustained release tablet delays absorption of fampridine, with a lower Cmax and delayed Tmax compared with a solution formulation, but no effect on the extent of absorption. Food has a small impact on Cmax and AUC (17% and 5% increase under fed conditions, respectively). Dr. Parepally considers that the results justify administration of fampridine-SR tablets with or without regard to food. Fampridine was largely unbound and had a high free drug fraction at all three concentrations tested.

Fampridine is not extensively metabolized and mainly eliminated as unchanged drug in urine. The two major metabolites 3-hydroxy-4-aminopyridine and 3-hydroxy-4- aminopyridine sulfate were both inactive.

In vitro studies with human liver microsomes indicate that CYP2E1 is the major enzyme responsible for the 3-hydroxylation of fampridine. 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%).

The elimination half-life of fampridine following administration of SR tablet formulation was 5.2 to 6.5 hours. Overall renal clearance of fampridine was 22.2 L/hour (370 mL/min), which suggests active tubular secretion since it is much higher than the glomerular filtration rate.

Drug-drug interactions
No significant interaction was identified with baclofen or Betaseron. In vitro data with human liver microsomes showed that fampridine is not a direct or time dependent inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Fampridine has little or no potential to induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5 enzyme activities in human hepatocytes. *In vitro* studies indicate that

fampridine is neither a substrate of the P-gp, nor an inhibitor of digoxin transport activity. Population PK data evaluating the effect of the co-administration of most commonly used concomitant medications in MS patients indicate no significant change in fampridine plasma levels.

Intrinsic factors
Renal impairment: following single-dose administration, the mean Cmax and AUC of fampridine was respectively 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, compared with normal subjects. The fampridine clearance showed a significant correlation with creatinine clearance. Based on that effect, OCPB is recommending for mild and moderate renal impairment patients a dose adjustment to 7.5 mg b.i.d. OCPB also believes that use of fampridine in severe renal impairment is not recommended. I agree that severe renal impairment must be a contraindication, as plasma levels in patients with severe renal impairment are expected to exceed those seen with 20 mg b.i.d., a dosing level that was associated with an increased risk of seizures.

The issue of mild and moderate renal impairment is more complex. The Advisory Committee panel unanimously recommended a contraindication of fampridine in patients with moderate or severe renal impairment, and "use with caution" in patients with mild renal impairment. As it is not clear what "use with caution" means in this setting (there are usually no premonitory signs for seizures), labeling should instead describe that in patients with mild renal impairment, fampridine may reach plasma levels that have been associated with an increased risk of seizures. Acorda agreed, as a post-marketing commitment, to develop a 7.5 mg dosage strength, that will allow adjusting the dose in patients with renal impairment.

Hepatic Impairment: Fampridine has not been studied in patients with hepatic impairment. Since fampridine is primarily excreted unchanged in the urine, hepatic insufficiency is not expected to 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 in females.

Race (Caucasian vs. Non-Caucasian): There were no effects of ethnicity observed on fampridine pharmacokinetics.

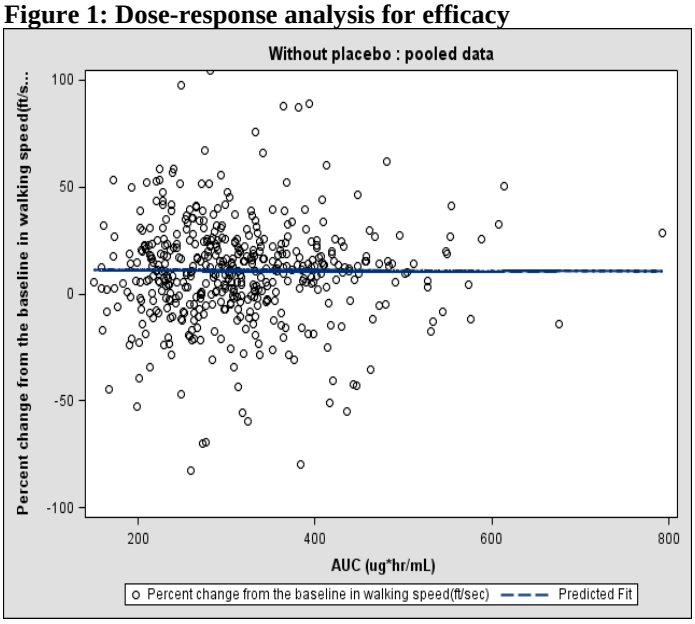
QT assessment
No clinically significant effect on the QT interval was identified in thorough QT study.

Pharmacometrics:
Dr. Joo-Yeon Lee analyzed fampridine exposure-response relationship, based on the percent change in walking speed from baseline to the end of the 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 1 (adapted from the clinical pharmacology and biopharmaceutics review) shows a flat relationship between exposure and change in walking speed (p=0.935), which suggests that the response reached a plateau at 10 mg bid, and did not improve with higher exposure.

Figure 1: 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. This issue was discussed at the AC meeting, and the panel recommended that the sponsor be required to conduct a study investigating lower doses, but did not recommend requiring that study prior to approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

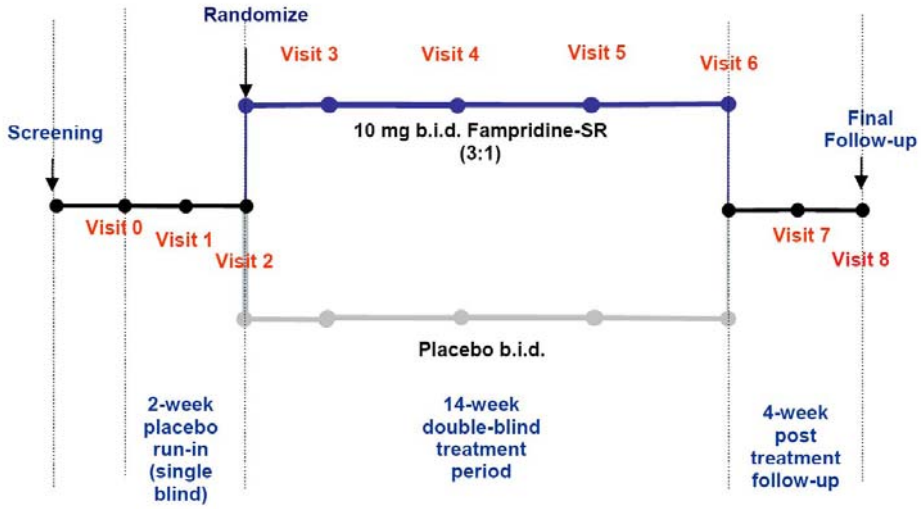
Acorda conducted two pivotal efficacy studies: Study MS-F203 and MS-F204.

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 2.

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 2, copied from the statistical review, shows the design of Study MS-F203.

Figure 2: 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). 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 ($p<.001$).

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

Study MS-F203	**Placebo (n=72)**	**Fampridine (n=224)**	**p value**
Baseline walking speed (ft/sec)	2.12	2.14	0.88
Visit 6 Walking speed (ft/sec)	2.16	2.35	0.19
Walking speed change Visit 6 vs. baseline (ft/sec)	0.05	.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 nominal 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.

The other contrasts with a nominal 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.

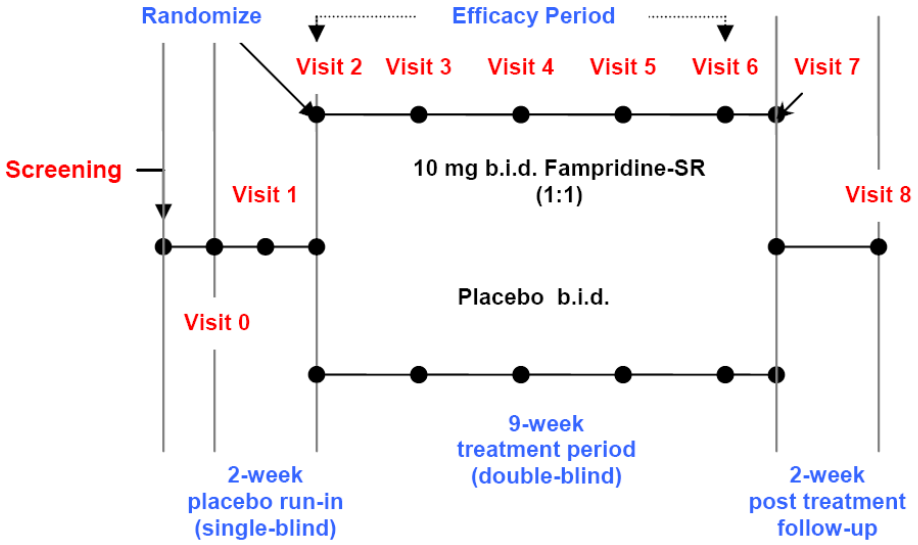
While there was a (not significant) trend favoring fampridine for the change from baseline to Visit 6 in MSWS-12 scores (p=0.06), most of the improvement occurred during the pre-treatment period (before patients were exposed to fampridine), which again leads to question the meaningfulness of that change.

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 past7 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 modest.

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^{th}) 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

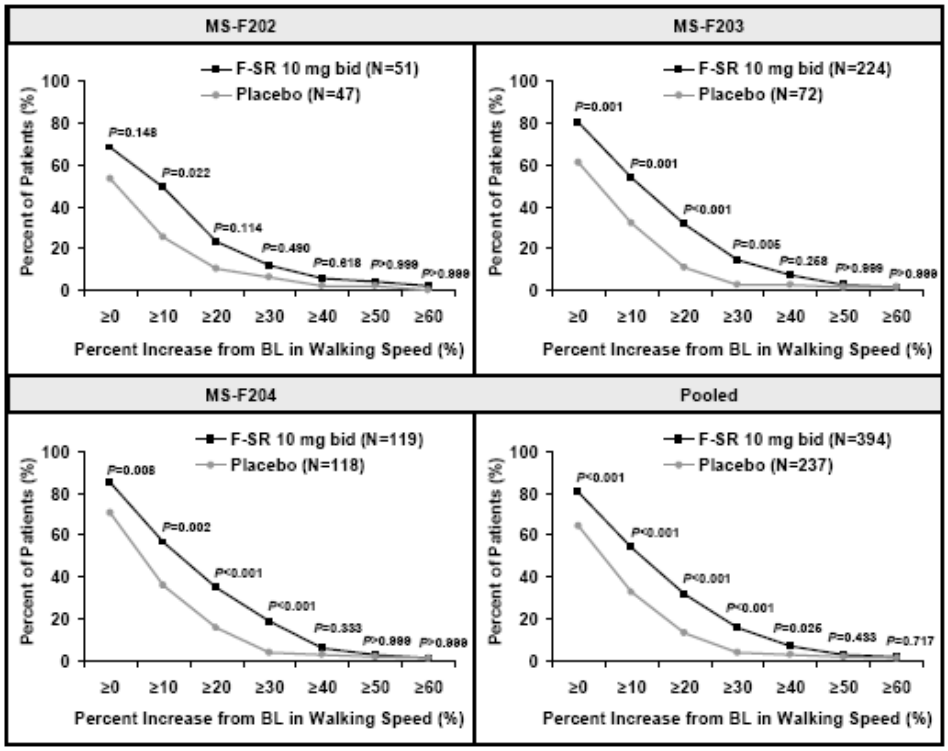
Study MS-F204	Placebo	Fampridine	p value
Baseline walking speed (ft/sec)	2.28	2.21	0.5463
Visit 6 Walking speed (ft/sec)	2.39	2.42	0.7284
Walking speed change Visit 6 vs. baseline (ft/sec)	.11	.22	0.0425
Walking speed change Visit 6 vs. baseline (%)	4.87%	10.64%	0.0392
Walking speed on drug (average)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

In Study MS-F204, the contrast for the MSW12 score changes had a nominal p value under 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).

Overall, the clinical meaningfulness of the benefit remains unclear to Dr. Illoh, and for that reason he is recommending a complete response action. I am however aligned with the recommendation on the advisory panel that substantial evidence of effectiveness has been provided. In particular, a post-hoc analysis showing efficacy of fampridine across a range of walking speed improvements provides additional support for the clinical meaningfulness of the effect. While I agree with Dr. Illoh that the clinical significance of a 20% improvement remains unclear, the fact that Acorda showed a positive effect of fampridine for up to 30% average increases in walking speed in both pivotal trials (Figure 4, copied from Figure 10 of Acorda's Advisory Committee Briefing Document) is reasonable persuasive.

Figure 4: Percentage of Patients with Average Percent Increase from Baseline in Walking Speed over the Double-Blind Treatment Period in Studies MS-F202, MS-F203, MS-F204, Separately and Pooled (ITT Population)



8. 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)

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)
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

The principal safety issue with fampridine is the risk of seizures. Dr. Boehm notes that data from the controlled clinical trials at the 10 mg b.i.d. 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 b.i.d. (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. It must also be noted that the 95% confidence interval of seizure rate seen at 10 mg b.i.d is 1.4% (Table **6**).

Table 6: Incidence of seizures in controlled clinical trials in patients with MS

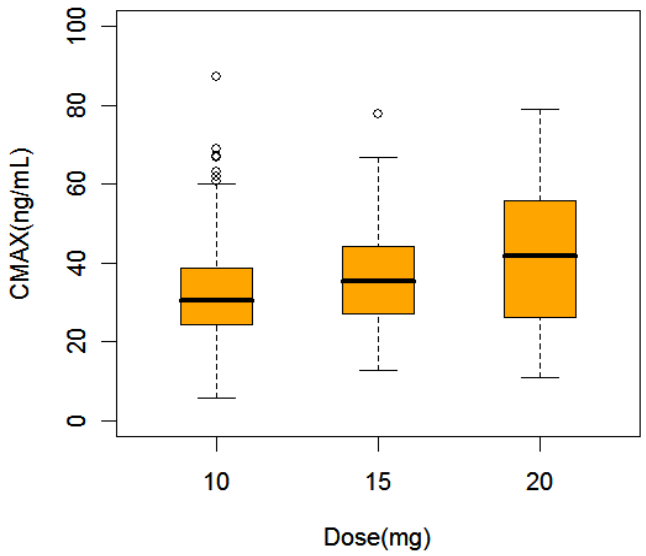
	Seizure incidence over 9 to 14 weeks of blinded treatment (95% CI)
Placebo (n=249)	0.4%
Fampridine 10mg b.i.d. (n=400)	0.25% [upper bound of 95% confidence interval = 1.4%]
Fampridine 10mg b.i.d. (n=50)	0%
Fampridine 10mg b.i.d. (n=57)	3.5%

Dr. Boehm notes that in open-label trials, the seizure risk at 10 mg b.i.d. 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. These data were inconclusive, because that the plasma level and seizure occurrence were separated by a delay of several hours or days.

Pharmacokinetic data (Figure 5) 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 5: 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 patients who rolled over into open-label extension trials. 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 (UTI) in fampridine-treated patients compared to patients who received placebo. Dr. Boehm notes that in many cases, these events were diagnosed based only on symptoms, and that urinanalysis 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.

9. Advisory Committee Meeting

An advisory committee (AC) meeting was held on October 14, 2009. The following is a summary of the questions and AC votes and other recommendations.

1. Has the sponsor demonstrated substantial evidence of effectiveness of fampridine as a treatment to improve walking in patients with multiple sclerosis (MS)? YES/NO/ABSTAIN

   YES: 12 NO: 1 ABSTAIN: 0

   a. If yes, 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? DISCUSSION

   Committee Discussion: *Panel members who did not feel there was a clinically meaningful effect placed emphasis on treated vs. untreated groups as a whole and the lack of a difference between walking speed in the treated group vs. untreated group as a basis for this decision. Some panel members also use the proportion of responders and prior demonstration of responders' subjective impression as a basis for their decision. Other panel members also emphasized the proportion of changes in walking speed and walking time to reach their conclusion of clinically meaningfulness of the effect.*

2. If yes to question #1, should the sponsor be required to evaluate the effects of doses lower than 10 mg twice daily (BID)? YES/NO/ABSTAIN

   YES: 12 NO: 1 ABSTAIN: 0

   a. If yes, should this be required prior to approval? YES/NO/ABSTAIN

   YES: 2 NO: 11* ABSTAIN: 0

Committee Discussion: *The majority of the committee agreed that doses lower than 10 mg twice daily should be evaluated to see if seizure risk and other adverse events are decreased while still maintaining efficacy, thus improving the benefit to risk ratio. The majority of the committee also agreed that the requirement of studies of lower dosages should not prohibit the approval of the product at the proposed 10 mg twice daily dosing.*

***NOTE: One panel member did not place a vote in the electronic voting system; however, the panel member verbally stated her vote as "NO".**

3. 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? YES/NO/ABSTAIN

   YES: 10 NO: 2 ABSTAIN: 1

   a. If yes, what are those conditions (e.g., specific enrollment criteria, specific monitoring, etc.)? DISCUSSION

Committee Discussion: *The committee was in agreement that fampridine should not be used in patients with moderate to severe renal insufficiency (baseline serum creatine or creatinine clearance should be obtained) and in patients with known seizure disorder or are at high risk for seizures. The committee also expressed a view that there is no need for pre-screening ECG before initiation of fampridine as there is no clinical evidence to support the use of ECG to predict seizure risk.*

10. Pediatrics

PREA does not apply to fampridine, as the product received an orphan drug designation early on during development (early nineties). While an orphan designation would not be granted for the proposed indication in 2009, the previous orphan designation granted to Elan was "grandfathered" to Acorda.

11. Other Relevant Regulatory Issues

The sponsor proposed as a REMS a Medication Guide and a communication plan. These were reviewed by DRISK, and they were found acceptable after revisions.

The sponsor original proposed name, AMAYA, was found acceptable by DMEPA. However, the sponsor proposed a new proprietary name, AMPRIVA, that was found unacceptable by DMEPA. Finally, the sponsor then proposed the name AMPYRA, which was accepted by DMEPA.

The USAN-approved established name, fampridine, was found to present a risk of confusion with famotidine, as in addition to the spelling similarities, both drugs share the same route of administration, and are available as a 10 mg dosage strength. Therefore the division asked Acorda to propose alternate names, and "dalfampridine" was accepted, after preliminary screening by David Lewis, the FDA representative at USAN.

Dr Reissig, from the controlled substance staff, notes Acorda has not provided data to perform a complete assessment of the abuse potential of fampridine-SR. He further notes that standard abuse liability assessments (both clinical and preclinical) have not been performed and characterization of the abuse potential of fampridine-SR is lacking. Dr. Reissig recommended several post-marketing requirements to assess the abuse potential of fampridine, and these are listed at the end of this document. I agree with the recommendation.

12. Labeling

Labeling includes a Medication Guide, that was reviewed by DRISK. There are no outstanding labeling issues.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Approval.

Risk Benefit Assessment: Efficacy of fampridine was established by the two pivotal efficacy trials, that met their primary endpoint (proportion of patients who met a responder criteria). The change in walking speed was numerically quite small. In addition, the magnitude of benefit seen with other secondary outcome measures, such as the Ashworth score (a spasticity measure), or lower extremity muscle strength was also limited. An Advisory Committee panel voted 12 to 1 that the sponsor demonstrated substantial evidence of effectiveness of fampridine as a treatment to improve walking in patients with multiple sclerosis.

While the limited controlled trial experience (up to 14 weeks of treatment) with fampridine 10 mg b.i.d. did not identify an increased seizure incidence compared to placebo, the therapeutic index of fampridine appears quite narrow, as the risk seen in controlled studies with 20 mg b.i.d was ten-fold higher than with 10 mg b.i.d. In open label extension trials in MS patients, the incidence of seizures during treatment with fampridine 15mg twice daily (1.7/100PY) was over 4 times higher than the incidence during treatment with 10 mg twice daily (0.4/100PY). In addition, the data are insufficient to clearly establish fampridine exposures at which seizures are not observed, and there is considerable overlap in the plasma exposures at 10 and 20 mg BID. The AC panel voted 10 to 2 (with 1 abstention) that there are conditions under which fampridine SR could be considered safe in use for this indication.

An additional important factor is that in fampridine studies, patients were screened by EEG, and patients with EEG abnormalities were excluded from the studies. Therefore, it is difficult to extrapolate the risk of seizures seen in clinical trials to a general MS population, or to compare the risk of seizures in the sample of MS patients included in these studies with published background seizure rates in MS patients. Regarding that question, the AC panel expressed a view that there is no need for pre-screening ECG before initiation of fampridine as there is no clinical evidence to support the use of ECG to predict seizure risk. I am not convinced that such a lack of evidence is sufficient to conclude that the risk of a drug causing

seizures is the same in a population with or without EEG abnormalities, and I recommend that labeling describes that the risk in patients with EEG abnormalities is unknown.

Considering the narrow therapeutic index, and flat dose-response, I agree with the review team that the sponsor should be required to explore the efficacy of lower doses of fampridine. Regarding this question, the majority of the advisory committee members agreed that doses lower than 10 mg twice daily should be evaluated, but also voted not to require that lower dose study prior to approval. Acorda agreed to conduct a study comparing 5 mg b.i.d. and 10 mg b.i.d as a post-marketing commitment.

Acorda also committed to develop a lower dosage strength (7.5 mg) of fampridine for use in patients with renal impairment. Until this lower dosage strength is available, labeling must warn that the risk of seizures in patients with mild renal impairment is unknown, but that fampridine plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose associated with an increased risk of seizures.

Postmarketing Risk Management Activities

I recommend the following Post-Marketing Requirements (PMRs)

1: Embryo-fetal development study in one non clinical species (the rat) to qualify (b) (4), a drug product impurity with a specification limit that exceeds the qualification threshold. This study is to be conducted on dalfampridine spiked with the impurity up to a level that provides a safety margin compared to the specification limit proposed, and to include a group receiving a high dose of dalfampridine alone.

2: An in vitro bacterial mutagenicity (Ames) assay for impurity, (b) (4) (tested directly) that has been identified as a potentially genotoxic impurity based on SAR. If data can be provided to document that plasma exposure (AUC) to the (b) (4) in mouse or rat provides an adequate margin (≥25-fold) above the presumed plasma exposure in humans resulting from the presence of the (b) (4) in the drug product, then the (b) (4) would be considered qualified and the genetic toxicology study would not be needed.

3: In vitro chromosomal aberration assay in mammalian cells or an in vitro mouse lymphoma tk assay for the impurity, (b) (4) (tested directly) that has been identified as a potentially genotoxic impurity based on SAR. If data can be provided to document that plasma exposure (AUC) to the (b) (4) in mouse or rat provides an adequate margin (≥25-fold) above the presumed plasma exposure in humans resulting from the presence of the (b) (4) in the drug product, then the (b) (4) would be considered qualified and the genetic toxicology study would not be needed.

4: A non-clinical self-administration study to assess the abuse potential of dalfampridine.

5: A receptor binding study (dopamine, serotonin, GABA [gamma-amino-butyric-acid], opioid, NMDA, monoamine, sodium channel, calcium channel, and cannabinoid receptor sites) to assess the abuse potential of dalfampridine.

6: Assessment of adverse events related to abuse potential from clinical studies and clinical trials. MedDRA terms that report incidents of euphoria-related behaviors should be emphasized: impaired attention, cognition, mood, and psychomotor events; and dissociative or psychotic behaviors (see below).

Recommendation for other Postmarketing Study Commitments (PMCs)

I recommend the following post-marketing commitments (PMCs)

1: A randomized prospective placebo controlled trial to evaluate the efficacy of dalfampridine SR 5 mg twice daily in patients with multiple sclerosis; the trial should include a 10 mg twice daily arm. The primary outcome measure should be the improvement in walking speed as measured by the Timed 25-Foot Walk during the treatment period of 4 weeks. The trial should not exclude patients with EEG abnormalities who do not have a history of seizures. The trial should incorporate testing to assess the risk for urinary tract infections.

2: Support the addition of a 7.5 mg dosage strength, for use in patients with mild or moderate renal impairment, a population at risk for drug accumulation. Such support may include an evaluation of the pharmacokinetics of the 7.5 mg dose. The proposal should be submitted to the Division for comment prior to study initiation.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS

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/s/

ERIC P BASTINGS
01/20/2010