CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-250s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	22,250
Applicant Name	Acorda Therapeutics, Inc
Date of Submission	
PDUFA Goal Date	January 22, 2010
Proprietary Name / **Established (USAN) Name**	Ampyra/Dalfampridine
Dosage Forms / Strength	Controlled Release Tablet
Proposed Indication(s)	1. Improvement of walking ability
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Kachikwu Illoh, MD, Gerard Boehm, MD
Statistical Review	Sharon Yan, PhD
Pharmacology Toxicology Review	Richard Houghtling
CMC Review/OBP Review	Lyudmila Soldatova
Microbiology Review	
Clinical Pharmacology Review	Parepally & Lee
DDMAC	Amy Toscano
DSI	Antoine El-Hage
CDTL Review	Eric Bastings, MD
OSE/DEpi	
OSE/DMEPA	Denise V. Baugh
OSE/DRISK	Jessica M. Diaz
Other – Div Dir Review Dep Dir for Safety Review	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

I. Background

Fampridine is 4-aminopydridine, a drug that is a potassium channel blocker never approved for use in the U.S. but widely used in the form of home brews, because of a putative ability to enhance nerve conduction in demyelinated nerve fibers, in various neurological disorders, such as Guillain-Barre Syndrome, spinal cord injury, and MS. The clinical data have been reviewed by Drs. Illoh (clinical), Yan (statistics), Boehm (safety), and Parepally and Lee (clinical pharmacology). Other critical reviewers are listed in the Division Director (Dr Katz) and CDRL (Dr Bastings) reviews, including reviewers of chemistry, pharm-tox, maternal health issues, carton and container labeling, tradename, the REMS and communication plan, and controlled substance issues.

The claim sought for dalfampridine is a novel one for multiple sclerosis. Past MS claims have been primarily reduction in exacerbations and, in some cases, decreased disability. There is no doubt that difficulties in walking are a significant problem for patients with MS.

II. Effectiveness

Acorda's application relies on 2 trials, MS-F203 and MS-F204, substantially identical trials, with 203 having a 14 week double-blind drug period and 204 a 9 week period. Study 203 used 3:1 randomization; 204 used 1:1 randomization. Both used a 2 week single-blind run-in period during which baseline walking speed was assessed by a timed 25 foot walk, was measured on 4 occasions (baseline and visits 0, 1, and 2), followed by the double blind period with 4 assessments, and a two week post-treatment follow-up, with a walking speed assessment at week 1. In addition to measuring walking speed, the blinded evaluator performed, among other assessments,

- Clinical global impression (CGI)
- Subject global impression (SGI)
- The Ashworth assessment of spasticity
- A 12 item MS walking scale (MSWS-12), that gives a subject's subjective assessment of ability to walk, run, climb over the preceding 2 weeks
- The LEMMT, an assessment of lower extremity muscle strength

As the clinical reviewers, Dr Katz and Dr. Bastings describe, there was considerable discussion of the meaningfulness of the study endpoint and the primary reviewer, Dr. Illoh, remains skeptical. The primary endpoint, with which we concurred, was a responder analysis of the 25 foot timed walk test; a "responder" was a patient whose walking speed in at least 3 (of the 4) on-drug visits was greater than any of the 5 off treatment measurements (baseline, 3 in the placebo lead in, one a week after double blind). They chose this measure because people so described in an early dose-response study (MS-F202) had an average > 25% increase in walking speed, which appeared clinically meaningful. This is plainly not the most obvious measure of improved walking speed (average walking speed in the drug and placebo groups or increase from baseline on drug vs increase on placebo would be more typical), but responder analyses may be particularly useful where response is confined to a subset. We considered at various meetings whether a co-primary endpoint should be looked at, such as SGI (Subject Global Impression) or whether the clinical meaningfulness of the endpoint should be supported in some other way, but did not insist on a particular method. In the study a variety of secondary analyses looked at these

more typical endpoints, but in addition, a somewhat different and unusual approach was used to address the meaningfulness of the endpoint. The MSWS-12 results were examined to see if there was significantly more improvement on that scale in "responders" than in the non-responders in both groups, i.e. drug and placebo responders and drug and placebo non-responders. This assessment was considered a requirement for a successful study (see stat review, p 7). That is, it was almost a study endpoint. I am somewhat troubled by that concept, but it may deserve more thought. Although this assessment does indeed appear to add to the "plausibility" of the meaningfulness of the 25 walking responder analysis, it is not really a study endpoint, as there is no drug vs placebo comparison. What it does show is that walking time results correlate with and MSWS-12 results.

Results are shown in the following table
Results (Stats review, Dr Yan)

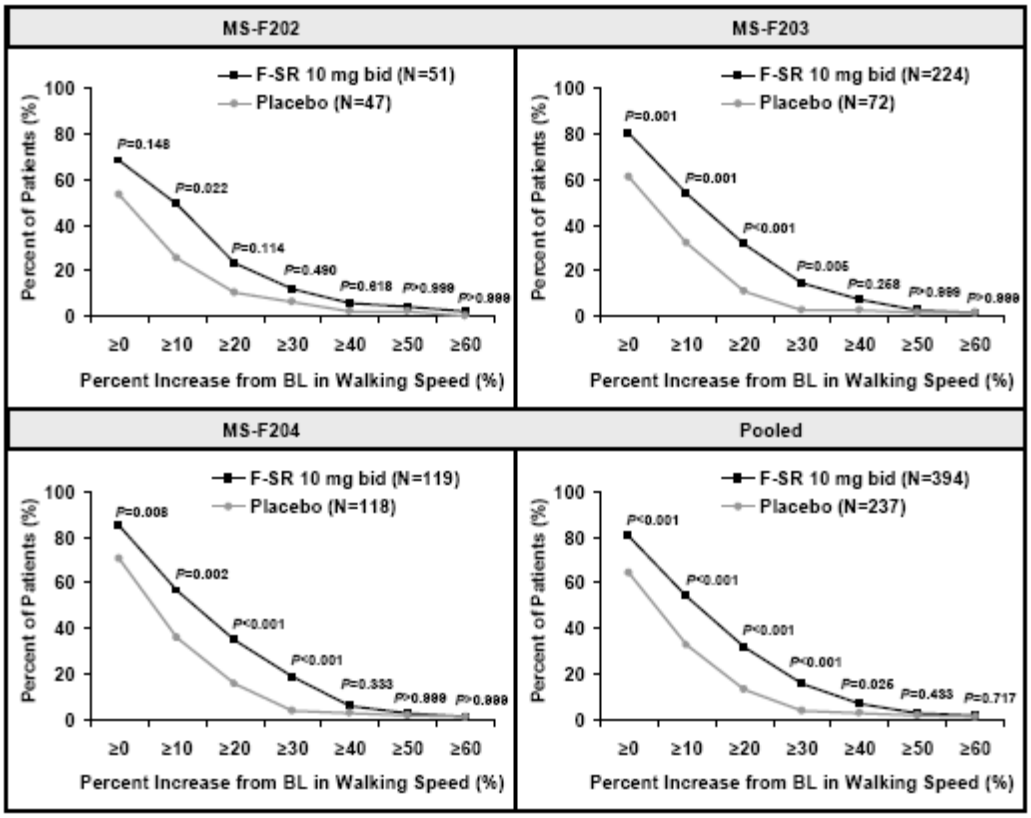
	Study 203			Study 204		
n	Dalfampridine 224	Placebo 72		Dalfampridine 119	Placebo 118	
Responder	78/224 (34.8%)	6/72 (8.3%)	p < 0.001	51/119 (42.9%)	11/118 (9.5%_	p < 0.001
Baseline (visit 2) speed	2.13 ft/sec	1.11 ft/sec	(NS)	2.22	2.28	(NS)
Speed (visit 6)	2.34	2.16		2.44	2.39	
change	0.21	0.05	p = 0.03	0.22	0.11	p = 0.04
MSWS-12 (visit 6) change	-1.56	+3.59	p = 0.06	-3.12	+0.72	p = 0.03
LEMMT (visit 6) change	0.13	0.04	p = 0.003	0.09	0.04	p=0.1
Ashwarth (visit 6) change	-0.16	-0.07	p = 0.02	-0.18	-0.06	p = 0.015

I note that with respect to walking speed, the studies are positive only for change from baseline, not on a direct comparison; it is, however, in my view, the change from baseline that is most pertinent.

Thus, in the responder analyses of 25 foot walk in both studies, in change in walking speed from last placebo visit to last on-treatment visit, in MSWS-12 in study 204 (but not quite in study 203, p = 0.06) and in Ashworth and LEMMT, both studies showed effects on walking speed, a "global" scale of walking quality (the MSWS-12), a measure of spasticity (Ashworth), and lower extremity muscle strength, all in all strong evidence of an effect on walking speed and walking more generally. Dr. Illoh was not convinced that this effect represented a clinically meaningful effect and indeed speed differences were numerically small, but the responder rate differences was not small (35-43% vs 8-9%) and Drs. Katz and Bastings, as well as the Peripheral and Central Nervous System Advisory Committee (meeting on Oct 9, 2009) do not agree. I do not agree either. The sponsor did show that the MSWS-12 response, an unequivocally clinical measure, was greater in people who were 25 foot walk responders and also showed an effect on the MSWS-12 in a direct comparison. In some ways a more clearly impressive result, as noted by Dr. Bastings is shown in the analysis of the cumulative distribution of results shown in labeling. Dr. Bastings shows (p 14) the conventional cumulative distribution presentation but even clearer is the display from labeling.

The cumulative distribution is shown below:

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)



The version in labeling is also shown

Figure 1: Average walking speed change (%) from baseline during the double-blind phase of Trial 1

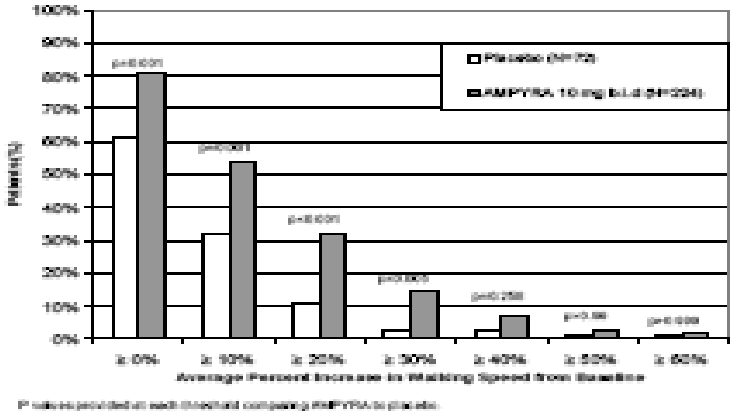


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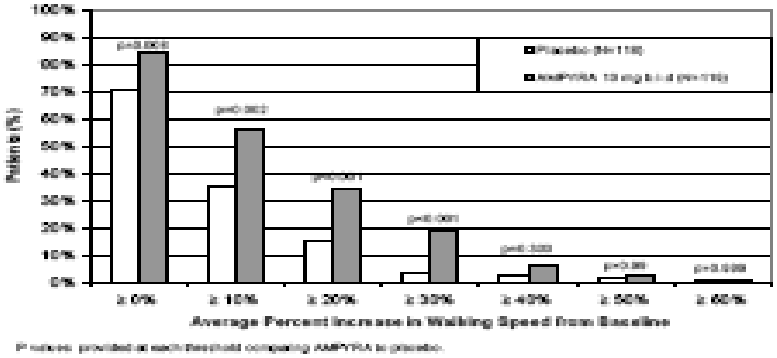
Figure 2: Average walking speed change (%) from baseline during the double-blind phase of Trial 2



This display shows that significantly more patients given dalfampridine had a 30% increase in walking speed (about 15-20% vs about 3% on placebo). That is a minority of the patients, of course, but would seem to be an obvious benefit, as Dr. Bastings notes.

III. Safety

Safety is well-discussed in Dr. Boehm's primary review and by Drs. Katz and Bastings. The main issue here is clearly the seizures observed; apart from that, there were some episodes of dizziness and balance disorder leading to discontinuation and some evidence in the controlled MS trials of drug-related insomnia, headache, asthenia, balance disorder, back pain, difficulty walking, vomiting, anxiety, and tremor, (all ≥ 2% and 2x placebo). Few of these seemed clearly dose-related although exposure at 15-20 mg bid was small (total n =107). Balance disorder and dizziness, and headaches, seemed most clearly dose-related.

In the 2 well-controlled studies supporting effectiveness there were just 2 seizures, one each on dalfampridine 10 mg bid (n=400) and on placebo (n = 238). In the dose response study MS-F202 there were 2 seizures on 20 mg bid (n=57) none on 10-15mg bid (n = 102). In open label experience in 660 patients at 10 mg bid, there were 5 seizures, a rate not clearly different from the rate on placebo. Past experience in MS gave various seizure rates, from about 0.1-1.0%. A concern is that, given the dose-related increase in seizures with dalfampridine, with a fairly clear effect at 20 mg, some people with renal compromise (dalfampridine is entirely renally excreted)

will attain dalfampridine blood levels that could induce seizures. It would therefore be desirable to know whether doses smaller than 10 mg bid were effective. There is, in fact, no useful data on any dose but 10 mg bid.

To minimize seizure risk, dalfampridine labeling will contraindicate in moderate or severe renal impairment, with a warning about potential seizures even in people with mild impairment. This is also stressed in Dosage and Administration, Specific Populations.

To determine whether a lower dose (further away from a dose giving potentially seizure-inducing blood levels) could be effective, the applicant has committed itself to conduct a study of 5 mg bid and will develop a 7.5 mg dosage form for use in people with mild or moderate renal impairment. It is clear from an early study that doses above 10 mg bid have little promise.

In addition a REMS has been required. It will include a Medguide emphasizing the risk of seizures. The applicant will also be required to examine potential embryo-fetal toxicity of (b) (4) an impurity and conduct an in vitro bacterial mutagenicity (Ames) test and an in vitro chromosomal aberration assay to evaluate another impurity, (b) (4) and abuse potential.

IV. Conclusions

Acorda has submitted two adequate and well-controlled studies providing substantial evidence that dalfampridine improves walking in patients with MS, shown primarily as improved walking speed. A fraction of drug-treated patients (but very few placebo patients) have an obviously substantial increase (30% decrease in time to walk 25 feet) and significant effects on the MSWS-12, a subjective walking assessment, were shown in one study and were nearly significant ($p = 0.06$) in the other. The risk of seizures will be managed by special attention to use and dosing in patients with reduced renal function.

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
01/22/2010