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Quick Pulse

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FDA Advisory Panel Votes Overwhelmingly to Approve Acorda's Fampridine-SR for Multiple Sclerosis

College Park, MD
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The FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted overwhelmingly (12 to 1) to recommend approval of Acorda Therapeutics' Ampriva (fampridine-SR), a 10 mg 4-aminopyridine (4-AP) sustained-release (SR) tablet for the symptomatic improvement of walking ability in patients with multiple sclerosis (MS). It would be a new indication, never before granted by the FDA, as currently-approved MS drugs are indicated to decrease relapse rate and, in some cases, to prevent the accumulation of disability.

Although the FDA's background documents said that the effects of fampridine may not be "clinically meaningful," the panel decided that fampridine-SR's benefits outweigh its risks, which include seizures and urinary tract infections. Panel members agreed that the risk of seizures was small, especially if only the ≤10 mg BID doses were prescribed. Although there was only a slight improvement on the 25-foot walk test for MS vs. placebo, the panel said that their patients would want to try it.

The panel also voted 12-1 that Acorda should evaluate doses <10 mg (5 mg or 7.5 mg), and it voted 10-2, with one abstention, that the low-dose testing could wait until after fampridine-SR is approved. Acorda said that an early formulation of the 5 mg drug had stability problems, but the company is working on a new version with Elan, who originally formulated the drug.

After the meeting, Dr. Ron Cohen, president/CEO of Acorda, said the company will be discussing a 7.5 mg tablet with the FDA, adding, "We're delighted that the panel voted 12-1. MS patients are much closer, hopefully, to getting a new drug."

Background

More than 2.5 million people worldwide have MS, which is caused by damage to myelin, the protective sheath around nerve cells in the brain and spinal cord. MS worsens as damage to myelin causes muscle weakness, trouble with coordination and critical thinking, and memory loss.

Fampridine is a BID potassium channel blocker aimed at improving walking ability in MS patients. Non-clinical evidence suggests that it may enhance action for potential conduction in demyelinated nerve fibers. It has a long history of use in the U.S.; many neurologists already use a generic version of fampridine, which can be procured at compounding pharmacies. Before its investigational and off-label use in humans, 4-AP was known mainly as a bird poison and as a research tool to characterize subtypes of potassium channels in bench research. In results

from a study released in February 2009, the drug helped 35% of MS patients walk faster compared to those on placebo.

The FDA said on May 6, 2009, that it would review fampridine-SR under an expedited "priority review" program for new drugs for serious illnesses. A priority review is supposed to be decided upon within six months, four months more quickly than the review process for most drugs.

Fampridine was first developed by Elan Corporation in the 1990s and was later licensed by Acorda. If approved, fampridine-SR would be manufactured by Elan. This is the first drug which Acorda has submitted to the FDA. The company also sells Zanaflex (tizanidine) capsules, a treatment for spastic muscles that the company acquired from Elan in 2004. In July 2009, Biogen agreed to pay as much as $510 million for the rights to market fampridine-SR outside of the U.S. after Acorda said that it would not be able to exist after next year without a partner.

The FDA Perspective

FDA reviewers questioned whether fampridine-SR is clinically meaningful, had doubts about the company's trial design, and said that the risks of side effects, most notably seizures, may not outweigh any benefits of the drug. The reviewers said that Acorda "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." Acorda conducted the two pivotal efficacy studies, MS-F203 and MS-F204, under a Special Protocol Assessment (SPA) with the FDA. The studies measured the time patients took to walk 25 feet. The FDA background document stated, "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 studies 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 this new drug application (NDA), the efficacy must be considered against a widely acknowledged safety signal for 4-aminopyridine and other pyridine compounds: seizures."

FDA Analysis of Study MS-F203

Measurement	Fampridine n=224	Placebo n=72	p-value
Baseline walking speed (ft/sec)	2.14	2.12	Nss, 0.88
Visit 6 walking speed (ft/sec)	2.35	2.16	Nss, 0.19
Walking speed change at Visit 6 vs. baseline (ft/sec)	0.21	0.05	0.03
Walking speed change at Visit 6 vs. baseline	10.90%	5.58%	Nss, 0.24
Walking speed on drug (average)	2.34	2.16	Nss, 0.17
Walking speed change on drug (average) vs. baseline	0.28	0.10	0.0004
Walking speed change on drug (average) vs. baseline	13.63%	4.71%	0.0003
MSWS-12 change on drug (average) vs. baseline	-2.72	0.62	Nss, 0.084
MSWS-12 change at Visit 6 vs. baseline	-1.56	3.59	Nss, 0.063
SGI change on drug vs. baseline	-0.0045	-0.1967	Nss, 0.12
LEMMT change on drug vs. baseline	0.13	0.04	0.003
Ashworth change on drug vs. baseline	-0.16	-0.07	0.021

The FDA reviewer said that while study MS-F203 met its primary efficacy endpoint of improvement in walking ability, "Improvement in walking speed was of questionable clinical significance." He said that the improvement patients on fampridine-SR experienced "was numerically quite small, and the average time to complete the 25-foot walk was not different between the treatment groups in either study. Walking speed at the end of the treatment (Visit 6) was also not statistically different. In addition to the lack of significant difference between fampridine-SR and placebo patients for average 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 with p-values <0.05), were "of small magnitude, with a walking speed increase of 0.21 ft/sec for fampridine-SR-treated patients between baseline and Visit 6, and a 0.05 ft/sec increase for placebo. That change translated into only a 0.88 second difference between fampridine-SR and placebo in the 25-foot walk…For these reasons, it appears that the clinical meaning of the differences seen on the primary outcomes is in question."

The FDA asked for a second step of the primary analysis consisting of testing whether the responders reported a significant improvement in the 12-item MS walking scale (MSWS-12) scores compared to non-responders, regardless of treatment group. MSWS-12 is a questionnaire asking patients to rate their limitations in mobility. The third step of the primary endpoint analysis tested whether patients who responded to fampridine-SR would still register significant improvement in walking speed compared to placebo. Secondary analyses included an evaluation of lower extremity motor strength (LEMMT), spasticity (Ashworth), and subject global impression of change (SGI). A major limitation of the MSWS-12 test is that it "measures the same domain as the timed 25-foot walk, and both are correlated. Therefore, it is not unexpected that patients doing better on the 25-foot also do better on the MSWS-12. Therefore, *a posteriori,* it is not clear that this truly validates the significance of the responder definition analysis."

While there was a trend (not significant) favoring fampridine-SR in the change from baseline to Visit 6 in MSWS-12 scores, most of the improvement occurred during the pre-treatment period, "which again leads us to question the meaningfulness of that change," the reviewers noted.

Safety

The FDA reviewers said, "The principal safety issue with fampridine is the risk of seizures…data from the controlled clinical trials at the 10 mg 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 two seizure events (one fampridine, one placebo)." In the 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 two events in 57 subjects, "a concerning finding suggesting…a narrow therapeutic index." For the five patients who had a seizure in controlled trials, "The data suggest that seizures occurred at exposure levels within the range expected for the 10 mg BID dose, as the maximum fampridine concentration observed for the 10 mg BID dosing regimen was 87.3 ng/ml."

Acorda provided safety information on 917 MS patients, 583 spinal cord injury (SCI) subjects, and 382 non-patient subjects. One or more serious adverse events occurred in 15.1% of MS and SCI subjects, most commonly MS relapse, convulsion, urinary tract infection, and cellulitis.

In the MS-controlled trials, serious adverse events were three times more frequent in fampridine-SR-treated subjects (6.5%) compared to placebo (2.1%), and the risk for all serious adverse events appeared dose related. Common adverse events in MS-controlled trials included urinary tract infection, insomnia, dizziness, headache, asthenia, nausea, fatigue, MS relapse, balance disorder, paresthesia, and back pain.

The FDA's Dr. Russell Katz, director of the Division of Neurology Products (DNP), Office of Drug Evaluation I, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), gave a brief overview. The primary outcome measure of the clinical trial was the responder rate, "an atypical outcome measure in MS trials. It's a little complicated…patients had to have at least three on-treatments and walking speed was measured…We agreed completely with the company that it was an appropriate measure...and there is no dispute between the Agency and the sponsor about the results on this primary outcome; there are clear and robust differences between fampridine-SR and placebo." However, he said that questions were raised about the clinical meaningfulness of the drug. The primary outcome depended on differences between the walking tests on and off drugs, "which themselves could be very small…It did appear to be small."

Serious Adverse Events in MS and SCI Clinical Studies

Measurement	Fampridine-SR
MS relapse	2.5%
Convulsion	1.3%
Urinary tract infection	1.2%
Cellulitis	1.1%
Pneumonia	0.9%
Sepsis	0.5%
Each of these: Muscle spasticity, asthenia, fall, nausea, pulmonary embolism, deep vein thrombosis	0.3%
Each of these: Anemia, atrial fibrillation, chest pain, influenza, urosepsis, hip fracture, osteoarthritis, breast cancer, encephalopathy, syncope, anxiety, decubitus ulcer	0.2%
Complex partial seizures	0.2%

Differences between patients on fampridine and placebo-treated patients on other outcome measures also appeared to be relatively small. Dr. Katz said, "In this case we believe a consideration of the size of the treatment effect (is warranted) in light of the ability of fampridine-SR to cause seizures… (The data in the controlled trials showed that the rate of seizures in patients on fampridine-SR was about the same as in the placebo group, and the open-label part of the study suggests that the rate at 10 mg BID was consistent with what was seen in the controlled trials)…But in bigger doses, the rate seems higher in the fampridine compared to placebo. In the open-label experience of 660 patients, the incidence of seizures at 10 mg BID was about the same, but at 15 mg BID in 175 patients, the incidence of seizures was about 1.4% (higher), about twice (that) seen at 10 mg BID and with the rate of about 1.7 seizures in 100 patient years. At 20 mg BID, where there are very little data, the incidence was about 3.5% in 57 patients with a rate of about 12 seizures per 100 patient years. These are very small numbers of events. In the open-label trials, there were 5 seizures in the 10 mg BID group, 2 seizures in the 15 mg BID group, and 2 seizures in the 20 mg BID group."

Dr. Katz said that the FDA reviewers were interested to see if they could learn anything from plasma levels, "There is some information about that, but it's not particularly reliable. We don't have good information on that…The open-label seizure data are difficult to interpret. We tried to look at this…those rates are highly variable…Patients in these studies were screened by EEGs, and patients with evidence of seizure activity were excluded from treatment of fampridine-SR, so this fact further complicates the interpretation of the seizure data. So, I summarize that the studies clearly demonstrate a robust effect on the outcome…The effect was based on differences in the timed walk which were generally relatively small. Differences in other outcome measures were generally statistically significant but also generally small. We were interested in seizures in doses only slightly higher than the proposed dose…Furthermore, 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 (one 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."

Fampridine-SR Seizure Risk

Study	Placebo	Fampridine-SR			
		Total	10 mg BID	15 mg BID	20 mg BID
MS-F202	0/47	1.3%	0/52	0/50	3.3%
MS-F203	0/72	0.4%	0.4%	0	0
MS-F204	0.8%	0/120	0/120	0	0
Total	1.6/ 100 PY	2.1/ 100 PY	0.9/ 100 PY	0	11.8/ 100 PY

Fampridine-SR Seizure Risk Incidence and Dose at Time of Occurrence in Open-Label Extension Trials in MS through November 30, 2008

Measurement	MS-F202 EXT 15 mg BID	MS-F202 EXT 10 mg BID	MS-F203 EXT 10 mg BID	MS-F204-EXT 10 mg BID	Total 10 mg BID
Percentage	1.14%	0.56%	1.5%	0	0.76%
Incidence per 100 PY	1.7	0.22	0.69	0	0.41

Dr. Gerard Boehm, a medical officer in the FDA's Division of Neurology Products, presented the seizure risk:

- Fampridine can cause seizures.
- Open-label extension trials' patients are a highly selected population.

Dr. Kachi Illoh, Division of Neurology Products, CDER, summarized:

- Overall, there was a small improvement in clinical variables with fampridine given at the dose of 10 mg BID.
- The clinical significance of the effects at the given dose remains unclear.
- There is a potential risk of increase in seizures.
- There is a limited evaluation of lower than 10 mg dose.

He concluded:

- Fampridine is associated with higher proportion of walking score responders.
- Improvement in walking score is of small magnitude and of uncertain clinical significance.
- Dose response suggests a need for evaluation of lower fampridine doses.

THE ACORDA PERSPECTIVE

Acorda president/CEO Dr. Cohen gave the historical background and mechanism of action of fampridine-SR, which is a new class of therapy for MS. It directly targets MS neuropathy of demyelination. He said that as many as several thousand MS patients take a compounded form of fampridine off-label. He added that there have been reports of serious dosing errors with compounded fampridine.

Timeline:

- **1991-1994:** Elan developed fampridine-SR oral tablet.
  - Pharmaceutical grade (cCGMP).
  - Reliable plasma levels.
  - Twice-daily dosing.
  - Minimal food effect.
- **1998:** Acorda obtained rights to fampridine-SR in MS.
- **2004:** End of Phase II meeting with the FDA.
- **2005-2008:** Sequential Phase III trials and SPAs.

The goals of the Phase III trial were to:

- Demonstrate that a proportion of MS patients show consistent improvement in walking speed.
- Establish the clinical meaningfulness of this improvement.
- Show that these effects occur irrespective of MS course type and concomitant immunomodulator therapy.
- Evaluate 10 mg BID dosing interval and durability of response.
- Show safety profile of fampridine-SR formulation to be acceptable.

Dr. Aaron Miller, a neurologist from Mount Sinai School of Medicine and medical director of the MS center there, spoke on behalf of the company, stating that 64%-85% of people with MS have difficulty walking, and 70% consider it to be the most challenging aspect of their disease. He said that while there are some therapies aimed at helping MS patients walk, there is no drug therapy currently indicated for the treatment of impaired ambulation in MS.

Dr. Aaron Blight, Acorda's chief scientific officer (CSO), described the two pivotal studies: MS-F203 and MS-F204. MS-F203 was a randomized, double-blind, placebo-controlled, 14-week Phase III study. Measurements included a timed 25-foot walk, the MSWS-12, SGI, clinician global impression (CGI), LEMMT, and the Ashworth score for spasticity.

The MS-F203 study established:

- Efficacy.
- Clinical significance of the primary endpoint (25-foot timed walk).
- Continuation of effect beyond three months.

The MS-F204 study (designed to confirm the primary end-point) established:

- Confirmation of efficacy.
- Duration of effect over 12-hour dosing interval.

Treatment Effect: Average Change in Walking Speed

Fampridine-SR n=224	Placebo n=72	p-value
13.62%	4.71%	p<0.001

Clinical Effect: Change in Walking Speed

Timed walk responders n=76	Timed walk non-responders n=146
25.15%	7.48%

Dr. Blight said that the MSWS-12 results showed positive improvement among timed walk responders vs. timed walk non-responders. He added that a post hoc analysis of the Phase II study, MS-F202, showed little difference in the response rate by dose group (10 mg BID, 15 mg, and 20 mg). He summarized:

- Primary outcome measure met with high statistical significance in two pivotal studies.
- Timed walk responders had:
  - 25% average increase in walking speed.
  - Significantly reduced MSWS-12 scores.
  - Significantly improved SGI and CGI scores.
- Significantly more fampridine-SR patients than placebo patients had ≥20%, ≥30%, and ≥40% increases in walking speed, and fewer had decreased speeds.
- Benefits were independent of
  - MS course type.
  - Level of disability.
  - Concomitant immunomodulator therapy.

Dr. Thomas Wessel, Acorda's CMO, summarized the trials' safety data:

- The drug was well tolerated, with retention rates >90%.

Adverse Events in Phase II and III Trials

Measurement	Fampridine-SR 10 mg n=400	Placebo n=238
Treatment-emergent adverse events	84.8%	73.5%
Treatment-emergent serious adverse events	5.5%	2.1%
Deaths	0	0
Most frequent treatment-emergent adverse events		
Fall	16.0%	16.4%
Urinary tract infection	14.5%	9.2%
Insomnia	9.3%	3.8%
Asthenia	8.3%	4.2%
Dizziness	7.8%	4.2%
Headache	7.5%	4.2%
Nausea	7.0%	2.5%
Fatigue	6.5%	4.6%
Upper respiratory tract infection	5.8%	7.1%
Balance disorder	5.8%	1.3%
Back pain	5.5%	2.1%
MS relapse	5.3%	3.8%
Treatment-emergent adverse events in extension studies		
Urinary tract infection	30.6%	---
Fall	28.5%	---
MS relapse	25.0%	---
Asthenia	16.4%	---
Arthralgia	13.0%	---
Upper respiratory tract infection	11.8%	---
Insomnia	11.1%	---
Edema peripheral	10.8%	---
Pain in extremity	10.5%	---
Fatigue	10%	---

Deaths on Fampridine-SR

Reason for death	Time on drug
During treatment	
Ischemic heart disease	14 weeks
During open-label extension studies	
Aortic dissection	25 days
Suicide	1 month
Suicide (after 2008 clinical data cutoff)	1 year two months
Intracranial hemorrhage	1 year 5 months
Unknown	2 years 2 months
Myocardial infarction	2 years 7 months
Accidental oxycodone toxicity	2 years 8 months
Cerebral hemorrhage	4 years 6 months

Incidence of MS Relapse with Fampridine-SR

Time period	Fampridine-SR	Placebo
On-treatment period	3.8%	3.8%
Post-treatment period	1.8%	0.4%

- The adverse event profile was consistent across studies, and adverse events were related to the pharmacologic action of drug.
- Increases in insomnia, dizziness, headache, nausea, and back pain were mostly mild-to-moderate, transient in nature, and not a principle cause of discontinuation.
- Seizure events: One event occurred on drug and one on placebo, and seizure incidence on 10 mg BID was consistent with background rate in MS.
- Adherence to 10 mg BID dosing will be addressed by Risk Evaluation Mitigation Strategies (REMS) program.

Dr. Wessel said that the data suggest that the risk of seizure is increased at 30 mg BID or higher. As of November 30, 2008, the cutoff date for the data, the incidence rate of seizures was 0.41 incidents per 100 patient years. In contrast, the current rate as of September 30, 2009, is 0.32 incidents per 100 patient years. Dr. Wessel clarified, "This new calculation has not been reviewed by the FDA…The literature shows incidence rates between 2 and 7 times that of the general population. The studies vary considerably in design and methodology."

Dr. Wessel summarized the seizure data:

- Seizures are associated with higher doses of fampridine-SR.
- Seizure risk is elevated in the MS population.
- No increased incidence of seizure was observed in the fampridine-SR program with 10 mg BID.
- There is a narrow therapeutic range.
- Medication should not exceed recommended dose.
- A REMS is necessary.

Dr. Wessel said that the focus of the REMS proposed by Acorda would be to ensure selection of the appropriate patients and to educate physicians to prescribe only 10 mg BID for patients. The REMS proposal includes:

- Distribution through specialty pharmacies.
- A medication guide.
- A communication plan with labeling, Dear Prescriber letters, and ongoing healthcare provider education outreach.
- Enhanced pharmacovigilance and frequent safety reporting to the FDA.
- Ongoing evaluation to ensure effectiveness of REMS tools.

Dr. Christine Short, division chief of physical medicine and rehabilitation, Queen Elizabeth II Health Sciences Centre, Halifax, Canada, told the panel that she has had 13 patients on instant-release (IR) fampridine, and five have had seizures. She no longer prescribes fampridine-IR because she doesn't think that it is safe. She had 19 patients on extended-release (ER) fampridine, and many have taken the 10 mg BID dose for more than 5 years. None of her patients on fampridine-ER have had any seizures, "Seeing improvements in walking… has a huge impact on…quality of life. I now have a drug that can help a significant number of patients with MS."

Dr. Miller, a neurologist, told the panel that the benefits of the drug outweigh the risks, "The studies have demonstrated an extent and breadth of response that is meaningful, and this benefit extends across all disease types, irrespective of duration of disease and without regard to the specific disability. The benefit extends across all people taking the drug (including non-responders), and that includes walking speed, lower extremity muscle, (and) the Ashcroft score."

He explained that he takes care of people with MS and, "like any other clinician, I always struggle with what is the risk:benefit ratio with any drug that I prescribe. Over the years, I've hardly ever prescribed compounded versions of 4-AP because of lack of data…because I had fear of seizures and because I was worried about the potential for compounding error…It was only after I started to see the results of the (fampridine-)SR trials and my own experience in those trials that I began, albeit with some trepidation, to start prescribing it…I am now very comfortable using fampridine-SR…I believe the seizure level is very low in this 10 mg BID group…The risk of seizures is probably lower than that for a number of other drugs that I commonly prescribe, such as some of the antidepressants…I'm not convinced that these alleged relapses that occurred following the discontinuation of fampridine-SR are a concern…I think they actually represented a return to baseline of more severely impaired walking ability…The data have shown that walking speed increased two weeks after beginning therapy and was sustained over the subsequent weeks. We should be able…to assess whether a patient is responding to fampridine-SR and if not, discontinue the drug so as to limit the exposure to any seizure risk." He asked the FDA to approve the drug, saying that the drug is valuable in that it will safely and substantially benefit a significant percentage of his patients.

PUBLIC WITNESSES

Eleven people spoke, some with great emotion, in favor of fampridine-SR's approval.

Nicholas LaRocca, representing the National Multiple Sclerosis Society, said that there is an unmet need for pharmacological therapies that improve walking for patients with MS. A survey of more than a thousand MS victims showed that two-thirds reported difficulty walking, and most said that it was the most challenging part of their disease. He said that difficulty walking is related to a wide range of activities and functions, "Even a modest improvement can translate to a great boost."

Susan Zurndorfer, who was diagnosed with MS in November 2000 and who uses a walker, said that fampridine-SR helped her immediately, "My legs felt stronger, and I could walk longer for longer distances…My life revolves around getting from A to B…I have to pace myself, and I have to plan…The bottom line is I just want to keep on walking… Thanks to drugs such as fampridine, I am still walking."

Karen Jackson, who has a progressive form of MS, walks with a cane and also uses a scooter, chairlift, and walker, said that she has to plan out every move of her day, "The possibilities that this drug hold for me are very exciting…It could improve my walking, which would improve my overall stamina, which would improve my quality of life…The mere promise of this drug's potential and benefits brings real hope to me." She told Dr. Miller that his clinical observations "were right on target for people like me."

Elissa Levy, president/founder of the non-profit group MS Hope for a Cure, and who has secondary progressive MS, spoke emotionally in favor of the drug. When she was diagnosed at age 35, she had to move into her parents' apartment building, and her social life ceased to exist. She is still getting worse, and she didn't qualify for the fampridine trial "because I can limp faster than any other girl with MS in New York City can limp…I did it too quickly." Her doctor tried the compounding pharmacy, and she said, "I wouldn't have my life without fampridine…As an adult, I want to be able to take that risk (of seizure) myself…MS is just an incredible, miserable disease, and fampridine is my miracle pill…But as a medical community maybe there are only 30% of us that it will affect, and I think that is significant and is worth taking the risks to make this drug available so that they have every opportunity to get their lives back."

Robert Engel, who has MS, said that if a product comes on the market that can improve mobility even for the smallest amount, it could change the quality of his life. He said that if his disease continues to progress, "There's no doubt in my mind that I will be wheelchair bound…I'm not getting better, and the disease is progressing…Let's give (the drug) a try." He told the FDA that it is the only hope he has, "If you think it is working and it can be helpful, don't wait. Bring it to market and bring it to market as quickly as you can…I need the hope that this drug can give."

Jacqueline Havener, a MS patient who has taken fampridine for 15 years, said that the drug changed her life. She was diagnosed in 1965 and has three wheelchairs, many canes, and a stairclimber. She said, "Everyone in this room should have to use a wheelchair for a time to understand the difference this drug made for me." She said that she spent two weeks in Italy this year, using only a cane or another person for balance. She can raise her legs and resist pressure exerted on them, and her life has been vastly improved as a result of the drug.

June Halper, an adult practicing nurse specializing in MS and representing the Consortium of MS Centers and a group of MS nurses, told the panel that any therapy that helps MS patients improve their mobility would be welcome. She said that fampridine-SR would "add to the hope chest of MS care."

Dr. Christopher Bever, an academic neurologist experienced with fampridine, told the panel that the drug improved walking speed in MS patients and that this is consistent with his experience. In clinical practice, he said patients can determine within a number of days whether it is working. He is concerned about the FDA's re-analysis showing no significant effect, "The drug is clinically meaningful. The primary issue is safety and seizure induction…Seizures are not increased with the current dose, and further studies (on a lower dose) would not be valuable here…Prudence suggests that an MS patient with a history of seizures not be given this drug… Fampridine-SR represents an important treatment…Seizure risk limits use but should not prohibit use."

Serena Lowe, representing the National Disability Institute, said that about 400,000 Americans have MS, and limited mobility is a huge problem for them. Even the most incremental increase in mobility could affect many MS patients.

Diane Dorman, representing the National Organization for Rare Disorders, said that walking a few extra feet unaided "may feel like a mile" to many MS patients.

Mimi Mosher, who is now confined to a wheelchair because of MS, said that she has used every piece of equipment available as a result of her disease. Her husband, Jonathan, said that she is now legally blind, and he is her caretaker. She was so emotionally wrought that she could barely speak. Jonathan said that the disease, which hit her right out of college, has made their life incredibly restrictive, "Loss of mobility is a three-word phrase that seems so neat and tidy, yet for us it grows and grows and is messy and unruly."

Panel Questions for Acorda Experts and the FDA

Smaller dose?

Dr. Sidney Wolfe, the consumer representative and director of Public Citizen Health Research Group, commented that the data showed little difference between the drug and placebo and asked, "Why haven't there been clinical trials using lower doses, 5 mg BID or lower? Why do the doses, no matter what they are, give the very same small clinical response?"

Dr. Blight, Acorda's CSO, responded that although there was no increase in response rate in the 10 mg BID, 15 mg BID, or 20 mg BID dose, there would be a more dramatic drop-off in efficacy if the dose were 5 mg BID. He said that the 10 mg

BID dose was the starting dose, explaining, "What we found …was that 10 mg, at the end of the day, showed almost maximal efficacy and the best tolerability, and that is maintained through a 12-hour dosing cycle, although some patients lose some benefit in the last hour." He added that the company had not tried a 5 mg dose in its clinical trials.

The FDA's Dr. Katz, asked whether a 5 mg dose could be tested and about how plasma concentration levels correspond to what is seen at 10 mg BID, suggesting, "Maybe lower doses might do something. At the low end of the plasma concentration curve, there are very few patients." Dr. Blight said that the percentage of improvement in walking speed starts to decrease with lower doses "although the data are limited." He said that a dose lower than 10 mg BID might contribute to efficacy only for part of the day.

Dr. Robert Temple, director of the FDA's Office of Drug Evaluation I (ODE I), OND, CDER, said, "One of the things that we've been encouraging people to do is show the cumulative distribution of responses…and we have put things like that in labeling for Alzheimer's drugs, etc…People vary, and you always see some people who worsen. What you see for an effective drug in general is a shift…and that's what you see… This has been true for Alzheimer's (and) for depression. I love these displays because they show how people are actually doing. This gives you not only one definition of a responder, so we like these displays, but they invariably show some people worsen. There are always some people who in the course of things are on the down side." Acorda president/CEO Dr. Cohen replied, "In our data, fewer patients got worse on fampridine-SR than on placebo…Throughout the study the number of patients or the percentage who got worse on fampridine-SR was smaller than placebo."

Risk Evaluation and Mitigation Strategy (REMS)

Elaine Morrato, PharmD, from the University of Colorado, Denver, with expertise in pediatrics and epidemiology, asked about the REMS proposal and noted that it was different from what she saw in the briefing documents. Surveys were referenced in those documents but were not in the information presented to the panel at the meeting. She said that she was disappointed at how little information was presented on the REMS proposal. An Acorda executive responded that it wasn't until just before the panel that the company realized that it could, for example, distribute the drug through specialty pharmacies. An Acorda consultant said that the REMS would include knowledge, attitude, and behavior surveys.

Asked if the survey instruments would be developed before any approval of the drug, the Acorda consultant replied, "They are in the process of being developed."

Asked who the specialty pharmacies would be, an Acorda executive said, "This has been evolving…We recently determined that we would be distributing through specialty pharmacies, but I don't have any specifics." He said that about six pharmacies would do the distribution.

Asked if the company would require EEGs before treatment, an Acorda executive explained that one of the exclusion criteria in the studies included the reading of an EEG (as an abundance of caution), "It has become apparent that there are serious questions that need to be resolved with respect to the risk:benefit of requiring EEGs, that being the potential to restrict access to the drug unnecessarily, such as people whose readings do not predict risk for seizure or erroneous readings." An Acorda scientist said that there are no data that validate EEGs as a screening tool to exclude patients in a population without seizures and said the sensitivity of EEG data would be "very low in this setting."

Dr. Stacy Rudnicki, a neurologist from the University of Arkansas, asked how many patients were excluded because of the EEG. An Acorda executive responded that source data showed 2.5%-4% of patients were excluded because of a history of seizure or abnormal EEG, and most were based on the EEG.

Placebo effect?

Dr. Mark Green, a neurologist from Mt. Sinai School of Medicine in New York, asked if he took the drug, would he feel or sense anything "in light of the relatively small therapeutic gain?" An Acorda clinical investigator said that most of his 20 patients "did not complain about any symptoms that would tell whether they were taking the drug, anything that would make them walk faster." Dr. Green observed, "It didn't look to me as if there was any learning with subsequent testing. Is that learned? Do people speed up over time in multiple testing?" The acting panel chair, Dr. Britt Anderson, a neurologist from the University of Waterloo, Canada, asked if there was some sort of placebo effect.

Study design

Gerald van Belle, PhD, a biostatistician from the University of Washington, asked for the rationale behind the 3:1 randomization in the F203 study. Acorda's Dr. Cohen explained that there was an effort to establish clinical meaningfulness in the trial, and about one-third of the fampridine-SR group was going to be timed walk responders for the next analysis (non-responders vs. responders). It was necessary to use the 3:1 in order to get equal groups.

The patient representative asked about a public speaker's concern about the FDA introducing a re-analysis of data "after I thought that there had been quite a bit of understanding with Acorda on the parameters of the studies and what the endpoints would be…How would the FDA want to design a study and treat the data in a way that would demonstrate benefit and be acceptable?" Dr. Katz replied, "We absolutely did agree with the company about looking at responder rates, and it's a perfectly reasonable thing to do…The fact that we did other analyses doesn't mean that the sponsor did an inappropriate analysis. We just want to get a sense of all the data. It's not uncommon at all…It's relatively standard, we're just

trying to get a handle on what the data mean…We're just trying to look at the data in multiple different ways. One of the aspects of looking at both groups in total has to do in part with preserving randomization…We have not backed-off from our agreement that the primary analysis is what the protocol said it was." An FDA reviewer said, "We have to have as much understanding as you can…as to what efficacy was." Dr. Temple added, "If you can't identify such people (non-responders) at the outset, you have to figure out some way (to define them).

Asked about the 7 point change in the MSWS-12 scores, the doctor who designed the scoring system and was speaking for the company said that a seven point change "has to be meaningful."

Some patients get worse

Dr. van Belle asked about the MSWS-12 and if the timed walk measures different aspects of walking, noting that some patients' timed walk speed actually decreased. Dr. Blight replied that more people get better and fewer people get worse in the fampridine-SR group. Dr. van Belle questioned, "So, about 25% get worse?" Dr. Blight replied that 35% of placebo and 15% of fampridine-treated patients get worse.

Personal view from a panel member with MS

Cynthia Sitcov, the patient representative, was diagnosed with MS more than 30 years ago. She asked, "Why were more than 60% of fampridine-SR-treated subjects not responders, and is the increase in speed something that is felt to be sustainable to 50 feet or 100 feet?" Dr. Cohen answered, "We don't know why only 35%-40% qualify as consistent 25-foot walk responders." Sitcov asked, "We can extrapolate that with an increase of 20%-25% in the 25-foot walk, there is a good feeling that one can make it 100 feet to the bathroom more quickly?" Dr. Anderson pointed out that the company did not measure more than 25 feet. Acorda's Dr. Blight said that the company did not measure farther than 25 feet because "it is difficult to do in a clinical setting." Dr. Cohen added that other measures were used in some centers, including long-distance walking.

Responders vs. non-responders

Dr. Olaf Stuve, a neurologist at the University of Texas Southwestern Medical Center in Dallas and director of the MS clinic at the Dallas VA, asked about responders vs. non-responders, "I was a little concerned that there was no prospective way of identifying responders and non-responders… Twenty percent of patients seemed to be getting worse clinically." Dr. Cohen said, "As with any clinical program for any drug, the measures that are used in the clinical program may not be specifically transferable to the clinical setting… We don't know in advance if they are going to respond…In this case, experienced clinicians in MS should be able to verify through examination and history if their patients are doing better. In this program, the results were seen relatively soon…Full effect on an average basis was seen as early as two weeks."

Asked if clinicians would be provided guidelines as to what constitutes response and what does not constitute response, especially in view of the "less than clinically exciting numbers that were presented," Dr. Cohen said, "The determination as with any medication would be to evaluate clinically through history and exam, and where appropriate, the timed walk… whether or not the patient is experiencing a benefit that is clinically meaningful to the patient."

Dr. Steven Brass, a neurologist from the University of California, Davis, asked about velocity measurements. Dr. Miller said, "In the clinical setting, what I would depend on more than the timed 25-foot walk is my conversation with the patient. I can't give you an arbitrary time to figure out if the patient is a responder, and I ultimately don't care. What I care about is if my patients are experiencing an improvement in their life. If the patient is staying at home all the time, it probably doesn't make much of a difference if you cut a few seconds off of the time to get somewhere. But if someone is walking up the street and sees the flashing time at the intersection showing how many seconds you have to cross the street, then that might make a difference…Even if (a patient) speeds up, but it doesn't make any difference to them, why would I give them the drug?"

Dr. Temple said that the FDA also wants to know how responders compare to non-responders, "There's a small improvement in walking time. What does that mean? We asked a lot of questions that aren't usually asked…Dr. Illoh showed a lot of numbers that aren't impressive…If you are a responder by walking time, you seem to do well, reasonably well on some of the other scales. That suggests that the walking time might be a reasonable measure. But on the 12 point scale you didn't see much difference in the population. But that is everybody."

Dr. Katz said, "We asked the sponsor to look at responders vs. non-responders for various secondary outcomes, and…the other measures do validate the responder definition as being clinically meaningful. That's one of the questions we're asking the committee to talk about…We wanted to look at a whole range of things to see how it all hangs together. One thing we want to talk about is the magnitude of the change. The claims were made that the MSWS-12 would measure clinical meaningfulness. We haven't talked about the amount of change we see." Dr. Temple said, "Imagine that there's something mysterious going on, and some people felt better. The fact that you see a correlation between walking better and feeling better on the 12 scale – that is a comparison that you worry about when it doesn't involve randomized groups. I wouldn't dismiss it, but that is what you worry about when there is not a randomized comparison."

Dr. Nathan Fountain, a neurologist from the University of Virginia, said that there were no differences in SGI, which asked about well-being, "There was a 2 point difference in the MSWS-12. For people with chronic diseases that affect their life…a small measurable difference in quality of life often translates to huge differences over their life…It seems to me that any improvement in quality of life is meaningful."

Dr. Fountain also asked about the magnitude of effect, "The differences are small, microscopic, but the assessments we are doing are not compared to the dotted-line of normal. The baseline is actually 8, so that's a difference. Starting out you had to start between 8 and 45 (in the time to complete the 25-foot walk in the MS-F204 trial). Looking at the percent change, it would seem to me, would be the way of looking at it." The FDA's Dr. Katz said, "That's the question. We just want to present a range of different ways of looking at the data…They are all after the fact analyses." The FDA's Dr. Temple commented, "The company thought that there was a responder/non-responder population and set up their endpoint to reflect that. But 70% of the population is not benefiting very much. The question is whether the 30% respond enough to make an impression."

Asked if there was a difference among responders and non-responders opting to go into the open-label study, Dr. Cohen said that there was no difference, "As a group, there was an increase in walking speed in the responder group. The non-responder group had some mean increase in walking speed of about 7% whereas the responder groups had mean increases of 25% or so over baseline, so the behavior was repeated in the extension study…Over two years, as one would expect from a progressive population of people with MS, there was a decline in movement, but you still see a maintenance of a gap between the original responders and the original non-responders. The non-responders eventually progressed below baseline as a group while the responders remained above baseline."

Asked why the non-responders continued in the open-label study, an Acorda physician said that people continue in studies for lots of reasons, including a sense of loyalty to the center and the nurses, and a sense of altruism. They may have sensed an increase in stamina or strength or other feelings.

Defining relapse

Dr. Myla Goldman, a neurologist from the University of Virginia, Charlottesville, told Dr. Cohen, "The term relapse has specific meaning, and it is used here in a confusing way."

Asked if the company analyzed an equal number of patients in both groups who had relapses, Dr. Blight said that a separate analysis was made, "Our ability to examine relapses was very limited."

Magnitude of effect

Dr. Goldman said, "It makes sense to look for a responder subset given what we know about the heterogeneity of MS… We talk about responders vs. non-responders. That makes sense. When you see 25% improvement within what we know about the 25-foot walk, the consensus is that >25% is clinically meaningful. The challenge is that we don't have a gold standard of what clinically meaningful means. They're using the MSWS-12…maybe using it related to free-moving ability. There are data that that is a useful tool, but more importantly perhaps are the additional data out there looking at what (is) a meaningful change in the 25-foot walk? When you try to answer that question, you have to look at the cohesiveness of studies across different parameters, and if you go into practice to determine what clinically meaningful means, that's even more challenging. I'm more interested in a change in the walk that is >25% and what that means in terms of a variety of quality of life and clinically meaningful measures for patients."

Dr. Temple said that 31.5% of people on fampridine-SR and 13.1% of people on placebo had ≥20% change in walking speed. Dr. Goldman said, "The general consensus is that ≥20% is meaningful, and if you look below that, >0% there is a difference, but the question is where does that impact day-to-day function in patients? If you look >20% and look at a variety of measures, that difference correlates to differences on several other measures besides the MSWS-12. This shows even at 1% or 5%, but certainly one could argue that that difference may not be experienced functionally in a patient. But where people are looking now is that >20%."

Dr. Brass asked if that >20% related to speed or time. Dr. Goldman said, "That's a fair point, and I don't know whether the company can comment whether they assessed that data."

Dr. van Belle said, "What we're talking about (is) the clinical body of the evidence and the side effects."

Dr. Wolfe said, "There seems to be a tug…A minority of people do better with the drug than placebo (and) have at least a 20% improvement in walking speed, but that runs ahead of the statement by the FDA that the walking speed was not different, suggesting that the magnitude of change is small. Certainly, it is reasonable to look at other measures, but for the neurology clinicians, I wonder what comments there could be on the fact that there isn't any difference between placebo and the drug group. That seems to be reasonably deposited. You can have a significant increase in the percent of responders, and yet the response itself can be so small that there is no difference in the walking speed."

The FDA reviewer said that the percentages of improvement give some perspective, "It's just different ways to look at the data. You can use mean values, and doing that there is not much difference between drug and placebo. The discussion is to get your opinion on whether the difference is enough to offset the risk of seizures."

The panel chair asked, "If we have a fixed distance of 25 feet, the speed and the time are interchangeable, but when you change from speed to time, you change the nature of distribution, and when you use time, you're looking at a highly skewed distribution with a large number of outliers. Why did the FDA choose to do means instead of medians?" The FDA reviewer replied, "Time was an easier way graphically to compare the groups." Dr. Temple added, "You see this in oncology all the time. Now that we know that there are genetic predictors of response, we test for it…That's why people look at responders. You can expect that the effect will be diluted." Dr. Katz said, "We wanted to look at the question of clinical meaningfulness…but the definition of responder means having to be faster on drugs than off drugs on the walking test. You could be .01 second faster on treatment measures, so even though the difference in the primary outcome is large and irrefutable, it could have been based on small differences in the walking test. That's why we tried to find out if it meant anything. That's why we're doing it."

Dr. Stuve, a neurologist, asked if there was a difference in the number of patients who switched from other modifying therapies during the trial. The company said that patients taking immunomodulators had to be on stable therapy before the study and stay on the therapy throughout the trial.

Compounded drug

Asked if the drug is not approved, will it continue to be compounded and whether there is a risk, Dr. Temple of the FDA said that he believes that if there is a real hazard from compounding, the FDA could intervene, "Ordinarily compounding is allowed."

Asked what percentage of doctors are using the compounded drug, Dr. Cohen said that the data are limited, and as far as he can tell, "It appears that there are certainly several thousand patients taking the compounded drug. The FDA 10 years ago had an estimate in the range of 10,000, and that is entirely possible. We've seen estimates as low as 4,000 or 5,000 and as high as 20,000. In terms of the practice, it's very individual. When we started the program, the dosing was probably higher, and we think in part because of the data we published, practices have changed somewhat. A not atypical dose might be 10 mg several times a day. But it is all highly individual."

Asked if doctors are titrating up if there is no effect, Dr. Cohen said, "It is my understanding that in some cases they do."

Dr. Goldman, a neurologist, said that the sustained demand for compounded for greater than a decade gives credence to clinical significance, at least seen by patients.

Renal questions

Asked if there is a dose adjustment suggestion for renal disease, Dr. Cohen said that 90% of the drug is excreted in the urine, and "There is minor metabolic component mediated by …one of the rarer enzymes…and there is no suggestion in the safety data of liver interactions or effect…On the other hand, because the drug is excreted in the urine and concentrated in the urine, there is concern about renal insufficiency and what effect that may have on dosing…In our studies – which included a renal insufficiency study – we excluded patients with severe renal insufficiency…Others were not excluded specifically because we wanted data on those patients. It turned out quite a few patients with renal insufficiency were accepted into the study, all of them except one were mild, and one was moderate. So we have no substantial data to speak of. However, we had 86 patients with renal insufficiency who received the drug at 10 mg BID, and we had 39 in the placebo group…In terms of response status, it was essentially the same …Three types of adverse events appeared to be more frequent: balance disorder, dizziness, and insomnia. So, the mildly renally impaired patients seemed to do the same as the non-renally impaired patients."

Asked if the company would reflect anything in the label re: renal insufficiency, Dr. Cohen said that it may be reasonable to allow mildly renally insufficient patients access to the drug with appropriately cautionary notes, asking doctors to monitor those patients very carefully. With moderate insufficiency, we just don't have the information…to make a reasonable judgment."

Possibility that the drug may harm?

Dr. van Belle said that a responder is defined as a person who scores higher on three visits than the baseline visit, "It could be possible that some people are harmed by the drug. So, I could define non-responder as someone who is hurt by the drug. So define the three lowest values at baseline and find out how others compare. You could see who responds in the opposite direction. The dose may be too high for some of these people. I don't think that's been analyzed, and I don't know if you could analyze it, but it seems as if some people could be harmed by this drug. I'm wondering if there are people lower significantly in their walking." The Acorda executive said that the company was interested in that question, too, "When you look at the average change in walking speed, the fampridine-SR group gets less worse (compared to placebo). There is no point in the population where the fampridine-SR group goes below the placebo group. There are no patients who seem to get worse than the placebo group, with regard to walking at least."

The industry representative said that based on that definition of a responder, it might be determined on a second visit. Dr. Cohen said, "We came to the same conclusion as to needing two visits to get there. If you have a baseline visit, give the drug, and look over the next two visits to see how they do, you can see how that might translate. I need to emphasize that this is not a recipe; it is a way to look at the data to see how long it takes to see if someone is a responder or not. If you didn't see an improvement in the first two visits and discontinued everyone who did not see improvement, and that may be in

four weeks, you could identify responders in the 70%-80% level. Clinical practice is not so tight…but it echoes that the effect of the drug is rapid, happens within the first two weeks, and is clinically discernible."

The FDA's Dr. Temple said that it is common practice to adjust a dose based on renal function, usually without asking for additional studies. "Do you have thoughts on making a smaller tablet size?" he wanted to know. Dr. Cohen said that in early studies, the company started out with 25-40 mg doses, "As time went on it was clear that was not right…That pushed us down the curve. When the program developed in MS, we had developed 10 mg formulations and above. We collaborated with Elan Pharmaceuticals, and for whatever reason, the original 5 mg formulation did not have the stability that would make it viable as a commercial product." He said that Acorda and Elan are working on a new formulation.

Asked if there were any data on numbers needed to treat or harm, Dr. Cohen said the number needed to treat is straightforward. If you take 35%-40% response on pre-specified responder analysis, or just the 20% improvement threshold, you are in the same ballpark. It equates to ~ 3:1. Three to treat to get one to respond."

Risk of seizure

Asked about the risk of seizure, Dr. Cohen said, "It looks good. There is a suggestion that it goes up between 15 (mg) and 20 (mg) and beyond that, but we don't know…We at least have 86 on drug and 39 on placebo…So far, we are not seeing a signal, and it absolutely will be monitored."

Dr. Fountain, a neurologist, asked about the differences between seizure risk in the Acorda and FDA presentations, "I'm trying to figure out the rate of convulsion by dose across all doses and all studies." Dr. Cohen said that he doesn't have the data in this form, "There were 22 seizures across all doses and formulations: 19 convulsions and 2 complex partial seizures (CPS) over the past 15 years. Looking just at fampridine-SR in the MS trials, there were 11 seizures; and in spinal cord injury, there were 6 seizures…What we're all grappling with is that we have a reasonably good handle…At ≥30 (mg) it's possible to say that the rate jumps so much – in the 4% range and higher – once you get to ≥30 (mg) BID, you see those rates even with small numbers. It is a strong signal even at small numbers that that is at least a threshold. But lower than that, we don't have a handle on that." Dr. Fountain responded, "I'm not sure looking at seizures per person year is enough…I guess I'd find more value in the rate than in the per person years…Looking at the FDA presentation, it was in per person year of exposure, and I'm suggesting that may not be that valuable." The FDA's Dr. Katz said, "We don't know that. Things change. MS patients continue to get additional lesions in their brains which may increase susceptibility…So, I don't think we have enough events to know." Dr. Cohen said, "We have looked at that relationship because we were concerned to see if the events were closer to the time the patient went on the drugs, and that was not the case. We have very few cases to work with at 10 mg. But the higher doses did occur within two months of dosing. Here, of the five events in the extension studies, four occurred ≥11 months after exposure. The fifth was a patient who took it successfully, but had a seizure 9 days into the extension study. That was coincident with her taking 12 mg of a bladder medication the day before. She was taken off the study and a year later took the same medication and promptly had a seizure. But those are the sorts of variables that we deal with."

PANEL DISCUSSION OF FDA QUESTIONS

QUESTION 1a. Has the company demonstrated substantial evidence of effectiveness of fampridine-SR as a treatment to improve walking in patients with MS?

VOTE: 12 YES, 1 NO

Asked before the vote which data to use to determine the answer, the FDA's Dr. Temple said that it went by the responder analysis, but the FDA thought that the panel should see what the whole patient population experienced.

Panel comments included:

- *Dr. van Belle, a biostatistician:* "The claim was made that there is no change when you look at the average across the trial, and that is not quite correct. There is a change if you look at the average over the period and not just Visit 6. The primary endpoint was walking speed from baseline. That is what I was told."
- *Dr. Wolfe, a consumer representative:* "Walking speed on average over the study for the two groups was absolutely the same."
- *The FDA's Dr. Temple:* "If you look at it from baseline you get two values, if you look at it another way, you get a totally different value."
- *Panel chair:* "Maybe those of us who treat patients, maybe you should talk about definitions of effectiveness."
- *Dr. Brass, a neurologist:* "Overall there are a lot of medications that we use in MS that may not respond in every single case. Even for the immunomodulating therapies, there are a lot of patients who do not respond. For the first question, based on the response rate, the answer is yes. In terms of clinically meaningful response, looking at the responder group, the sponsor showed evidence that there was a response. In terms of the absolute value for the whole study, there was no change in walking speed in baseline vs. follow-up, so I don't know. It's a little conflicting. But when focusing just on responder rate, there is a little more meat there."
- *Dr. Fountain, a neurologist:* "Statistically, a lot of the measures were statistically significant."

- *Dr. Eluen Yeh, a neurologist from State University of New York, Buffalo:* "Grouping patients into responders and non-responders is a helpful way to look at this...It seems that anything we do, a third will respond, and two-thirds won't…I would be prepared to look at the data the way the sponsor presented the data, looking at the responders as a special subgroup."
- *Dr. Goldman, a neurologist:* "What we know about MS is that the underlying pathology varies from person to person…It makes sense that there would be some people who wouldn't respond, and so it doesn't surprise me that when you look at the population as a whole, the (data) wouldn't look as good…As a clinician, my experience… is that understanding the concept of clinical meaningfulness is somewhat elusive…One thing to think about is what is the risk tolerance. What is the trade-off here? The relative risk is small relative to the potential benefit to this subset of people."
- *Dr. Morrato, an epidemiologist:* "As I'm interpreting substantial, substantial evidence would be if we saw a strong effect in both responders and non-responders. My vote is going to reflect that. Substantial is reflecting the totality."
- *Dr. Stuve, a neurologist:* "I would say yes…The responder rate was higher in the treatment group than in the placebo group…As a clinician, I would feel more comfortable if there were some sort of algorithm that very early on identifies responders and non-responders. The word substantial is hard to grasp."
- *The FDA's Dr. Katz:* "The primary outcome was the responder rate – on treatment vs. off treatment. It was clearly dependent on the walking speed, but the primary outcome was the responder rate...We use the word substantial…not intended to mean the preponderance of the data...It's defined as evidence from well-controlled and adequate investigations…It is a term of law."

QUESTION 1b. If yes, has the sponsor demonstrated that the effect is clinically meaningful, either in the group of fampridine-SR treated patients as a whole, or in a specific subset?

No vote but consensus was YES.

Panel member comments included:

- *The panel chair* said that Dr. Wolfe didn't think there was proof of effectiveness, nor did he think that the data were clinically meaningful. Some put emphasis on the differences in walking speed or walking time, and some looked at individual responders. The panel chair commented, "It seems as if the responder has that benefit…it is clinically meaningful, and you see a greater proportion of those subjects in the treated group, and for me personally, that establishes clinically meaningful."
- *Dr. Wolfe:* "I'm really going with the FDA's own assessment of the various cases…In each case there was a change, but it was very small. I think that one can ask the question, yes there is statistical evidence via the way people chose to vote on the first one, but what is the clinical importance of that?...That is to say nothing of the risk component…There are a number of fairly commonly occurring and statistically higher rates of balance disorder, insomnia, and other things, and even if they don't rise to the level of a seizure, they are on the downside and they affect those two-thirds who do not benefit at all…So these adverse effects take on ever larger importance. It brings in adverse effects, and aside from no difference in the walking speed, you don't have other patient-oriented measures that seem to be importantly in the right direction."
- *Patient representative:* "Just because it is only a third, it should not be discounted."
- *Dr. van Belle, a biostatistician:* "I would have to abstain or vote no."
- *Dr. Fountain:* "I'd say, would you like to try taking this drug? You have a one in three chance of improving your walking speed by 30%. That is the ultimate risk:benefit ratio to present to the patient. Or, if you don't like the responder rate, you'd say, you have the chance of an average improvement of 21% in your speed. If I said that …I think they'd all say yes…all presupposed on the idea that the risk of seizure isn't predisposed."
- *The FDA's Dr. Katz:* "No one should read our questions to mean that we have reached a conclusion…It shouldn't be taken to mean that we, in any way, have taken a position on what the answers should be."
- *The FDA's Dr. Temple:* "I like dichotomized data, and I was interested in what Dr. van Belle said, walking speed effect and the greater than 20% which most people seem to think is meaningful, that's another way of looking at the overall data. Do people have views on that? To someone who has little knowledge of MS that doesn't look so bad. Is it meaningless?"
- *Dr. Stuve, a neurologist:* "To me, it does look meaningful in that subgroup of patients. I think Dr. Goldman is the expert on this, and she said, if there is a greater than 20% improvement, then it is significant."
- *Dr. Goldman:* "Dr. Brass's point was important, and this speaks to the issue directly. I think about a 25-foot walk as time, and that's how I do it every day. But the data I was speaking of…was in time. And so, I think that my opinion about whether or not this is meaningful is different from some of the data that is available with the cutoff of 20%, and so mathematically I tried to extrapolate what that would be: time vs. speed…This is a spin on how we traditionally think of it that makes it a little more challenging…What we are struggling with in using the measure in terms of time is what's noise, and what is

really change in progression and improvement. I think that this is clinically meaningful, however."

- *Acorda's Dr. Blight:* "Most of the literature deals with time. The curiosity is that a 20% increase in time – which is the disease getting worse…is like a 16.6% worsening in speed."

QUESTION 2a. Should the sponsor be required to evaluate the effects of doses lower than 10 mg twice daily?

VOTE: 12 YES, 1 NO

The no vote was the patient representative.

Panel member comments included:

- *Dr. Wolfe, a consumer representative:* "What we're being asked is should the company be required to show that it actually works at a lower dose? There were comments by a number of FDA people that because there was a flat response curve, that you should go down lower, and the answer from the sponsor was that when you start going lower, there was a fall-off. But those 15-17 ng/ml correspond to a much lower dose than 10 mg. It may be that the effect doesn't start going down at 5 mg or below. The company has no data on that dose. The side effects appear to be dose related and this would increase the risk:benefit ratio. Reducing the risk in half – the FDA hinted that that would be a good idea to have a trial of 5 mg BID...In the FDA presentation about distribution of C_{max} – there clearly is an overlap between 10 (mg) and 15 (mg) – so I think that's one of the reasons they put it in there. But your own reviewer said, why aren't there studies at a lower dose? At least two or three times in the documents mailed to us they said…'Why aren't there studies below 10 mg?'"

- *Dr. Katz:* "Marginally, we agree with Dr. Wolfe's summary of the issue…The underpinnings are the risks. I'm not sure that anywhere have we intimated that if it should be done, that it be done prior to approval. If we look at the experience at 15 mg BID, the percentage of seizures 1.4%, and the rate is around 1.7 per 100 patient years. If you compare it to the rate of seizures in MS patients, the highest rate per 100 patient years in the literature is around 0.3. So 1.7 is about five times the highest background rate. These patients were screened with EEG. So it appears to us that at 15 mg BID, which isn't much higher than 10 mg BID, there is a possibility that there is an increased seizure rate. We heard with mild renal impairment, and we don't know how many patients qualify…that the C_{max} you would get at 10 mg BID is between 15 and 20. We want people to say whether we know enough, whether there is enough to overlap…that's the issue we're trying to get at. Do we need to know about lower levels? That's the background for the question."

- *Dr. Fountain, a neurologist:* "It makes sense to study a lower dose. Maybe it's linear between 5 and 10 mg – maybe 5 is good, maybe 1 is good. Whether before or after approval is a separate question."

- *Dr. Katz:* "Do we have enough comfort at 10 mg to say 10's OK at least for the moment?"

- *Panel chair:* "It seems from Question 2b that it should be debated whether it should be studied before or after approval."

- *The FDA's Dr. Temple:* "It's not uncommon to vote for a drug and require that studies of lower doses be done."

- *Asked how long it would take to do studies on a lower dose*, Dr. Cohen said that typically you like to see a minimum of two years stability before it goes on the shelves, "We have a current formulation that has just gone up on stability testing. That implies that we won't know for sure for two years. We could begin testing within six months to a year, but if it failed along the way, we could be back to square one. It would be optimistically – let's say two to three years to test and have it submitted – you're out about three years if it all goes well."

- *Dr. Temple:* "It doesn't always take that long. You can also do the testing before the two years or even six months."

- *Dr. Stuve, a neurologist:* "A lower dose may work. As a clinician you're always nervous with a drug that has a narrow index."

QUESTION 2b. If yes, should this be required prior to approval?

VOTE: 2 YES, 10 NO, 1 ABSTAIN

The two yes votes were Dr. Wolfe and Dr. Stuve. The patient representative abstained.

Dr. Morrato, an epidemiologist, said that an assumption is being made that seizure risk will decrease with lower doses, but there is no evidence that suggests by waiting for the results that you would get benefit.

QUESTION 3a. 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?

VOTE: 10 YES, 2 NO, 1 ABSTAIN

Dr. Rudnicki and Dr. Wolfe voted no, and Dr. van Belle abstained.

Panel member comments included:

- *Dr. Wolfe, a consumer representative*, referred to a paper published two weeks ago, the author of which was an

investigator for the company. The paper predicted a swell of new prescriptions, ostensibly for off-label experimentation. The investigator wrote that, at his own clinic, about three-quarters of people in the clinic would want the drug and would take more than the 10 mg dose because of perceptions that increased doses would work better. Dr. Wolfe said, "This drug has a very narrow therapeutic index, so I am very concerned about one of the investigators saying that there would be massive off-label use… The only point I'm making is that…in the real world… people will self-administer higher doses, doctors will prescribe off-label. That is the reality, and for a lot of drugs there is off-label prescription." Dr. Temple asked if the researcher mentioned other uses, and Dr. Wolfe clarified, "The self-administering of a higher dose because it didn't work was at the patient level but doctors might be willing to use it for other indications."

- *Panel chair* said that people may misuse the drug, i.e., take a double dose because they missed a dose, or get it for resale, "That is a concern, but it is slightly different than the question."
- *Dr. Temple:* "What you're saying is an indication saying don't even think about using it at higher doses, and don't double up if you miss a dose."
- *Dr. Wolfe:* "That's at the patient level, but there would have to be a lot of attention paid to reducing off-label use."
- *The FDA's Dr. Katz:* "That's a good point for Question 3b, but the question we're considering is whether you can think of conditions under which fampridine-SR could be considered safe for use."
- *Dr. Morrato* asked if there should be indications as to who should be given the drug, "There is no precedent, but I'm talking about responders vs. non-responders."
- *Panel chair:* "Off-label use is a component of active clinical practice…I don't think off-label use in and of itself constitutes a misuse of a medication…It should not preclude us from recommending…for an indication. How about the issues of seizures and screening for EEGs?"
- *Dr. Fountain, a neurologist:* "I think the comments about EEG were right on the mark. We would not consider EEG for screening in any context. Statistically it doesn't make any sense. All we're left with is that is what they did. I suppose this could be another opportunity for looking at clinical trials to see if there was an increased risk…You do more disservice than service by giving EEGs."
- *Dr. Rudnicki, a neurologist:* "The MS drugs, if you have an exacerbation, the MRI gets worse, it's clear that you are not responding, but it's different here. You continue to have the side effects, and the question on clinically meaningfulness – we did not vote on that."
- *Dr. Goldman, a neurologist:* "I agree that there is a culture among patients and in medicine that more is always better, in that they would take more and get more benefit, but in this instance there is a mechanism to prevent that, and that is the REMS…My other thought was about recognizing responders vs. non-responders and what that means, and in this study it is relevant…In practice we do this every day…but we don't prospectively collect data or try to quantify or anticipate which headache medicine you're going to respond to. So I think we use the concept of responder vs. non-responder every day in clinical practice."
- *Dr. Wolfe:* "The comfort level of everyone including myself will increase enormously if we get data (on a lower dose)."
- *The FDA's Dr. Katz:* "We wanted to get a sense, and I think that we got that sense."
- *Dr. Goldman:* "I think you're assuming that people who stayed in the study stayed because the didn't know they were non-responders. But the data showed that they knew they were non-responders (in the survey), and there are other reasons and motivations to stay in a study despite a lack of benefit."
- *Panel chair:* "How much of a patient's willingness to take risk enters into our consideration?"
- *Patient representative:* "People with MS are willing to take risks. If I were told that I'd be able to walk with greater ease to get into my car or to do anything related to daily activity, and there was what I considered to be a fairly small risk of seizure, I would certainly take that risk, and I think I am reflecting the population. I have had MS for many years and know many people with MS. I'd also weigh it against…I find it disturbing that pharmacies just formulate this stuff. That has tremendous potential for damage. If I were to take the drug under those circumstances and have a seizure…who would know that?... There is less of a willingness with 20 mg and 30 mg."
- *Dr. Goldman:* "What is the risk of seizure in the MS population if this drug is not approved? Based on what is happening, which is that they are getting it from compounded pharmacies."
- *Dr. Fountain:* "If we did EEGs in the normal population, which is routinely done with Air Force pilots, somewhere between 0.7% and 1.4% have abnormal EEGs. But the risk of having a seizure after that is infinitesimally small …even 4%-5% in MS patients would be too low to predict if they are going to have a seizure. You can't discount it because it is what the company did and we don't know."
- *Dr. Morrato:* "I would hope that there is pretesting of the educational materials before they are put into place. We know that labeling and Dear Prescriber letters are important, but we don't know the level of communication and

the goals you have. I'm not sure what is meant by the ongoing provider education – that could be as simple as a market launch."

- *Dr. Stuve, a neurologist:* "The panel focused on the seizures, but some attention needs to be paid to the other side effects. It seemed that side effects were more prevalent in the fampridine-SR group than the placebo groups. Some more data on that could help determine the safety profile."

QUESTION 3b. If yes, what are those conditions (e.g., specific enrollment criteria, specific monitoring, etc.)?

The panel chair summarized that the panel's consensus is that people with a history of seizure disorders should not get the medication. The question of renal impairment is a real one. There was a consensus that there was no need for pre-screening with EEG prior to use. Dr. Temple asked if the panel wants renal tests before giving the drug. The panel chair asked if moderate renal insufficiency should preclude the use of the medication. An unofficial roundtable vote showed that most agreed that the drug should be used with caution in patients with mild renal insufficiency and should be a contra-indication in patients with moderate and severe renal insufficiency and history of seizures.

Panel member comments included:

- *Dr. Jason Todd of the Summit Sleep Disorder Center in Winston-Salem NC* asked if the seizure risk could be put in context of other medications.
- *Dr. Fountain, a neurologist*, said that the seizure risk is not increased with 10 mg BID, "I don't know but I can tell you that in antidepressants, the increased risk in patients was not nearly as high as was anticipated."
- *Dr. Green, a neurologist*, asked if it was common that some patients, for example, those with epilepsy, might be excluded. The FDA's Dr. Katz said, "We typically describe the patient population in labeling. We don't describe everything. We describe some exclusions but not others, and there is a distinction between describing and mandating screening."
- *The FDA's Dr. Temple:* "It is typical that people with mild-to-moderate liver disease be excluded from a drug?"
- *Dr. Todd:* "There are some patients between epilepsy and MS population, for example a patient who had childhood epilepsy. For a patient with a single seizure that might be related to a drug withdrawal. Would it still be possible to screen those kinds of patients?"
- *Dr. Morrato, an epidemiologist:* "The sponsors said that they proposed contraindications for some patients, including severe renal impairment. A question could be what to do about patients with mild-to-moderate renal impairment."
- *The panel chair* took a straw poll to see if doctors would do an EEG for any contraindications. Most panel members said no. Dr. van Belle, Dr. Wolfe, and Dr. Morrato abstained. The panel chair asked about mild-to-moderate renal impairment, and Dr. Green said that since there is not a lower dose, "The only solution would be a contraindication for patients with moderate-to-severe renal insufficiency."
- *Dr. Goldman, a neurologist* stated that clinicians use seizure precautions all the time and asked, could that be useful in patients with mild-to-moderate renal impairment?
- *Dr. Fountain:* "I guess if we thought they were going to have seizures, we wouldn't give it to them. I agree with Dr. Green that if there is no way to give them a smaller dose…I would think that it would be contraindicated. Certainly for severe. Moderate, I'm not so sure about."
- *The FDA's Dr. Temple:* "I don't think once a day helps very much because it's the peak we're concerned about. There's no accumulation of this drug…There was only one person with moderate renal impairment."
- *Panel chair:* "They had data in their pharmacological data that showed moderate. Even the 67% bump reached my level of (concern), and I would consider mild-to-moderate a contraindication. I would view the presence of mild-to-moderate renal insufficiency to sway me against it."

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