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Peripheral and Central Nervous System Drugs Advisory Committee

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The Inn and Conference Center
University of Maryland, University College
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Eric Bastings. M.D.

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Jacqueline Havener
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P R O C E E D I N G S

LCDR NGO: Good morning everyone. I would like to first remind everyone to silence your cell phones, pagers and other electronic devices if you haven't already done so. Also, I would like to identify the FDA press contact, Ms. Karen Riley, for the morning. Is she here? Okay. And Ms. Sandy Walsh. Ms. Sandy Walsh is the primary press contact so, when she comes, I will introduce her again.

Call to Order and Opening Remarks

DR. ANDERSON: Good morning. I am Britt Anderson and I have the honor of chairing today's session.

I would like to begin by having us go around the table and make introductions, state our name, our role on the committee and our current affiliation. If I could begin in the corner with Dr. Twyman, if you would start, and then we will just go around the table in order.

DR. TWYMAN: Sure, Britt. My name is Roy Twyman. I am the industry rep. I am from Johnson & Johnson.

DR. FOUNTAIN: I am Nathan Fountain from the University of Virginia. My specialty is epilepsy and neurology.

DR. VAN BELLE: Gerald van Belle, Department of

Biostatistics from the University of Washington, specialty biostatistics.

DR. GOLDMAN: Myla Goldman, University of Virginia, Department of the Neurology. Area of specialty is multiple sclerosis.

DR. YEH: Eluen Yeh, SUNY, Buffalo. Area of specialty is child neurology and multiple sclerosis.

DR. BRASS: Steven Brass. I am the University of California at Davis in Sacramento and my area of expertise is both in sleep and in multiple sclerosis.

LCDR NGO: Lieutenant Commander Diem-Kieu Ngo, Designated Federal Official for the meeting.

DR. ANDERSON: I am Britt Anderson. I am a neurologist and I am currently in Waterloo, Ontario, Canada.

DR. GREEN: I am Mark Green. I am at Columbia University. My specialty is headache medicine.

MS. SITCOV: I am Cynthia Sitcov. I am the Patient Representative on the Committee, on the panel, and I have been diagnosed with MS for 34 years.

DR. WOLFE: I am Sid Wolfe. I am a general internist and with the Health Research Group and Public Citizen.

DR. MORRATO: I am Elaine Morrato from the University of Colorado. I am an epidemiologist and my area of interest is in pharmaceutical risk management.

DR. RUDNICKI: Stacy Rudnicki from the University of Arkansas in Little Rock. I am a neurologist who specializes in neuromuscular disease.

DR. BASTINGS: Eric Bastings. I am Deputy Director of the Division of Neurology Products, FDA.

DR. KATZ: Russ Katz, Director, Division of Neurology Products, FDA.

DR. ANDERSON: All right. I have a little script to read here.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be fair and an open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee

Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or at lunch.

Thank you.

Now we will have the Conflict of Interest statements read.

Conflict of Interest Statement

DR. NGO: The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the Committee are special Government employees or regular Federal

employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found in 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this Committee are in compliance with Federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208(b)(3), Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 208(b)(1), Congress has authorized FDA to grant waivers to regular Government employees who have potential financial conflicts when it is determined that the financial interest is not so substantial to be likely to affect the integrity of the individual's service

to the government.

Under Section 12 of the of the FD&C Act, Congress has authorized FDA to grant waivers to special and to regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of the Committee who are special and regular Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting, expert witness testimony: contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda the Committee will discuss and make recommendations regarding New Drug Application 22-250, fampridine-SR 10 mg tablets, proposed trade name Ampriva, for the improvement of walking ability in patients with multiple sclerosis. This is a particular matter involving specific parties.

Based on the agenda and all financial interests reported by the members and temporary voting members of the Committee, it has been determined that all interests in firm regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Roy Twyman is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Twyman's role at this meeting is to represent industry in general and not any particular company. Dr. Twyman is employed by Johnson & Johnson.

We would like to remind members and temporary voting members of the Committee that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be

noted for the record.

FDA encourages all other participants, including the sponsor's non-employee presenters, to advise the Committee of any financial relationships that they may have with the firm at issue, including consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Thank you.

DR. ANDERSON: At this point, we will hear some introductory remarks from the Division Director, Dr. Katz.

FDA Introductory Remarks

DR. KATZ: First, I want to welcome everybody here this morning and in particular the members of the PCNS Advisory Committee, especially invited guests for the Committee who bring their special expertise in matters that we hope to get into today. So, thanks everybody very much for coming and what I hope will be an interesting and important discussion.

As you know, of course, today we are going to be discussing NDA 22-250 submitted by Acorda Therapeutics for the use of fampridine Sustained Release in patients with

multiple sclerosis to improve their walking ability.

Of course, you have seen the briefing documents and you know what we think the issues are, but I just want to very, very briefly just go over what the primary issues are that we would like you to help us with today.

You know the application contains the results of two controlled trials in which patients were randomized to receive either fampridine-SR, 10 mg twice a day, or placebo for up to 14 weeks under double-blind conditions.

The primary outcome measure was the responder rate. This is an atypical outcome measure in MS trials as is the proposed indication. It is a little complicated. Hopefully, you understood the documents as to what exactly constituted a responder. But, in any event, patients had to have at least 3 on-treatment, 25-foot timed walking speeds greater than any of the number of off-treatment walking speeds.

Although the outcome is in a typical measure, we did agree absolutely with the company that this was an appropriate measure to look at to gauge walking speed and, presumably by extension, walking ability in these patients.

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 and placebo in both studies. Other measures were also assessed which you know of and we will talk about at length I am sure today, and they, too, were in general, although not uniformly statistically significantly favorable for fampridine.

However, questions have been raised about the clinical meaning of the differences seen on several of these outcomes, and as I say, although the differences between fampridine and placebo were robust on the primary outcome, the primary outcome itself depends upon differences between the timed walking test on and off drug, that themselves could be fairly small.

Indeed, analyses of mean differences between fampridine- and placebo-treated patients on the timed walk whether in an analysis that compared responders to non-responders, or just the both full randomized groups, it did appear to be small.

Differences between fampridine- and placebo-treated patients on other outcome measures in addition to the primary outcome measure, including those that were

specifically designed to establish the clinical meaning of the changes seen in the primary outcome also appeared relatively small.

Although it needs to be noted that analyses of cumulative distributions of various outcomes do demonstrate that the differences seen between fampridine and placebo persist across a wide range of treatment differences, and it is important to know.

In this particular case, we believe consideration of the size of the treatment effects takes on particular urgency in light of the potential for fampridine to cause seizures.

Both the sponsor and the Agency I believe agree that fampridine can cause seizures. Evidence of this comes from animal studies and other high doses of fampridine not proposed as therapeutic in this case and in particular when given with other formulations of fampridine, specifically, media release formulations.

The data in our view from the controlled trials suggest that at the proposed therapeutic dose, 10 mg twice a day, the rate of seizures is about the same as was seen in the placebo group. In addition, the open-label experience

at 10 mg b.i.d. also suggests that the rate at that dose was consistent with the rate seen in the controlled trials, again, no greater than placebo.

But the rate of seizures at doses that are not much greater than 10 mg b.i.d. seems to be greater than the rate at 10 mg b.i.d., and we will get into the specifics of the data in great detail, I am sure, over the course of the day. But just to briefly give you an overview from our point of view, in open-label experience in about 660 patients, the incidence of seizures as I say at 10 mg b.i.d. was about 0.75 percent, a rate of about 0.5 seizures per 100 patient years.

At a dose of 15 mg b.i.d., in about 175 patients, much less experience, the incidence of seizures was about 1.4 percent, which was about twice what was seen at 10 mg b.i.d., and with a rate of about 1.7 seizures per 100 patient years. The upper bound of the 95 percent confidence interval around that estimate was about 6 seizures per 100 patient years.

At 20 mg b.i.d., where there is very little experience, and essentially, no open-label experience, only experience in a handful of patients in controlled trials.

But, at 20 mg b.i.d., the incidence of seizures is about 3.5 percent in 57 patients, with a rate of about 12 seizures per 100 patient years.

It has to be acknowledged that these estimates are based on very small numbers of events. In the open-label experience at 10 mg b.i.d., there were 5 seizures, and in the open-label experience at 15 mg b.i.d., there were 2 seizures and, also, there were only 2 seizures in the 20 mg b.i.d. group. The latter was all from control data.

We were interested to assess whether or not we knew anything about the plasma levels that were associated with seizures in these patients. There is some information about that, but it is not particularly reliable. We might or might not get into that, but we don't think we really have good information about what plasma levels were associated with seizures in these patients.

We do believe that there is some overlap in the plasma levels achieved at all three doses studied, 10, 15, and 20 mg b.i.d.

The open-label seizure data are difficult to interpret. We tried to look at these in reference to background rates published for seizures in patients with MS.

Those rates are highly variable. Critically, patients in these studies were screened with EEGs. Patients who had a history of, or evidence of, seizure activity on EEGs were excluded from treatment with fampridine.

The background rates that are published in patients with MS as far as we know did not exclude anyone based on EEG findings. So, this fact further complicates the interpretation of the seizure data that we have seen here.

In summary, the studies clearly demonstrated robust effect on the outcome, an unusual outcome, but one with which we agree that the company was important. The effect is based on differences on the 25-foot timed walk, which were in general relatively small.

Differences on other outcome measures, in addition to the primary outcome measure, were also generally statistically significant but also generally small and, against these findings, we are concerned about an increased risk of seizures at doses only slightly greater than the proposed dose.

Importantly, the possibility that there will be patients who received 10 mg b.i.d. who might achieve plasma

levels that are associated with seizures at other doses.

So, we have come here today to ask your help in helping us weigh these risks and benefits. I just want to thank you again for coming. I want to particularly thank you for the work you have done in preparation for the meeting and certainly for the work you are about to do.

With that, I will turn it back to Dr. Anderson.

DR. ANDERSON: We have one committee member who joined us just a little bit late. Dr. Todd, we all sort of read our name into the record and stated our affiliation. Could you go ahead and join us, please.

DR. TODD: Dr. Jason Todd, a neurologist with Summit Sleep Disorder Center.

DR. ANDERSON: Dr. Temple, as well.

DR. TEMPLE: Bob Temple. Good morning. I am the Office Director.

DR. ANDERSON: At this point, we are going to now proceed with the sponsor's presentation. It looks like Dr. Cohen is going to begin.

INDUSTRY PRESENTATION

Background and Introduction

[Slide.]

DR. COHEN: Good morning. I am Ron Cohen, CEO of Acorda Therapeutics.

[Slide.]

DR. COHEN: Before we begin my formal remarks, I would like to acknowledge and thank many clinical investigators, nurses, and study coordinators, and most especially the many MS patients and their families who participated in our programs. Without their dedication, clearly, medical progress could not be made and we would not be here today.

[Slide.]

Dr. Anderson, members of the Committee, and the FDA, thank you for the opportunity to discuss fampridine-SR, a potentially important new therapy for people with MS.

Fampridine is the U.S.-adopted name of 4-aminopyridine or 4-AP. This is a compound that has been found to improve conduction in demyelinated segments of the nervous system.

[Slide.]

In the next few slides, I will illustrate the mechanism of action of the drug. But first, I will remind everyone that the proposed indication that we will be

discussing today is the use of fampridine-SR to improve walking ability in patients with multiple sclerosis.

[Slide.]

There are broadly two classes of therapy that are available today to treat people with MS. Just by way of providing context, one of those is the immunomodulators, also known as the "disease-modifying agents."

These are drugs that reduce the immune attack on the nervous system and thereby reduce relapse rates primarily in patients with the relapsing remitting form of MS. But, in some cases, they have been shown to slow progression time to accumulated disability.

The other large class are symptomatic agents. These are not disease-specific, but target particular symptoms--for example, baclofen, which can be used for spasticity, or tolterodine for bladder control issues, and so forth.

[Slide.]

Fampridine represents a new class of therapy in MS, one that targets the demyelinated nervous system directly and targets the MS neuropathology at the level of the nervous system directly, alleviating the neuronal

conduction block that occurs due to demyelination and thereby improving neurological function.

[Slide.]

In this illustration, we see an axon as one might find in the brain or spinal cord, in blue, and then covered with packets of myelin arranged with small gaps called the "nodes of Ranvier," which permit very rapid and efficient conduction in the normal nervous system.

You see the action potential proceeding from left to right as shown on that oscilloscope tracing in red. In the middle, there is a demyelinated segment.

[Slide.]

In a demyelinated axon, potassium channels are exposed and leak potassium representing a loss of potassium-mediated current.

[Slide.]

The action potential cannot traverse that area of current loss and when one measures this as one has in many publications, both in vitro and in vivo, one finds that the action potential does not proceed distally to the end of the axon.

[Slide.]

Fampridine in therapeutic concentrations is a highly specific blocker of these channels and, although the myelin is not there, or is damaged, the potassium current no longer can leak.

[Slide.]

And in studies, what is seen is a rapid recovery of conduction through the demyelinated segment, as illustrated here again in the red and blue oscilloscope tracings. As long as the drug is in the system, the nerve continues to be able to conduct. The effect is reversible so that, when the drug leaves the system, the channels are unblocked and once again the axon becomes conduction block.

[Slide.]

These findings, which were made by the 1970s, led to academic clinical investigations in a variety of conditions that were characterized by conduction block or demyelination. By far the most frequently studied of these was multiple sclerosis, and, between the 1980s and 1990s, several groups published a number of studies showing positive effects in patients with MS on such functions as visual function, motor function, and also walking function. These primarily used pharmacy-compounded formulations.

Local pharmacists would mix the chemical and excipients and they would give these capsules to patients in an immediate release formulation.

Following, I will show you an illustrative video of findings that were presented during that time. This particular video was presented by the team of Dusan Stefoski at the American Neurological Association meeting in 1986. It depicts a 32-year-old man with MS and marked walking impairment both before and after dosing with an IR formulation of fampridine.

[Slide.]

This is the pre-dose, and this is 3.5 hours post a 12.5 mg dose.

[Slide.]

Based on these reports, a fairly widespread practice began of prescribing compounded formulations of fampridine for patients with MS. Several observations were made both in the community and particularly in the literature, one being that seizures occurred at higher doses and plasma levels, also, that plasma levels were difficult to regulate with the available compounded formulations.

They were immediate release with rapid, 30-minute

times to Cmax. The peak Cmaxes were quite high and the half-life was relatively short at about 3 hours, requiring multiple doses during the day and difficulty remaining within a desired plasma level range.

There were also marked food effects which compounded the difficulties of keeping within a desired range.

Despite these shortcomings, the practice continued and indeed continues to the present time, and it has been estimated that there are several thousand patients with MS who now have access to these formulations although they are not approved by FDA for any indication, and there have been reports of serious dosing errors in the community with serious consequences particularly seizures.

[Slide.]

In response to this literature, Elan Pharmaceuticals between 1991 and 1994 began work on developing a more rational pharmaceutical grade formulation of this compound and, in 1994, finished development of the sustained release or SR tablet that was used in the development program we are discussing today.

This was manufactured under cGMP or current good

manufacturing practices. It provided quite reliable plasma levels, linear pharmacokinetics, the ability to dose only twice daily, and also had a minimal food effect.

In 1998, Acorda obtained rights to develop fampridine-SR in multiple sclerosis and initiated a Phase 2 program comprising mainly two trials, which we called MS-F201 and 202. From these trials, we arrived at an optimal dose of 10 mg b.i.d. and also determined the walking outcomes that would be used in the Phase 2 program.

These were discussed at length with the Division of Neurology Products and, as you have heard from Dr. Katz, agreement was reached on the outcomes and we did two sequential Phase 3 trials both under special protocol assessments or agreements with the FDA.

[Slide.]

The goals of the Phase 3 program were based on the findings in the Phase 2 program and the design of the Phase 3 that emerged.

The first was to demonstrate that a proportion of patients with MS showed consistent improvement in walking speed on the timed 25-foot walk, and this arose from the observation in Phase 2 that a proportion of the patients

treated appeared to be truly responsive to the drug and others did not.

Second, we wished to establish the clinical meaningfulness of the improvements that were seen in walking speed and to show that these effects occurred irrespective of MS course type or concomitant treatment with immunomodulators. Based on mechanism of action, there was every reason to believe that this might be the case.

We also further wanted to evaluate the 10 mg b.i.d. dosing interval and the durability of the response, and to show that the safety profile of this SR formulation was acceptable.

We believe that the program achieved all of these goals successfully as will be presented in the next set of presentations by my colleagues.

[Slide.]

This is an agenda of the succeeding presentations. Dr. Aaron Miller will discuss the medical need and outcome measures, followed by Drs. Blight and Wessel presenting the efficacy and safety programs, and closing with Dr. Christine Short to provide a brief clinical perspective, and Dr. Miller again for a benefit/risk assessment.

[Slide.]

I also want to call your attention to the slides in your packets.

[Slide.]

We have several expert consultants with us today who are available for questions.

[Slide.]

Their short bio information is found in your packets on these slides.

Thank you very much.

I would like to call Dr. Miller to discuss the medical need.

Medical Need and Outcome Measures

DR. MILLER: Thanks, Ron.

[Slide.]

DR. MILLER: Good morning, ladies and gentlemen of the panel, members of the FDA, and audience, I appreciate the opportunity to speak with you this morning about the important medical need for an agent to improve the walking of people with multiple sclerosis.

[Slide.]

Over 30 years ago, my first clinical mentor in

multiple sclerosis was Dr. Labe Scheinberg. Dr. Scheinberg was a sometimes eccentric, but always brilliant, clinical neurologist whose is generally regarded as the father of comprehensive care in multiple sclerosis.

Dr. Scheinberg taught me in those days that MS disabled patients by impairing their ability to walk, by fatigue and by difficulty controlling their urinary function. Now, more than 30 years later and, with 50- to 60,000 patient visits under my belt, those words still ring true to me almost every single day.

[Slide.]

The truth of his words are indicated here, because in some surveys, between 64 and 85 percent of people with multiple sclerosis report difficulty in walking.

In the NARCOMS database, 70 percent of people with multiple sclerosis who have difficulty walking report that it is the most challenging aspect of their multiple sclerosis.

[Slide.]

It doesn't matter whether you have had multiple sclerosis for a short time or a long time. As indicated in the yellow bars here, even people with MS for under five

years rate walking the functional impairment that is of most concern to them, as do patients who have had MS for a long period of time as indicated in the blue bars here.

[Slide.]

There is good reason for that, because walking impairment has a very major effect on the quality of life of people with MS. This is a Canadian Community Health Survey that looked at quality of life as measured across the eight domains listed below on the x axis.

As you will see from the yellow bar representing the MS patients, there was a marked impairment in the quality of life overall of people with multiple sclerosis compared to the general Canadian population surveyed.

[Slide.]

But the preponderance of this impairment in quality of life and most of the amount of that impairment was driven by an impairment in ambulation, as you can see in the highlighted bars here.

[Slide.]

Of course, this is no surprise, because we know that walking impairment has an incredible importance in one's ability to function in everyday life. It impacts the

ability to navigate between the rooms in one's own house, to go to the bathroom, to shower, to care for one's children, to cross the street safely, to stay employed, to shop for groceries and then cook a meal, to climb stairs, to exercise, and to participate in social activities.

[Slide.]

Dr. Scheinberg also told many of us years ago that the posture of neurologists in those days was diagnose and adios. Fortunately, that is not the case necessarily today. We have many treatments for multiple sclerosis, as Dr. Cohen said.

We have treatments that at least partially manage the prognosis of the disease, the natural course of the disease and we have some symptomatic therapies. But sadly we lack a specific therapy for the symptom impairment of walking that is the most dramatic manifestation of multiple sclerosis.

To be sure, we do have some therapies that help individual symptoms or signs that may contribute to that impairment in walking, such as antispasticity agents, and we routinely recommend the use of rehabilitative therapies to improve mobility, to allow patients to maximize the function

with what residual neurological function they do have, but we have no drug therapy that is currently indicated specifically for the treatment of impaired ambulation in MS.

[Slide.]

The approval of fampridine-SR could go a long way to alleviating this problem for at least a significant percentage of people with multiple sclerosis.

[Slide.]

The primary endpoint in these trials, as you will see, has been driven by the use of the timed 25-foot walk, which in turn allows the calculation of walking speed.

The timed 25-foot walk has become a very standard part of the neurological examination for those of us who deal regularly with people with multiple sclerosis and it has been incorporated as part of the multiple sclerosis functional composite, a widely used clinical instrument in clinical trials, incorporated by a special task force of the national MS Society's Committee on Clinical Trials of New Drugs.

The timed 25-foot walk is simple to do, it requires only a stop watch and a measured 25-foot course. It has been standardized and most MS neurologists have a

clear sense of what a time on this test means.

I have a clear mental picture in my mind of what a person looks like who, say, takes 8 seconds to walk 25 feet in contrast to the normal speed of 4.5 to 5 seconds, and I can immediate conjure up the picture of the patient using a cane and walking 20 to 25 seconds to do this 25-foot walk.

[Slide.]

Now, improvement in walking speed is highly clinically important to many patients. Almost every day in the clinic when I ask a patient do you have any problems with your bladder function, will I get the answer "Yes, I often lose my urine, but frequently it is because I can't get to the bathroom on time."

[Slide.]

But it is not only walking speed that is important, but walking speed is highly correlated, as shown by Schwid and others, with performance on long distance walking and on endurance.

This is illustrated by one of my patients in one of the early fampridine trials who came back after a weekend and told me that she had taken a long hike in the Poconos where she had a leisure home with her husband, something

that she hadn't been able to do for the previous 20 years.

Not only is this correlation found, but it is found across a range of ambulatory abilities in multiple sclerosis. Walking impairment also sometimes has other social consequences.

For example, we know that the children of parents with multiple sclerosis are often embarrassed to bring their parents to school because of the way that parent walks. The ability to improve that speed of walking might substantially improve the comfort level of that child in letting that parent pick him up from school at the end of the day.

[Slide.]

Not only will you see that walking speed has been impacted, but there has been a correlative qualitative benefit of fampridine in patients with MS as measured by the MS Walking Scale 12.

This scale assesses 12 different clinical aspects of walking and it has been validated against ambulation and quality of life measures. It provides a fuller picture of the clinical benefit for patients who have responded on the timed 25-foot walk.

[Slide.]

This question goes into a number of consequences of gait and functional limitations, and it asks for the patient's assessment of how they have done over the past two weeks on a dozen issues. I won't read all of these here, but I will leave the slide up for you to look at them for a moment.

A person who has significant benefit on the MSWS-12 has experienced a real improvement in their walking ability and in their quality of life. Not only is it the MSWS-12, but other measures, such as manual muscle testing, spasticity, and some additional subjective measures that you will hear about later were also improved.

So, as you assess the fampridine program, I hope you will focus on how important the improvement in walking is for patients with multiple sclerosis.

I thank you for your attention and I will turn this over now to Dr. Andrew Blight, who is going to review the efficacy of the clinical program.

Clinical Program: Efficacy

[Slide.]

DR. BLIGHT: Good morning, ladies and gentlemen.

[Slide.]

As you have heard, the indication proposed for fampridine-SR to improve walking ability in patients in multiple sclerosis is based on the results of two pivotal Phase 3 studies.

The prospectively defined primary outcome measure used in both of these trials was consistently improved walking speed or timed walk response during the period of treatment.

I would ascribe the development of the criterion we used to identify timed walk responders, and I have also described the characteristics of timed walk response and how its clinical meaningfulness was demonstrated particularly as you have heard by reference to the MSWS-12 scale.

The findings of an earlier Phase 2 study MS-F202, particularly that 10 mg twice a day of fampridine-SR was optimal to take forward to Phase 3, or they spoke on efficacy and tolerability and that it was possible to identify patients who responded to drug by consistent improvement in walking speed.

[Slide.]

We were required as part of the FDA or special protocol assessment for MS-F203 to achieve three things: to

show efficacy on the primary endpoint, to show that the endpoint itself was clinically meaningful and to show that the effect was maintained over a full 3 months of treatment consistent with potential chronic use.

All three goals were achieved in MS-F203 and, therefore the requirement for the MS-F204 study was simply to confirm efficacy on the primary endpoint in a second prospective randomized trial.

The Division also required or requested that we find a way to examine the degree to which efficacy was maintained over the 12-hour inter-dosing period and these two requirements were met in the MS-F204 study.

[Slide.]

I will begin with the background to the primary endpoint that we used in these studies.

[Slide.]

As you have heard , we used the 25-foot walk as the most suitable objective measure walking for a clinic-based, multicenter trial that was well validated, widely used and readily performed by trained staff in a typical institutional setting.

The test can be used over a wide range of walking

impairment with patients using their usual aids to ambulation.

[Slide.]

We have used walking speed rather than time because of its superiority as a measure which has been determined independently by a number of investigators both in MS and other neurological conditions where the 25-foot walk or equivalent tests have been used.

This includes its closer correlation with real world ambulation including the maximum distance walked in MS patients as measured with GPS devices, the average daily step count in Friedreich's ataxia measured with accelerometers or the classes of community-based ambulation seen in post-stroke patients. But, fundamentally, the data using speed are also more symmetrically distributed and less subject to the influence of outliers with extremely long walk times.

[Slide.]

These histograms show the distribution of screening walking times in the upper row and walking speeds in the lower row. And you can see that the distribution of walking times is highly skewed to the left so that the mean

value of around 14 to 15 seconds is hardly representative of the bulk of the distribution.

The distribution of speeds around the mean of approximately 2 feet per second is much more symmetrical and has much better measurement characteristics for the analyses that were performed.

It is also important to notice that there is a wide range of either times of speeds involved so that the meaning of any absolute change in one or the other is difficult to interpret depending on the baseline disability of the patient.

Therefore, we have primarily used percent change from baseline both for the analysis and the description of changes that occurred.

[Slide.]

We used a responder analysis for a number of reasons. First, the variability of MS symptoms from day to day produces considerable spontaneous variation in the capabilities of patients on their walking ability and that can confirm the analysis of treatment effects.

It was clear from the Phase 2 data that some patients appeared to respond to treatment by improving their

walking speed while on drug and then returning towards baseline at discontinuation of treatment, whereas, other patients did not show that pattern.

As with most medical therapies, a subset of patients is actually responsive to the drug, and the responder analysis allows us to identify those patients and characterize the response more fully, particularly with regard to its clinical impact.

The meaning of an average change is difficult to assess if the effect is diluted by a sizable proportion of patients who do not respond.

We also found that looking at consistency of response rather than an arbitrary magnitude of change produced a better differentiation of response, and this is not surprising since by, looking at consistency, we are using more of the available information to distinguish changes that are truly drug related.

[Slide.]

The definition of timed walk response was derived from the trial design. There were 4 off-drug visits before randomization and 1 and 2 weeks following discontinuation of treatment, and there were 4 visits during the double-blind

treatment itself.

The definition of a timed walk responder was a patient whose walking speed for at least 3 of the on-drug visits was faster than the fastest of any of the 5 off-drug visits.

In other words, we chose the fastest speed recorded in the off-drug period as the best that a patient could normally be expected to do and to exceed that range for the majority of visits on treatment was a difficult hurdle.

The follow-up visit was specifically included to reduce the potential for false positives from patients who were simply improving over time and not necessarily related to treatment. And it is known that a subset of MS patients followed for a period of time will show improvement over time while others are declining.

[Slide.]

When we applied the criterion retrospectively to the data from the MS-F202 study, we found a clear difference in response rate between all three dose groups and placebo, response rates varying from 35.3 to 38.6 between the 10, 15, and 20 mg b.i.d. doses compared to 8.5 percent of people in

the placebo group.

[Slide.]

Turning now to the Phase 3 study, which used this endpoint in a prospective manner.

[Slide.]

The most important characteristics of the MS-F203 study are shown here. The patients were randomized in a 3:1 ratio to drug versus placebo. The range of baseline disability was restricted by requiring 25-foot walk times at screening between 8 to 45 seconds.

This was done to provide enough room for improvement in those patients who were less disabled and to exclude patients at the more disabled end who would not always be able to complete the timed 25-foot walk.

The study was open to patients with any type of MS as long as they showed sufficient ambulatory deficits at screening. Patients were allowed to remain on stable doses of their concomitant medications including the common immunomodulators.

[Slide.]

The potential measurements of efficacy in the trial included the following: The timed 25-foot walk on the

MSWS-12 scale, which we will cover in detail; a subject global impression, which was used to assess the patient's overall satisfaction with treatment on a terrible to delighted scale, and at the last visit on double-blind treatment, we included the clinician global impression of the change in overall status of the patient compared to baseline.

The MSWS-12 and the global measures were incorporated to characterize the clinical relevance of the timed walk response criterion itself. In addition, we included a lower extremity manual muscle test and the Ashworth score for spasticity, a physician measure of hyperreflexia in the leg muscles.

And these two measures were incorporated because earlier studies had shown effects of treatment on these outcomes, and it was important to determine the extent to which they might be responsible for the improvement in the timed walk responders.

Because of their role in characterizing response, all of these additional variables were analyzed primarily with respect to timed walk response and not as treatment group comparisons. Patients were not selected for these

endpoints and the trials were not powered to use them as traditional endpoints.

[Slide.]

The patient demographics were as expected and provide an unusually broad range of the MS population with respect to diagnosis type, age, and EDSS score and compared to the majority of large-scale trials in MS, which have tended to focus on earlier stages of relapsing disease.

The demographics were well randomized between the treatment groups with a small difference in gender distribution but did not have any significant impact on the study outcome as evaluated by sensitivity analyses.

[Slide.]

The patient disposition is shown here. There was a higher rate of discontinuation in the larger fampridine group. Five randomized patients were excluded from the modified ITT population because they discontinued before any double-blind efficacy data were obtained. This had no effect on the outcome of the study also as addressed in a subsequent sensitivity analysis.

[Slide.]

The study successfully showed that treatment with

fampridine-SR increased the proportion of patients who qualified as timed walk responders compared to placebo in the prospectively designed ITT analysis.

As you can see, 34.8 percent of the fampridine-treated patients qualified as responders compared to 8.3 percent of the placebo population, and this was highly significant at p less than 0.001.

In addition, these response rates were very similar to those seen in the retrospective analysis of the Phase 2 study.

[Slide.]

It is important to translate response into the actual change in walking speed experienced by those who respond to treatment. These two histograms show, on the left, the change in walking speed between baseline and the double-blind treatment period for the fampridine-treated population and the placebo population.

As you can see, there is a significant increase in walking speed in the fampridine-treated group compared to placebo but, on the right, you see that almost all the change experienced by the fampridine-treated group is occurring in the timed walk responders, who as a group

increased their walking speed an average of 25 percent over baseline.

This means that to understand the impact of the drug's effect, we need to focus on the treated timed walk responders rather than the whole fampridine-treated group.

[Slide.]

This issue is not unique to these studies or this indication, and the recent FDA guidance on patient-reported outcomes clearly reviews this issue. Here is a quote from that review that expresses the problem succinctly. When only a proportion of treated patients respond to treatment as is often the case, that subset may experience meaningful changes even if the apparent mean difference between treatment groups appears to be small.

[Slide.]

This leads us to the first of the two additional requirements for the MS-F203 study, which was to establish that the timed walk response definition showed not only statistically significance but identified effects that either the patient or the physician could recognize and appreciate as clinically meaningful.

[Slide.]

The approach to answering the question of clinical meaningfulness was prospectively defined in the protocol for MS-F203. The primary test was to show that patients who qualified as timed walk responders independent of treatment demonstrate an improvement in self-assessed walking disability on the MSWS-12 scale.

This instrument also allows the broader impact of response on other aspects of ambulation to be examined. The secondary approach was to look for improvement on the subject in clinician global impression scores among timed walk responders. These global measurements would allow any negative aspects of response to be weighed against its positive characteristics.

[Slide.]

You have seen the MSWS-12 questionnaire and its 12 questions.

[Slide.]

In practice, each of those questions is answered on a 5-point scale, from not at all to extremely. The total score is then arithmetically transformed to a 0 to 100-point scale covering the range from no disability to extreme disability.

The average baseline score for the patients in the MS-F203 study was approximately 70.

[Slide.]

A change from baseline MSWS-12 score during the treatment period was compared between timed walk responders and time walk non-responders independent of treatment assignment, because we were interested in characterizing the criterion itself, not in demonstrating the treatment effect, which had already been demonstrated by the response rate analysis.

There was a significant improvement in self-assessed ambulation on the MSWS-12 for timed walk responders compared to non-responders. This serves to show that the changes associated with consistent improvement in walking speed experienced by timed walk responders are recognized by the patients as they assess the impact of their MS on their daily life.

It is also noteworthy that the approximately 7 percent improvement in walking speed experienced by the timed walk non-responders did not lead to any overall change in the MSWS-12 score and this supports the original conception. But it is possible that small improvements in

walking speed may not be clinically meaningful, while it shows that the larger changes seen in timed walk responders are meaningful.

[Slide.]

We also saw that the improved MSWS-12 scores were not dependent on any particular function or quality of walking addressed by the instrument but were driven by all 12 aspects of ambulation in daily life.

[Slide.]

Within their briefing document, you will see that the FDA has subsequently questioned the usefulness of the MSWS-12 in this role of validating the significance of the response definition since, "the MSWS-12 measures the same domain as the timed 25-foot walk."

In fact, to show clinical meaningfulness of the criterion, it is important that the two instruments both relate to walking but that they measure different aspects of the walking domain.

Looking at the relationship between changes in MSWS-12 score and timed walk speed in the study, although significantly related, they show a great deal of independence measuring different aspects of the complex

walking function such that only about 16 percent of the change in MSWS-12 score appears directly related to change in walking speed.

As complementary measures, these two instruments appear well suited for the task of measuring clinically meaningful changes in walking but are both objectively demonstrable and subjectively recognized as beneficial.

[Slide.]

The findings of our studies are consistent with a number of other published reports. The particular study shown here looked at the relationship between the 20 percent worsening of the timed 25-foot walk with progression of disease against changes in the Guy's Neurological Disability Score in a cohort of more than 500 MS patients, and was able to show the changes in self-assessment of lower extremity disability were associated with this change in objective function.

The timed walk responders in the MS-F203 study showed an average improvement in walking speed of 25 percent rather than 20 percent.

[Slide.]

The two global impression measures were also

significantly approved on the prospectively designed analysis comparing timed walk responders compared to non-responders, confirming that response was meaningful and that the perceived benefits of response were not offset by any associated negative effects.

[Slide.]

It may be difficult to grasp intuitively the impact of what may seem like small numbers and abstract percentages in terms of walking times and speeds. To put these number into a more real world context, we plotted the timed walk speed for all patients in the two pivotal studies ordered across the horizontal axis at a baseline walking speed shown in green.

In essence, each patient in these studies is represented by a pixel along that line. The corresponding average walking speed during the double-blind treatment for each patient is then plotted on the same vertical axis as that green pixel so that increases in walking speed are shown above the line and decreases below the line.

The fampridine-treated timed walk responders are shown in gold, the fampridine-treated non-responders in blue, and the placebo patients are shown in white. You can

see that there is a lot of change in walking speed in this population, and we can provide a context for these changes from studies that have involved walking impairment in the stroke population where walking disability is more stable from day to day and it is easier to do that kind of division.

[Slide.]

Studies in post-stroke patients have shown that it is possible to divide them into three broad classes of ambulation based on important transition speeds, such as those with walking speeds below 1.31 feet per second, which is 0.4 meters per second, are generally only able to use ambulation in the household setting.

Those with walking speeds above 1.3, but below 2.6 feet per second, are able to walk outside the home. But have limited access to the community based on limitations in maximum distance they can walk and also in their need for assistance.

Those walking faster than 2.6 feet per second are classified as full community ambulators with access to most of the wider activities of daily life. These classifications are marked here by the horizontal lines at

the appropriate speed in feet per second, and the line at the top represents the lower end of the walking speed range for an unaffected healthy population.

[Slide.]

When we superimpose the fampridine-SR data on this functional map, we see that the observed changes cannot only take patients from the poor end to the good end of their category but also, in many cases, can move them from one category to another.

[Slide.]

Quantifying this further, in this diagram we show the proportion of patients whose walking speed changes in the fampridine-SR studies, both MS-F203 and 204, between baseline and double-blind treatment, were sufficient to change their category on the gait speed classification.

We can see here that fampridine-treated timed walk responders improve across these category boundaries at a net rate of 31.8 percent compared to 8.8 percent for the fampridine non-responders and 8.5 percent for the placebo patients.

This means there is a marked reduction in the proportion of time walked responders who would fall within

the range of walking speeds associated with household ambulation and an increase in the proportion who fall in the full community ambulation category.

It is important to note that responders also improve more robustly within categories, which can also be clinically meaningful.

[Slide.]

The second additional requirement for the MS-F203 study was to establish that improvements in walking speed seen in timed walk responders were maintained over the full three months of treatment.

[Slide.]

These two graphs show the average change in walking speed from baseline to each of the four visits over the three-month treatment period.

The graph on the left shows the change in speed for fampridine-treated patients compared to placebo, demonstrating a significant improvement in walking speed at the end of the treatment period.

The graph on the right shows the increase in walking speed for fampridine-treated timed walk responders and non-responders and you see they maintained 25 percent

improvement among timed walk responders across the entire treatment period.

The timed walk non-responders showed a similar improvement to the placebo-treated group at approximately 7 percent overall.

In summary, there was no indication of a loss of efficacy over three months of treatment and the requirement for the study was met.

[Slide.]

Turning to the second Phase 3 study--

[Slide.]

It was agreed that MS-F203 had demonstrated both efficacy and clinical meaningfulness of the timed walk response and, accordingly, the protocol for MS-F204 should be designed simply to confirm efficacy on the primary endpoint.

The study is an overall similar design but with a few elements that differed based on the simpler goal. Fewer patients were enrolled and they were randomized in a 1:1 ratio of drug to placebo.

The period for evaluation of timed walk response was reduced to 8 weeks with 4 visits at 2-week intervals.

An additional double-blind treatment weekend visit were added specifically to collect data from the end of the 12-hour dosing period to examine maintenance of effect over that time.

Recruitment criteria and baseline demographics were similar to those shown for 203.

[Slide.]

Here is the patient disposition data. The discontinuation rate in this equally randomized study was more symmetrical and only two patients, one from each group, were excluded from the modified ITT population based on the absence of double-blind efficacy measurements.

[Slide.]

The results of the MS-F204 study were consistent with those from MS-F203 and, again, the difference in response rate between fampridine and placebo was highly significant at p less than 0.001.

[Slide.]

The additional requirement for the MS-F204 study was to examine the extent to which improvement in walking was maintained over the 12 hours between doses.

[Slide.]

Looking at data from individual MS patients in a formal pharmacokinetic study, we can see that the concern was that the fampridine plasma concentration drops as we approach the 12-hour time point, which might result in a loss of efficacy particularly for those patients at the lower end of the variability in pharmacokinetics.

Therefore, the protocol allowed for an extra week of treatment and specific visit in which patients were brought in during the last three hours of this time and they were evaluated three times on the timed walk with an hour between tests.

[Slide.]

This graph shows the percent change in walking speed in four time periods. On the far left, the average of the double-blind efficacy periods of visits 3 to 6, showing the fampridine-treated timed walk responders in gold, the non-responders in blue, and the placebo patients in white.

To the right we see the 3 time bins, 9 to 10 hours, 10 to 11 hours, and 11 to 12 hours post-dose, and the average change in walking speed for the same three groups during that period.

We see that the 25 percent improvement in walking

speed seen during the efficacy period is maintained up to the last hour of the inter-dosing period, at which point there is a decrease in the average improvement to about 20 percent and it was clear that there was some loss of efficacy at this last hour, perhaps for a subset of the responders included.

[Slide.]

We also collected plasma samples for evaluation of fampridine concentrations at all visits in the 204 study. We plot them here against the time post-dose at which the samples were collected, and we see the expected pharmacokinetic profile for the 10 mg dose.

We then took these fampridine concentration measurements and plotted them against the change in walking speed at the same time as the fampridine plasma concentration samples were obtained.

[Slide.]

So, here we show with the fampridine plasma concentrations now in the horizontal axis in 2 nanogram per ml bins across that axis against the percent change in walking speed seen in the same patients as those samples were collected.

What we see here is that as concentration falls below about 15 nanograms per ml, moving to the left, there is a marked reduction in the walking speed improvement in the all fampridine-treated patients.

This is consistent with the observation of a reduction in efficacy at the last hour of the dosing interval based on the pharmacokinetics. It also indicates that 10 mg is the lowest dose that would be expected to maintain efficacy on a b.i.d. dosing regimen in the majority of patients.

It is also possible to see from the information here that there is no increase in benefit on walking speed at higher plasma concentrations. This is consistent with our original selection of 10 mg b.i.d. based on the lack of increased efficacy at higher doses as measured with the timed walk response.

[Slide.]

As a reminder, this is the data from 202, which shows no increase in response rate at higher doses that would produce those higher plasma concentrations.

[Slide.]

Having established in the two Phase 3 studies the

statistical and clinical significance of the treatment effect, we were concerned to look for evidence within the data that there might be subgroups of patients more likely to respond, who could therefore be identified ahead of treatment.

[Slide.]

Subgroup analyses were performed based on baseline disease characteristics, baseline demographics, baseline objective and subjective measures, and concomitant drug use including the immunomodulators.

We have not detected any of these variables that appears to be related to responsiveness on the timed 25-foot walk.

[Slide.]

As an example, this plot shows the odds ratio for response relative to MS disease characteristics including disease course types, duration of disease, and baseline EDSS score.

The plot shows the difference between fampridine- and placebo-treated subgroups in the odds or likelihood of timed walk response. There was no indication of a meaningful effect of any of these factors on responsiveness

to treatment. Our briefing book provides the full set of these plots for the other variables.

[Slide.]

Although we used a wide range of different measures for characterizing response in these studies, there are numerous other forms of analysis that could obviously be applied.

We understand that the novelty of the response criterion we developed has led to questions about the meaning of the observations. I will briefly review the results of a more traditional approach to defining response and also look at direct dose-group comparisons of all the potential efficacy measures that were used.

These additional analyses were unplanned but are presented here to show the robust and consistent nature of the data.

[Slide.]

If we look at the potential for a more traditional definition of response based on an ITT analysis of the proportion of patients achieving at least a given percent mean change from baseline and walking speed throughout the treatment period, we see these distributions across the

three adequate and well-controlled studies.

The fampridine-SR treated group shows a higher rate of response no matter what threshold improvement is chosen, and this difference is significant at 10, 20, 30, and 40 percent thresholds of improvement.

It is also significant within the individual studies for the 10, 20, and 30 percent improvements independently.

Most importantly, given the wider understanding of the clinical meaningfulness of a 20 percent change in walking speed, 31.5 percent of the fampridine-treated group compared to 13.1 percent of the placebo group had a mean increase in walking speed of 20 percent or more.

This sensitivity analysis teaches us that regardless of the definition of response, there is still a significant effect of the drug on a number of patients who respond.

[Slide.]

Looking at the three objective measures of lower extremity function included in these trials, these plots show the difference between fampridine and placebo groups for changes from baseline in walking speed, lower extremity,

manual muscle test, and Ashworth spasticity score.

The plot shows the mean differences together with the 95 percent confidence intervals across the two pivotal studies and the pooled data from the two studies.

Individual p values are provided to give the full clinical picture although these were not planned analyses. Every measure in each trial favored fampridine against placebo and, in most cases, significantly so.

[Slide.]

Similar plots for the subjective variables of MSWS-12 score, SGI and CGI score show the same pattern with all measures favoring the fampridine-SR treated group.

[Slide.]

As depicted in this table, direct group comparisons of all objective and subjective measures used in the adequate, well-controlled studies, all favor fampridine and most were statistically significant. There was no case in which there was either no direction of indication or a negative direction.

[Slide.]

In summary, the prospectively defined primary outcome was met in both the pivotal studies. Timed walk

responders had a 25 percent average increase in walking speed and reported significant decrease in the impact of MS on their daily walking activity.

Benefits were independent of MS course type, level of disability, or concomitant immunomodulator therapy. The results were strikingly consistent across all measures and studies and provide evidence of a meaningful, immediate, and maintained benefit for people with MS that is not available with currently available medications.

The beneficiaries include those with progressive forms of the disease for whom there are no approved therapeutic alternative.

Dr. Wessel will now address the safety data from the development program.

Clinical Program: Safety

[Slide.]

DR. WESSEL: Today's discussion of safety will include data from our controlled studies, our open-label extension studies and an examination of two topics of special interest, MS relapse and seizure.

There are over 2,100 subjects in the safety database including more than 1,000 MS patients, 700 spinal

cord injury patients, and over 400 clinical pharmacology subjects. This number includes subject exposed to fampridine at any dose or placebo.

[Slide.]

Over 1,900 subjects including over 900 MS patients were exposed to fampridine in the clinical program. Over 600 MS patients were treated for 6 months or longer and more than 450 patients were treated for 7 months or longer with 10 mg or higher. The total number exceeds ICH guidelines.

[Slide.]

The Studies 202, 203, and 204 differ in size, study duration, and randomization ratios. They do share one important characteristic. The patients in these studies have an average duration of disease of about 13 years.

The 202 study had four arms of approximately 50 patients each with two dose groups higher than the proposed 10 mg dose. The 203 study had a 3:1 randomization while the 204 study had a 1:1 randomization ratio.

These studies allow a detailed comparison of safety events in the placebo and fampridine-treated patients. Both placebo and fampridine-SR arms had a completion rate of over 90 percent.

[Slide.]

Discontinuations occurred for a variety of reasons. The discontinuation rate due to adverse events was higher in the fampridine group, at 3.8 percent, versus 2.1 in the placebo group.

[Slide.]

The percentage of patients with treatment-emergent adverse events and serious adverse events were higher in the fampridine-treated group. There were no deaths in these studies, but one death was reported for a patient who had completed the 203 study. This death occurred 5 weeks post-treatment, outside the reporting window, and the autopsy established the cause of death as due to ischemic heart disease.

[Slide.]

The most frequent events reported in both groups are typical of the MS population particularly in older group with more advanced disease. A number of these events occurred more frequently in the fampridine group compared to placebo.

[Slide.]

The most pronounced differences, highlighted here

in yellow, were the adverse events UTI and the CNS events of insomnia, asthenia, dizziness, headache, nausea, and balance disorder where the AE rates for the fampridine-treated patients were higher than in the placebo group.

Most of these adverse events were mild or moderate, transient in nature, and did not result in discontinuations.

[Slide.]

Treatment-emergent serious adverse events were infrequent. There were a variety of events in the placebo and fampridine-treated groups with no obvious pattern of distribution to particular organ system. In the fampridine group, adverse events occurred in either single patients or in the case of pneumonia, UTI, and syncope, in two patients each.

Recall that the patient year exposure was substantially greater for the fampridine group than for the placebo group.

[Slide.]

When we looked at treatment-emergent adverse events leading to discontinuation, we saw a similar wide variety of events with no obvious pattern. Each of these

events occurred in either a single patient, or in the case of balance disorder, dizziness, and headache, in two patients each.

[Slide.]

Two patients experienced seizure-related events across the three studies. The event in the fampridine group was an apparent focal seizure observed in the emergency room in a patient presenting in sepsis. The investigator involved did not report the seizure event as a separate AE, but considered it part of the sepsis event. The complex partial seizure occurred in a placebo-treated patient.

We had agreed with our investigators at the beginning of the development program that we would report all seizure-related events as serious adverse events because of the existing understanding of the risk of seizure at high doses of fampridine, and I will discuss this issue in greater detail in a moment.

[Slide.]

Overall, fampridine was well tolerated with retention rates across studies of over 90 percent. The most prominent differences across studies were in the CNS events that I mentioned and that can be considered as mild or

moderate and transient. Most did not lead to discontinuations. There was no signal for increased seizure risk in these studies at 10 mg b.i.d. of fampridine-SR.

[Slide.]

The safety profile for fampridine is further informed by the results of the extension studies. This diagram shows the sequence of extension studies and the number of patient years on 10 mg b.i.d. with a cutoff of November 2008, the cutoff for our safety update to the FDA.

The oldest of these studies still has 93 patients who have been treated for approximately five years, and the total exposure across these studies at 10 mg b.i.d. was over 1,200 patient years as of November 2008.

[Slide.]

660 patients entered into the extension studies and approximately 460 were still enrolled at the time of the safety update, for a combined retention rate of approximately 70 percent.

The spectrum of frequent adverse events observed in these studies is similar to what might be expected in this older, more disabled cohort of MS patient.

[Slide.]

Cumulatively, the most frequent adverse events reported were UTI and falls. Twenty-five percent of patients experienced an MS relapse or worsening of MS symptoms coded to MS relapse, and 16 percent had asthenia.

[Slide.]

The most frequent serious adverse events in the extension studies were also those that would be expected in this population. The most frequent events reported were MS relapse, cellulitis, and UTIs. All other SAEs occurred in less than 1 percent of patients.

[Slide.]

A variety of adverse events led to discontinuations in these studies, but all were under 1 percent. The most frequent were asthenia and trigeminal neuralgia, each in 4 patients. This was followed by balance disorder, convulsion, and MS release, each in 3 patients.

The 3 patients with convulsion and the 2 with complex partial seizure were required to discontinue by protocol. Both MS relapse and seizure are part of the discussion of events of special interest in a moment.

[Slide.]

To date, there have been a total of 9 deaths in

the MS development program. One occurred in our double-blind studies and 8 occurred in the open-label extension studies. The death in the double-blind study I had previously mentioned was the patient with ischemic heart disease.

Of the 8 deaths that occurred in the extension studies, 2 cases suicide and myocardial infarction occurred after the November 2008 clinical cutoff at the bottom of this table.

Of all the deaths, 2 were confirmed suicides, and we considered 1 additional case a possible suicide related to oxycodone overdose. There was 1 death of undetermined cause.

[Slide.]

We will focus on MS relapse and seizures as events of special interest.

[Slide.]

The incidence of MS relapse during active treatment was no different in the placebo and the fampridine-treated groups at 3.8 percent. However, there were 7 patients in the fampridine group that experienced MS relapse symptoms during the immediate post-treatment period.

[Slide.]

However, we see that there is no difference in incidence rate during active treatment and, as you can see, both active and placebo have similar incidence per 100 patient year exposure. This is comparable to the experience in the long-term, open-label extension study.

[Slide.]

This schematic depicts the time frame of post-treatment events coded to MS relapse. There were 7 patients in the fampridine-SR group compared to 1 patient in the placebo group. These events were recorded as MS exacerbations by our investigators. All of these events were reported as worsening of pre-existing MS symptoms particularly difficulty walking and leg weakness.

None of these patients were hospitalized and no new neurological deficits were reported. Four of 7 patients experiences worsening within 3 days of stopping treatment, and all 7 patients reported their symptoms within 6 days.

All of these patients were subsequently enrolled in the long-term extension study and 5 of the 7 patients treated with fampridine-SR are still active in these studies today.

[Slide.]

We know from preclinical pharmacology experiments that high plasma concentrations promote the onset of seizure activity and that accidental overdoses and pharmacy compounding errors have led to seizures, some of which are reported in the literature.

We have also seen an increased incidence of seizures at higher doses of fampridine during the development program but, at a 10 mg b.i.d. of fampridine-SR, there has been no difference in the incidence of seizure events in MS patients in the controlled studies.

The incidence of seizures in the extension studies at this dose is consistent with expected background rates in the population.

[Slide.]

Over the 15 years of the development program, 1,922 patients were exposed to fampridine including all doses and all formulations. Within the safety database, there were 22 seizure-related events comprising 19 convulsions and 3 complex partial seizures. These included 11 seizures in the multiple sclerosis program, 6 seizures in the spinal cord injury program, and an additional 5 seizures

on other formulations.

Fampridine doses were up to 40 mg b.i.d. in MS and up to 60 mg b.i.d. in the spinal cord injury program.

[Slide.]

Of the 17 patients with seizures, with fampridine-SR in the MS and spinal cord injury studies, 5 were on 10 mg b.i.d., and the rest were on higher doses. Note that these do not include the two events in the double-blind studies that were previously discussed, one, a focal seizure in the setting of sepsis that was not coded to seizure, and the other seizure that occurred on placebo.

[Slide.]

There was one patient in the spinal cord injury program, in the controlled studies, that had a seizure at 40 mg b.i.d. This patient had a history of traumatic brain injury and seizure.

[Slide.]

This table shows the number of MS patients with seizure-related events at a range of doses in our controlled studies. Two patients randomized to the 20 mg group experienced seizure. One of these was a patient who, in fact, took two tablets at one time on two separate occasions

and experienced a complex partial seizure on both occasions.

To provide an accurate assessment of dose-related seizure risk, this patient is represented in the 40 mg column here. Doses above 20 mg were explored in a small dose ranging study that exposed 25 patients to ascending doses between 10 and 40 mg b.i.d., each dose for one week.

Two of those patients experienced seizures, one at 30 mg and one at 35 mg b.i.d., and these patients were discontinued from the study. Twenty patients tolerated doses of 40 mg and did not experience seizure events at that dose.

The percentage of patients experiencing seizures at these doses is depicted in the next slide.

[Slide.]

Although the numbers were small, there is a strong suggestion here that the incidence of seizure is increased at doses of 30 mg b.i.d. or higher. The data between 15 and 25 mg b.i.d. are too limited to make an accurate estimate of incidence.

[Slide.]

In our open-label extension studies in MS with over 1,200 patient years of exposure, we have observed 5

seizures. As of November 30, 2008, at the time of the safety update, this gave an incidence rate of 0.41 events per 100 patient years.

Since then, we have not recorded any further seizures in the extension studies. The current rate as of September 30, 2009, is 0.32 per 100 patient years with 95 percent confidence intervals ranging from 0.1 to 0.74. This new calculation has not yet been reviewed by the FDA.

We examined the literature for reports of seizure rates in MS. Among approximately 30 studies, most showed incidence rates between 2 and 7 times that of the general population. These studies varied considerably in their design, cohort sizes, and methodology.

A study reported by Eriksson et al., in 2002, appeared to provide a relevant comparator as it was population-based, well-designed and, importantly, focused on incidence of first seizure.

This was comparable to our study population in which patients with a prior history of seizure were deliberately excluded.

[Slide.]

This study, based on over 6,000 patient years of

data, reported an incidence rate for first seizure of 0.35 per 100 patient years with confidence intervals that overlap our observed rate of 0.41 from our safety update.

The conclusions of this study are in line with other epidemiological studies that show a high rate of seizure in the MS population, which is about 3 or 4 times higher than the general population.

Drug-related seizures are generally expected to occur soon after initiation. We looked to see whether there was any indication of such a relationship in our studies.

[Slide.]

We found that the events appeared to be unrelated to the period of treatment. This finding is consistent with a study background rate of seizure occurrence in the study population. Although we cannot exclude a contribution of fampridine to the seizures, all but one of these seizures occurred at least 11 months after entry into the extension study.

The exception was the woman who had taken fampridine-SR for 14 weeks in the double-blind study without incident and then had a seizure 9 days after entry into the extension study.

[Slide.]

The risk of seizure has long been associated with higher exposures to fampridine. Furthermore, there is an intrinsic elevated risk of seizure in MS patients.

No increased incidence was seen in this program at the proposed dose of 10 mg b.i.d. of fampridine-SR, a formulation that was specifically developed to maintain plasma levels in a narrow range. However, we recognize that with any approved drug, the data that can be collected during a development program may not fully characterize the risk for infrequent events.

Patients and physicians should be thoroughly informed regarding the risks of higher doses. For this reason, we have proposed a REMS program to further characterize and mitigate the risk factors for seizure.

[Slide.]

One of the key goals of the REMS program is to prevent prescribing or use above 10 mg b.i.d. To this end, the program will do the following: Ensure selection of appropriate patients and raise awareness for the contraindication in patients with a history of seizure; promote informed prescribing and promote informed use by

patients.

A second key goal is to further characterize the risk factors for seizure.

[Slide.]

The key element of the REMS program includes distribution of the drug through specialty pharmacies which will facilitate appropriate patient selection and compliance, as well as collection of postmarketing data.

In addition, we will provide a medication guide and implement a detailed communication program that will go beyond the labeling of the drug and include a Dear Prescriber letter and an ongoing healthcare provider education program.

We will also collect additional data on spontaneously reported seizures by use of structured questionnaires. In addition, there will be an ongoing evaluation to ensure the effectiveness of the REMS tools.

[Slide.]

Overall, fampridine was well tolerated. There was no increased incidence of seizure in the controlled studies at 10 mg b.i.d. of fampridine-SR. Seizure incidence in open-label studies on 10 mg b.i.d. was consistent with the

expected background rate in MS.

The data indicate that there is a dose-dependent risk of seizures, and we will be able to promote and monitor adherence to the 10 mg b.i.d. dose through our REMS program.

I would now like to introduce one of our investigators, Dr. Christine Short, who will describe her clinical experience with fampridine.

A Clinical Perspective

[Slide.]

DR. SHORT: Good morning. I would like to thank the FDA and the Committee for the opportunity to present this morning. My name is Dr. Christine Short. I am the Division Chief for the Division of Physical Medicine and Rehabilitation at the QE II Health Sciences Centre, which is part of the Dalhousie Medical School.

I am also the Co-Director of Rehab Services for our Capital District Health Authority and I worked with the Dalhousie MS Research Group. In our Dalhousie MS clinic we have a database of over 3,000 individuals with multiple sclerosis that we manage on an ongoing time.

I am also the site investigator for the MS 203 and 204 studies related to the fampridine clinical trials.

[Slide.]

For my MS patients, from the moment that they are diagnosed, walking is one of their most serious concerns. They have great anxiety about their walking ability because they know over time, as this slide demonstrates, it is going to deteriorate. We know that by 8 years, more than half of MS patients will have a walking impairment, by 20 years they will require a cane and, by 30 years, a wheelchair.

This progresses faster in some individuals than others. Individuals are diagnosed with multiple sclerosis at a young age, so they are meeting these milestones early in their life.

Walking is fundamental to their ability to engage fully in activities that we often take for granted. How often do you have to think about before you get up and walk if your legs are going to support you or take you far enough to get to the bathroom or to get to the grocery store, to walk the kids to school?

These are simple daily abilities that my patients with MS worry about every day and, over time, they are gradually robbed of these abilities. Presently, we do have therapies to help with ambulation and walking in people with

multiple sclerosis, but these therapies are limited.

We can provide intensive coordinated physiotherapy programs, and the literature shows that they do work. But the difficulty with this is to sustain them in the community after the program is completed and, if you can't sustain the exercise program, the value of the program is lost quickly.

We also use walking aids, such as braces, crutches, walkers, and canes, and individuals do find these helpful but often find it difficult to accept these adaptive aids because they often see them as a badge of their disability rather than an agent that might enable better walking.

At the present time, there are no approved pharmacologic agents for walking in MS. 4-aminopyridine is available in an unapproved, immediate release compounded form. As mentioned earlier, the compounded forms have been used since the early and mid-eighties.

I have some experience with the compounded forms. I have had 13 patients on immediate release 4-aminopyridine, and 5 have had seizures. So, with this experience, as well as the literature publications that have shown serious adverse events associated with compounding errors, I no

longer prescribed immediate release 4-AP for my patients with MS. I don't feel that I can guarantee a level of safety with this form of the compound.

In stark contrast to this has been my experience with fampridine-SR through the 203 and the 204 trials. I have had 19 patients on this drug, 16 remain on active drug, and many of them have been taking the 10 mg dose b.i.d. for over 5 years. I have seen no seizures in my patient group.

So, I feel comfortable with the fampridine-SR data that has been presented today and my experience that it has a good margin of safety for use in my patients.

[Slide.]

So, what does walking faster mean to somebody with MS? Yes, we are seeing individuals at our site and other sites walking faster, but what does this mean? What do two or three seconds mean?

Well, if you look at an example, if you are walking 25 feet in 15 seconds and you walk 2 seconds faster, you walk about 15 extra feet per minute. That doesn't sound like a lot, but that is 900 extra feet per hour. That is three football fields. So that is a lot of walking over the day and that leads to improved function. And my patients in

the study tell me this over and over again.

We know that the literature supports a good correlation between the 25-foot walk test and walking endurance. My patients tell me when they are walking faster, they are also walking farther.

For example, one of our subjects, a 45-year-old gentleman with secondary progressive MS, reported walking faster, being less fatigued, and he was actually confident enough to walk without his knee brace which he used to need 100 percent of the time.

Not only did he walk faster on his 25-foot walk test. But, in our ambulation profile which we use to follow people in our center, his endurance walk went from 19 meters, which is about 100 yards, off drug, to 360 meters, which would be about 400 yards on drug. So, this is quite significant improvement. And it wasn't just this individual. We have seen these types of results in several cases at our site.

These individuals didn't just walk faster on the flat with their 25-foot walk test but walked faster over gravel, up and down inclines, on stairs, and this is what leads to improvements in daily function and quality of life.

One of our subjects, a 66-year-old gentleman with primary progressive MS was able to walk the golf course during his winter vacation with his wife. They reported back to us that that was the first time he had been able to do that in several years, and he was reporting walking faster and farther.

So, to summarize, when my patients are diagnosed with MS, they are sentenced to a life in which they are slowly robbed of their independence and their physical abilities.

Seeing improvements in walking as a result of taking fampridine in someone with a diagnosis in which they are supposed to get worse, has a huge positive impact, not just on function but on sense of well-being and on quality of life.

With the fampridine-SR trials, I am confident that I now have a drug that can safely provide this for a significant number of patients with MS.

Thank you.

I will now invite Dr. Miller to come up and talk about benefit and risk.

Benefit/Risk Assessment

[Slide.]

DR. MILLER: The prospect of having fampridine available for my patients is professionally very important to me. Dr. Short has already shown us what some of the potential benefits for improved walking are to patients, and I am not going to belabor that point by adding additional vignettes.

I do want to emphasize that, from my point of view, the studies have demonstrated an extent, breadth, and duration of fampridine response that is meaningful.

[Slide.]

This benefit on walking extends across all disease types irrespective of the duration of disease and without regard to the specific level of disability on the EDSS score.

[Slide.]

Even though we have looked primarily at responders, these data show that this benefit extends even across all people taking the drug. And that is true both on objective measures, such as walking speed, the lower extremity manual muscle test, or the Ashworth score for spasticity.

[Slide.]

Furthermore, the results are consistent across all subjective measures with benefit being seen on the MS Walking Scale 12 score, the subjective global impression of patients, and the clinician's global impression.

I spend almost all of my time--my professional time that is--taking care of people with multiple sclerosis and, like every other clinician, I always struggle with the question of what is the risk/benefit ratio with any drug that I prescribe for patients.

Over the years, I have hardly ever prescribed compounded versions of 4-AP, because I was unconvinced of the efficacy because of a lack of data from good controlled clinical trials, because I had fear of seizures and because I was worried about the potential for compounding errors, a point that has been highlighted by a number of recent reports of significant problems with overdosage because of compounding errors.

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 it with some trepidation, to start prescribing compounded 4-AP.

Incidentally, a number of pharmacies are saying that they provide sustained release preparations of compounded 4-aminopyridine but we have no information whatsoever on what validation is for that compounding or how that compounding was actually prepared.

I am now very comfortable using fampridine-SR in the 10 mg b.i.d. dose that has been tested and recommended. I believe the seizure level is very low in this group and probably doesn't exceed the background level of seizures in my advanced MS patient population.

Furthermore, I think the risk of seizures with fampridine-SR 10 mg b.i.d. is probably lower than that for a number of other drugs that I routinely use in my MS clinical practice, drugs such a bupropion that we commonly prescribe for depression, the tricyclic antidepressants that we don't use so much anymore but which, over my career, we have used extensively, not only for depression but for its side effect of anticholinergic properties in treating MS bladder dysfunction, and even for baclofen that we widely prescribe as an antispasticity agent.

I am not convinced that these alleged relapses that occurred following the discontinuation of fampridine

are a concern. I really think they actually represented a return to baseline, more severely impaired walking ability after the drug was discontinued.

Now, one really important thing I think about fampridine is the fact that we should be able to assess the response to this drug very quickly.

The data have shown that walking speed increased by 2 weeks after initiation of therapy and was sustained on repeated measures over the subsequent several weeks so we should be able readily, by taking a clinical history from a patient and watching the gait, be able to assess within a few weeks whether a patient is responding to fampridine and, if not, discontinue the drug so as to limit the exposure to any potential seizure risk.

So, from my own personal or professional perspective, I would be seriously disappointed if the FDA incident not improve fampridine-SR. I think it is a valuable medication that will substantially benefit a significant percentage of my patients and I think it can do so safely.

Thank you very much.

Clarifying Questions

DR. ANDERSON: Thank you.

I will mention that we have a member of the Committee who is joining us by phone, Olaf Stuve, and that explains some of the beeps that are going on intermittently, it is our ability to try to keep him on line where he is joining our session.

Now, we have some time for clarifying questions for the industry's presentation, so if there is anyone at the table--we will start with Dr. Wolfe.

DR. WOLFE: Yes. In your Slide 42, where you looked at the timed walk responders, the percentage of timed walk responders as a function of dose, you showed that they were all significantly better than a placebo, but that pretty much the response was the same, 35.3, 36, 38.6.

In FDA's presentation, which I think everyone is aware of, they have a chart looking at the relationship between the area under the curve and the percent change from baseline, and it is pretty much flat. The comment they made was that even though--and I think we will discuss later--this is an extremely small clinical response, it seems to be the same at the doses 10 b.i.d., 15 b.i.d., and 20 b.i.d. The FDA raised the question about since we haven't come to

lowest dose that might work, whatever work means, why haven't there been clinical trials using lower doses, 5 or even lower.

I mean I just put the question to the company, have there been trials? We don't see the results here. What is your interpretation of the fact that at exactly, that the doses no matter what they are give the same, I would say, very small clinical response?

DR. COHEN: I am going to ask Dr. Blight to respond, Dr. Wolfe.

DR. BLIGHT: Thank you. Slide up, please.

[Slide.]

This is the data that you referred to I believe, which shows that there is no increase in response rate with doses above 10 mg. Of course, the measurement of response was obtained during these trials throughout the dosing period and one of the things we did as part of the 204 study was to examine what happens towards the end of the dosing period, which isn't necessarily represented by this response rate.

The question is not just is there a response rate at mostly around the higher levels of plasma concentration,

but is that response really representing a full benefit throughout the day. And our data indicate, when we look at plasma concentrations versus improvement in walking speed, that, in fact, if we were to go below the 10 mg dose, we would see an even more dramatic dropoff in efficacy, not just in the last hour, but also in earlier hours in the cycle.

The fact was that the program originally began with 10 mg as its suboptimal dose based upon the literature, there had been a lot of academic studies does which indicated that one needed to titrate upwards in order to see true efficacy.

That may have been a side effect of using initially immediate release formulations or intravenous use where maintaining plasma levels was a real problem. What we found in the course of our program was that 10 mg at the end of the day showed almost maximal efficacy and the best tolerability, an as we saw in 204, maintains that through the 12-hour dosing cycle although some of the patients with the lowest plasma concentrations appear already to be losing some benefit particularly in that last hour.

I think that relates also to some of the anecdotes

we hear from patients that they do feel that to be occurring.

DR. WOLFE: Just a follow-up question. Then, the answer is you have not done clinical trials using a dose less than 10 b.i.d., is that correct?

DR. BLIGHT: We have not used the lower doses in that role, no.

DR. WOLFE: Thank you.

DR. ANDERSON: Dr. Morrato.

DR. MORRATO: Thank you. My questions are with regard to Slide 118, which discusses the REMs. I guess, as an aside, I find it disappointing that we have over 120 pages in the briefing document and the information around the risk management plan takes less than 2 pages.

My questions, there seems to be some discrepancy between what is on this slide and what was presented to us in the briefing document, so I am seeking to clarify.

One is: Could you provide more information on who are these specialty pharmacies, how will they be selected and oversight?

In the briefing document, there was indication that there are going to be knowledge, attitude, and behavior

surveys among both physicians, as well as patients, and that is not referenced here on this slide. So what is the status of that?

I would like more clarity with regard to whether or not materials are going to be pre-tested, is that part of the development plan, as well as what is the plan frequency if you are doing these surveys during the launch period.

The briefing material also talked about a drug utilization study that is not mentioned on this slide either.

DR. COHEN: This has been an evolving process within the company so we are continuing to evolve. For example, it wasn't until relatively recently that we determined that we would be able to distribute the drug through specialty pharmacies, so that was one of the reasons for the change. And we are continuing to develop the plan and we are also hoping to discuss that in more detail with the Agency.

I would like to ask Dr. Stemhagen, who is our consultant and an authority on REMS plans to address some of the specific questions that you have asked.

DR. STEMHAGEN: Thank you. Annette Stemhagen.

Actually, the elaboration of the last point on this slide, if I could have Slide RV-14.

[Slide.]

This gets to the questions you were asking about the assessment of the program. For any REMS program, it is critical that it is not only put in place but that it is continuously evaluated to make sure that it is working. So, there are going to be several aspects to that.

As you mentioned, one is the knowledge, attitudes, and behavior surveys, and they will be administered both to prescribers and also to patients. They have not been developed yet.

They will be following standard psychometric properties. They will be evaluated with at least some qualitative testing with patients before they are actually administered, and they will look at the key risk messages of the REMS to be sure that patients understand all of those key risk messages, as well as prescribers understand them and are also following them.

The prescribed utilization survey, there are a couple different ways that that might be taken into account. We are not sure exactly yet because of the now use of

possibly specialty pharmacy, there may be ways to collect data that way, otherwise using some databases to actually look at who is getting prescribed, what doses they are getting prescribed, and a lot of information that is needed in terms of looking at the risk minimization.

The third is enhanced pharmacovigilance so, of course, that is important for keeping the label current. But it is also that any of the key events of interest, primarily seizures, there will be standardized data collection tools so that, whenever a report of seizure comes in, it is accurately described and the information is collected to actually be able to determine the circumstances and any patient risk factors.

DR. MORRATO: So, just as a follow-up, will that work be completed before the drug is approved in terms of the measurement of the risk management, is that the thinking, or is that going to be developed as the surveys roll out after approval?

DR. STEMHAGEN: I guess I am not totally sure of your question in terms of are you asking whether the survey instruments will be developed before the REMS?

DR. MORRATO: Right. It sounds like we have

conceptual ideas of the aims and goals of what is being collected but, in terms of the exact measurements, the instruments themselves, those have not been developed as I understand.

DR. STEMHAGEN: They are in the process of being developed.

DR. MORRATO: So, will they have been developed by the time the drug is approved, or is this going to be something that is an ongoing post-approval commitment?

DR. STEMHAGEN: The FDA requires that they review them at least 90 days before they are put in the field so they will be definitely available and tested before that time period, before they are actually used.

DR. ANDERSON: The nature of the pharmacy question?

DR. MORRATO: Yes, that's a good point, thank you.

So, who are the specialty pharmacies, and how are they being selected, and are they receiving any special training?

DR. COHEN: I don't have that information yet. As I mentioned, this has been evolving within the company and it was fairly recently, after we submitted the briefing

book, that we determined that we would, in fact, be distributing through specialty pharmacies. So we are committed to doing that. But I don't have specific information yet.

My understanding from our commercial group is that we will likely have something in the range of half a dozen pharmacies or so. The selection of the specific pharmacies is a process that is ongoing.

DR. ANDERSON: Dr. Katz.

DR. KATZ: I have two follow-up questions. I know we are going to have multiple discussions, I am sure, about REMS and the components, but the patients in your development program, for the most part were screened with EEGs. Would you anticipate requiring EEGs as part of a REMS prior to treatment?

DR. COHEN: We have spent a lot of time internally not only discussing this but researching it and reaching out to expert consultants in this area. Clearly, in our program, one of the criteria, as has been mentioned, as an exclusion criteria, was a reading of epileptiform activity on a screening EEG.

There is some historical background to this,

primarily, that at the time we first designed our Phase 2 programs and then carried that over into Phase 3, we really felt we didn't have a good handle on the safety profile particularly with respect to seizures and dose. Out of an abundance of caution we inserted that as one of the criteria.

Subsequently, having had the opportunity to review the data in depth, it has become apparent to us that there are serious questions that need to be resolved with respect to the risk/benefit, if you will, of requiring EEGs, and that being the potential to restrict access to the drug unnecessarily for people who have, for example, readings that do not, in fact, predict seizure, a risk for seizure, or who have erroneous readings.

I would like to ask Dr. Haut, who is an epileptologist, to speak to this in more detail.

DR. HAUT: Thank you. As Dr. Cohen mentioned, the decision to utilize screening EEGs and to exclude patients on the basis of epileptiform activity on those EEGs was apparently done in the spirit of a very conservative approach, interview of the seizure risk.

It has subsequently been suggested that this has

affected the homogeneity of the population and perhaps screened out patients who would have been at risk for seizures. Certainly, the exclusion of patients with seizures continues as the plan--so we really only have to consider the impact of screening out patients with epileptiform activity on this so-called screening EEG.

To address this, we have to take a step back and consider what is really the utility of a screening EEG, and those of us who spend a lot of time reading EEGs recognize that there is actually no data that validates EEG as a screening tool in a population without seizures in order to predict who is going to have a seizure.

If we look into the population of patients with actual epilepsy, the sensitivity of EEG to detect epileptiform activity probably ranges from 30 to 50 percent, maybe as low as 12 percent if you look at a group who have only had one seizure.

In this case, we are looking at a group who have not had any seizures. We can only conclude that the sensitivity is very low in this setting. Looking conversely, let's consider the impact of the epileptiform activity that was seen in those patients who were screened.

We do know that if there is true epileptiform activity on an EEG, then, the positive predictive value for recurrent seizures is high if you are looking at patients who have already had a seizure.

We also know--and I did review all of the EEG reports of these patients who were excluded on this basis--we recognized that there is an extreme amount of variability in the interpretation of EEG and that what is read at as epileptiform activity in one setting, often may be interpreted differently.

I can say, looking at those reports, the decision to exclude was very liberal and that certain patients who were excluded probably would not have been if the EEG was read elsewhere. So, what we conclude all together what is really the utility of one routine screening EEG to both detect epileptiform activity to confirm that this epileptiform activity is in some sense predictive.

We conclude that it is quite low and that the idea of doing screening EEGs on everybody, while, of course, at low risk, because the EEG is not a risky procedure, will add significantly to patient burden and expense, will delay the onset the treatment up until the EEG is performed and

interpreted, with really little yield in return.

DR. ANDERSON: There are a few people on the list. Is this a direct follow-up to that, Dr. Katz? I think Dr. Rudnicki has one sort of directly related to the EEG.

DR. RUDNICKI: I am just curious how many people were excluded because of that EEG.

DR. COHEN: Slide up.

[Slide.]

We have somewhat imperfect information because the way the data were collected. There was a check box on exclusion for either a history of seizure or EEG so we had a limited ability to parse that, but we were able to go back to the source data.

So, you see here that depending on the study, it was between 2.5 and 4 percent. Most of those were actually based on EEG as it turned out, but I can't give you a specific number. But I can assert with confidence that most of those were based on EEG rather than a history of seizure.

DR. ANDERSON: I am going to try to stick with the questions on EEG and seizure for a moment. Maybe we can run that thread. So, my panel with their hands up, are there others who want to pursue this issue further at this time?

Okay. I am going to get everybody, but I am going to now switch to my righthand side, which I have ignored so far. So I think the first on my righthand side is Dr. Twyman, you had a question.

DR. TWYMAN: I have a couple questions on Slide 62 and 63. On Slide 62, it's an interesting plot and a comparison to the stroke patients themselves. If one presumes that the disability is similar, I am just trying to understand the shift analysis on the following slide.

DR. COHEN: Slide up, please.

[Slide.]

DR. TWYMAN: What does the 21.7 percent shift actually mean? Is that from a group from a limited community household shifting to full community?

DR. COHEN: That's correct.

DR. TWYMAN: So, that's the subset of patients who are in that category were shifted to the full community category.

DR. COHEN: Correct. The way to read this is for each box horizontally, an up arrow goes from the category on the bottom in that box to the category above it, and then in the lower half, it is the opposite, so going from full

community to limited community--in other words, people who are getting worse.

Again, I think it is important to clarify that we provided this as one among many possible ways of providing a context for the numbers that we are talking about. It can be difficult. I think we all acknowledge it can be difficult to intuit the meaning, clinical meaning of numbers, of small numbers like 2.5 feet per second or a few feet here and there.

This is one way of contextualizing it based on data in the literature.

DR. ANDERSON: Dr. Green.

DR. GREEN: I have two questions for the clinicians. I really have had little understanding of the walking speed test before they explained it, so I appreciate that, but it seems to me it is still somewhat--calling up the right word--subjective.

In terms of the agent--this is an unscientific question but, in terms of the agent, if I took this agent, would I feel anything, would I sense anything? I am trying to understand, given the relatively small therapeutic gain, whether these people had those benefits accruing from some

other sensation of the drug.

DR. MILLER: In my experience as a clinical investigator, in all three of the trials that were cited, 202, 203, 204, which probably amounts to roughly 20 patients, most of those patients did not complain about any symptoms that I thought would tell them whether they were actually taking the drug.

I don't think it's that they are getting a subjective benefit that makes them walk faster. Also, in the performance of the 25-foot walk, it is fairly standardized. It's a simple instruction basically to walk 25 feet from the word go or whatever is your signal as fast as you feel safe.

On repeated testing, generally, people perform, we usually do it, I do this 50 times a week, every patient that we see, we do a timed 25-foot walk on and, on the two trials, they are generally within 10 percent of one another on the two trials. So, it is a pretty consistent response.

DR. GREEN: I am trying to address whether blind is truly blind, and you believe it is. It didn't look to me in the data that there was any learning that appeared with subsequent testing is that true? Is that task not typically

learned? Do people speed up over time with multiple testing? Okay. Thank you.

DR. ANDERSON: To follow up Dr. Green's question, you had a lot of CNS sort of nonspecific side effects that you have mentioned in that category, like dizziness and those sorts of things. Did you ever look at the subgroup analysis defined by those with CNS side effects to see if there was a disproportionate number of responders to sort of confirm this notion that there was some sort of placebo effect induced by detecting a drug in your system?

DR. BLIGHT: We looked at adverse events by responder status and did not see meaningful differences between the fampridine-treated responders and non-responders.

DR. ANDERSON: Turn it the other way around; you want to look, not at adverse events by responder status, but responder status by adverse event status?

DR. BLIGHT: One would think you would see it both ways, right? If we could have slide up.

DR. ANDERSON: If we are not clear, we will go on to the next question. I will muse about it and we can come back to it later.

My next person on the list was Dr. van Belle.

DR. VAN BELLE: I have two questions. One question is in Study F203, the placebo arm had one quarter the number of subjects as the other arm. What was the rationale for that, and why was that not applied to the subsequent study as well?

My second question deals with Slide CC-57. Maybe that could be put up while you answer the first question.

DR. COHEN: Slide up.

[Slide.]

The rationale for the 3:1 randomization ratio in the 203 study was that, in that study, part of the design of the study was not only to show the primary efficacy variable, which was the timed walk response in a direct group comparison between drug and placebo, but there was an additional requirement to demonstrate clinical meaningfulness of the response criterion itself, that being the timed walk response. Given that our prior data had indicated that about a third, 35 percent of the fampridine group were, in fact, going to be timed walk responders, for that next order analysis in which we were looking at responders versus non-responders, it was necessary to have

equal groups to maximize our power. So about a third of the 3:1 would then equate to placebo in that case.

DR. VAN BELLE: My next question deals with that slide. If you were to draw a vertical line at zero and the average change in walking speed, there are a large number of people whose walking speed in fact goes down during the active trial.

I wouldn't mind knowing the exact proportion of people whose walking speed actually decreases on the trial compared to the pre-trial data. Maybe you could get that in the next few minutes.

DR. COHEN: Dr. Blight.

DR. BLIGHT: We have a v-plot which will show that.

What you see when you look at the whole population is that patients, even untreated, show a great deal of variability.

Slide up, please.

[Slide.]

We show here, this is a plot which shows a lot of things because it shows all the data for all the patients in the two pivotal trials. So you can imagine here across the

horizontal axis, if you look just at the left side for the moment, which considers the population broken into the fampridine and the placebo treated groups, you see on the vertical axis the change in walking speed from baseline.

So, this is the average walking speed during double-blind treatment minus the walking speed at baseline, and you see that there is a subpopulation of patients even treated with placebo who show marked reduction in walking speed, so up to about 40 percent slower. And then there are others who show improvement in walking speed towards the right, up to as much as 50 percent faster simply based on the variation in their MS symptomatology.

You also see from this diagram that the fampridine-treated patients across the whole population are walking faster than the placebo-treated patients on a population basis. So, these are all organized by baseline to treatment walking change.

If you look on the right side, you see that with the fampridine broken out between the timed walk non-responders and the responders. It is a little difficult to see, to get your head into this, but it does show how many people get worse, how many people get better both in the

drug group and the placebo group.

So, you can see that more people get better, less people get worse in the fampridine group.

DR. VAN BELLE: So, roughly, I would say about 25 percent do worse, if I read those slides correctly.

DR. BLIGHT: If we could have the slide up again.

[Slide.]

For the fampridine-treated group, approximately 35 percent get worse--I am sorry--35 percent of placebo--and about 15 of the fampridine get worse during treatment. This is related we can see here to the underlying disease since the placebo patients are varying quite widely from their baseline speed based on disease processes.

DR. ANDERSON: Ms. Sitcov.

MS. SITCOV: Yes, I have two questions. What is the feeling for why more than 60 percent of fampridine-treated subjects were not responders, and is the increase in speed, the 25-foot increase in speed, is that something that is thought to be sustainable to 50 feet or 100 feet, or that was not tested?

DR. COHEN: If I may, I will try to answer the first question first and then I will do them sequentially.

We don't know why only about 35 to 40 percent qualify as consistent timed walk responders. One point to focus on is that we are measuring a particular type of response here, which is a consistent improvement in walking speed, and for that particular type of response, depending on the geography, if you will, of an individual MS patient's lesions in the central nervous system, the distribution of demyelinated plaques, they be more or less responsive.

We do know that in MS, while a hallmark of the pathology is demyelination, that axonal destruction also occurs and, in those tracks and patients who have tracks which are destroyed, we would not expect the drug to have an effect, because it relies on having demyelinated axons as a substrate.

So, there may be a variety of reasons having to do with the variation in the pathology of the disease itself, as well as quite a bit of variability among individual patients.

With respect to the timed 25-foot walk, that is perhaps the most widely used assessment in the MS field for walking, and it is used quite widely in other areas. As Dr. Blight's presentation showed, quite a number of publications

have correlated timed walk speed on the timed 25-foot walk test very strongly with longer walks, with measures of endurance, with long distances, and so forth.

So, yes, the timed 25-foot walk has been shown to be a good predictor of not just how fast you walk on 25 feet but how much you can sustain walking during the day, how far you can walk, how much endurance you have.

Maybe I can put this into another real world context to illustrate it. There is a bathroom that is specialized for the disabled in this facility. That bathroom is approximately 100 yards. It is actually about 102 yards from right over there in the room depending on where you measure from here.

An able-bodied person would walk on average about maybe 5 feet per second and, to get from here to there and back would constitute an annoyance, but only an annoyance. They could do it in about 2 minutes.

If you take the average walking speed on the timed walk test for our patient population, on average, they were walking at 2 feet per second. That would be a 5-minute walk. If you consider that MS patients in particular often have issues with bladder control, that in a daily experience

becomes a very significant amount of time.

A 25 percent increase, which was shown on average in this study that was sustained over the entire dosing period, 3 months or 8 weeks, would represent a full minute off that journey. If you now multiply that by the hundreds of little daily activities that people have to do, you begin to get a sense of how to translate what is in that test into the patient experience.

MS. SITCOV: I appreciate that, I understand that, but what was actually studied and measured was 25 feet. It wasn't 50 feet or 100 feet. So I guess what we can do is we can extrapolate that with an increase of 20 to 25 percent in the 25-yard walk, there is a good feeling that one can make it 100 yards to the bathroom more quickly, correct.

DR. COHEN: It's more than a feeling. Dr. Blight can talk to some of the data that actually has looked at the timed 25-foot walk and how that translates into longer walks.

DR. ANDERSON: But she was asking you didn't measure any distance greater than 25 feet.

DR. COHEN: Not in these studies.

DR. ANDERSON: Do you want Dr. Blight to go

through the related data or was that your question?

MS. SITCOV: He can respond. That would be helpful.

DR. BLIGHT: I understand that you may not accept that because everyone else sees a relationship between walking speed and distance, there is no reason to believe that we, in our special case, would see that if we looked.

We did not include longer distance walking measurements in the trial for a number of reasons. They increased the patient burden. They are difficult to do in a very well controlled way in a lot of institutional settings where you don't have places to walk people in a controlled fashion.

What data we do have relates to, for example, the MSWS-12 where one of the questions relates to how has your MS limited the distance you can walk, and we do show movement on that measurement, which is consistent with and at least at large as their response in terms of how much has your MS slowed down your walking.

So, we have that data within the dataset, saying that yes, we should see a typical relationship between walking speed and endurance. We also have a wealth

obviously of anecdotal data, and you have heard some of it today from individual patients who report, not that they are walking faster, generally speaking, but that they are able to walk further for longer periods of time.

So, there is internal data. It is not a hard measurement in terms of, for example, a maximum distance walked measure.

DR. COHEN: One last point just as a reminder. Even within our investigator group, some of our investigators had other measures because they were equipped to do them. For example, Dr. Short had noted that in their center, they use other measures as a rehabilitation center including long distance walking.

So, for example, there was a patient who was in the study showing increased speed on timed 25-foot walk but also showed that they could go on endurance from 90 meters before drug to 380 after.

MS. SITCOV: Let me just add from a personal perspective as someone who lives with MS, that yes, the days that I walk faster, I can also walk longer. I haven't been tested or held that up to a clinical test or examination, but I just believe that to be the case.

I guess my point was, was there any specific study of endurance that this has been helpful. Thank you.

DR. ANDERSON: I am going to give a chance to our distant member. Dr. Stuve, are you there?

DR. STUVE: Yes, I am here.

DR. ANDERSON: Could you first just introduce yourself, so everyone knows who you are and where you are, and then if you have any questions, please feel free to ask.

DR. STUVE: I am a neurologist at UT Southwestern. I am associate professor in the Department of Neurology and Immunology. I also Chief of the Neurology Section at the Dallas VA, a hospital that serves veterans, and Director of the MS Clinic at the Dallas VA.

Perhaps the one question I had concerns responders versus non-responders. I found it a little concerning that there is no prospective way of identifying responders versus non-responders specifically considering that it appears that as recently shown, 20 percent of patients actually appear to be getting worse clinically. I was wondering whether that could be addressed.

DR. ANDERSON: Thank you.

DR. COHEN: I am sorry, Dr. Stuve, I didn't quite

hear the last thing about getting worse. Could you kindly repeat that?

DR. STUVE: A few minutes ago, I think there was a brief discussion on one of the data slides, how many of the patients treated with fampridine actually showed a decline in their ability to ambulate. I think it was somewhere between 15 and 20 percent.

I guess I am just concerned with the fact that in clinical practice, one would not be able to distinguish responders from non-responders and was wondering whether there are any plans to address that in any future studies.

DR. COHEN: You raise a point that we have discussed at length, and it is something that requires discussion. 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 exactly as they were used in the clinical program.

With almost any drug that we use in the clinic, it is necessary to treat the patient, because we don't know in advance if they are going to respond. So an assessment has to be made after treating the patient to see if they are responding to the drug. This would go across any variety of

drug classes, antidepressants, antiepileptic, pain agents, and so forth.

In this case, experienced clinicians in MS should be able to verify through examination and history if their patients are doing better. One of the features that emerged from this program is that the results were seen relatively soon so that one does not appear to need to put a patient on drug for several months before ascertaining an effect.

We showed that the full effect on an average basis was seen as early as two weeks. So, within a few weeks certainly it should be possible for experienced clinicians to make that determination.

In MS, there is the added complication that patients vary, and some of them will get worse for a time, some of them will get better for a time, so that it is necessary for both the patient and the physician to collaborate with respect to whether they are experiencing a real improvement or not.

I would like to ask Dr. Miller to comment with respect to his own clinical practice.

DR. MILLER: Dr. Stuve, I am sure that you as an MS neurologist, just as the other MS neurologists in the

room, are fully aware of the variability from week to week, even day to day in the MS population.

These trials have gone on for two to three months. Most of these patients have fairly advanced disease obviously, many of them are progressing patients, and certainly during the course of time, a number of them are going to have disease progression.

In addition, they have a lot of other qualities, such as spasticity, which may be impacting on their gait, and spasticity can vary. As you know, if a patient is constipated, if a patient has a low grade infection, obviously, even without a fever, that may impact on their ability to walk.

It would be very surprising if, in the course of a study like this, one did not see some patients who worsen. But I think the important thing is that the percentage of patients worsening is substantially greater in the placebo group than in the fampridine-SR treated group.

DR. ANDERSON: I think next up on our roster is Dr. Goldman.

DR. GOLDMAN: Thank you. I have two questions.

One is I am looking for some additional

clarification on the relapse issue in reference to Slides 104 and 106 and, specifically, I want to know how was relapse defined and confirmed, or as was suggested in Slide 106, and by Dr. Miller, was this thought to be a worsening of MS symptoms or what we might call a pseudo-relapse. Could you clarify that, please?

[Slide.]

DR. COHEN: The patients who were coded based on the term that was used by the clinician to MS relapse, seven of them, the excess occurred entirely, excess over placebo occurred entirely in the post-drug period, as you have heard, between 3 and 6 days.

There was no specific methodology for determining a relapse. It was left up to the investigator, and the terminology that was coded to relapse included terms like, in addition to relapse, MS exacerbation, worsening of symptoms, and so forth. There was no MRI confirmation.

We did go back after a discussion with the Division and looked at the source documents and look in great detail at all of these cases to see what transpired to the degree that we could.

What we found was that all of those cases were, in

fact, worsening of existing symptoms, in particular, walking, leg strength, balance, and that they resolved within a few weeks and all those patients then went into the open-label studies. I think you heard 5 of the 7 are still in the open-label studies without further incident.

It does appear that these are a discontinuation response to drug or a response to withdrawal of the effects of drug.

DR. GOLDMAN: Thank you. I think I would just comment that as an MS neurologist, the term relapse has a specific meaning, and I think its use here might--it is potentially confusing based on your description there.

DR. COHEN: We agree. The coding in the safety database is structured according to a specific dictionary, the MedRA dictionary and using as conservative a coding as we could, all of those terms were coded to relapse, and some of them were, in fact, called relapse or exacerbation by the investigator. But when one looked at the specific descriptions, it was clear that we were talking about worsening of symptoms.

DR. GOLDMAN: My second brief question is with regard to increasing dosing. I appreciate that there is no

average change when you looked at the 15 mg and the 20 mg b.i.d. My question is whether the percent of responders changes as you increase the dose, meaning do you capture more people at higher doses who didn't get a benefit at the 10 mg.

DR. COHEN: We did not appear to. Slide up.

[Slide.]

In the 202 study, where we looked at a dose comparison of 10, 15, and 20 versus placebo, these were the changes we saw. As Dr. Blight mentioned earlier, these capture the overall area under the curve of treatment rather than what happens as patients get to the end of the dosing cycle. So that was left for the 204 study analysis.

DR. ANDERSON: Dr. Katz.

DR. KATZ: I had a question about what we think we know about the response at doses lower than 10 mg b.i.d., to pick up what Dr. Wolfe had asked about a while ago. If you could go to Slide 74, which was the slide we saw.

You conclude from this presumably that, at the low plasma level range, the effect seems to wear off. So you suspect that doses below 10 b.i.d. won't be effective. I wonder if you could talk a little bit more about this.

You could look at this and sort of convince yourself, I suppose, at a plasma concentration of 13, 14, it is hard to tell exactly, you get about as much of an effect as you do at the higher concentrations. I know it looks like it's on the downward part of the curve.

I wonder if you could talk about, and maybe you did already mention, whether these are AUCs--well, these are concentrations-- are they Cmax's, are they random in time from dose, specifically, how these levels correspond to the levels that you see, let's say, on average at 10 b.i.d.

In other words, the average, or if the analogous plasma level at 10 b.i.d. is 20 and, at 13 it, looks like you are just as good, maybe lower doses might do something.

I would also point out that the low end of the plasma concentrations that occur here has very few patients, so I don't know if people dropped out, if there is a relationship between how people did and what their plasma levels were, and that was a cause for--I mean if you included everybody in the study, maybe those plasma levels, maybe you would see a very different shape of the curve.

I wonder if you could just sort of expand on this a little bit more.

DR. COHEN: Dr. Blight.

DR. BLIGHT: There were, in fact, all patients in the 204 study at all visits, so these were plasma samples that were obtained when the patient came in for evaluation at all visits. By their nature, they are heavily weighted towards the plasma levels associated with the middle of the day when patients have higher plasma levels on drug.

The samples that come from the lower end, from values below about 15 nanograms per ml are coming from patients who, generally speaking, are towards the end of the dosing period or very rarely close to the beginning so there are limited samples from those periods.

That explains the distribution of the samples, that they mostly come from the efficacy visits. It is another way of looking at the data. We looked at with respect to the improvement in walking speed relative to time post-dose.

Both views of the data certainly give the impression that at about 15 nanograms per ml, you start heading down in terms of the percent improvement in walking speed. Although the data are limited in the number of samples that contribute, they do seem to be consistent with

a drop in efficacy as the plasma level drops.

With relation to doses, the 15 nanogram per ml level is about the Cmin average for the 20 mg dose, and it is close to what you would expect the Cmax, say, at 5 mg for the average with some variation around those values. That would inform the potential for a lower dose to contribute to efficacy, perhaps only for a short period during the day.

DR. ANDERSON: Dr. Temple.

DR. TEMPLE: There has been a question about how some of the people seem to actually get worse, and there was some concern about that. This goes to two things that have been on our minds. I just want to say a little something about them.

One is individualization of therapy. There is a widespread belief that if you could manage it, you could figure out who responds and who doesn't. That turns out to be harder than everybody hopes it is so far, at least once you leave oncology.

One of the things that we have been encouraging people to do, and it is a particular interest of mine, is showing the cumulative distribution of responses, which you sort of do on your CC-80 and on page 63 of your book.

We have put things like that in labeling for Alzheimer's drugs and for the effect on choreiform movements of tetrabenazine. What you invariably see in these, because as somebody said, people vary for various reasons, their disease gets worse or whatever.

You always see some people who worsen. What you see for an effective drug in general is that there is always a shift. So, there are fewer worsenings in the people on the drug and more people have a big effect, more people have little effect, and that is what you see on that thing you showed there.

But this has been true for Alzheimer's, for depression. Personally, I love these displays, because they give you a better idea of how people are actually doing than a mean effect of whatever it is. Of course, their whole approach was to pick a definition of responder.

What is nice about these is it gives you not only one definition of a responder but it says, okay, I think a responder is someone with a 30 percent improvement; let's see how they did; oh, 15.5 versus 3.8; or I think 20 percent is good; oh, I can look at that.

So, we like these displays and have been putting

them in but they invariably show that some people worsen, whether it's a blood pressure trial or a depression trial or a schizophrenia trial. There are always some people who, in the course of things, are on the down side.

We would love to have an explanation for what those are but so far nobody has been able to figure out how to do that in most cases.

[Slide.]

DR. COHEN: If I may, just by way of clarification, it has come up a couple of times, so I just want to make sure that there is a general understanding that in our data, fewer patients got worse on fampridine than on placebo, so that we always saw distributions, as Dr. Temple said, where some patients got worse during the study.

In MS, as you have heard from Dr. Miller, that is completely expected based on the disease itself. But, throughout the studies, the number of patients who got worse or the percentage who got worse on fampridine was less than those who got worse on placebo. We have other distributions that show that, as well.

DR. ANDERSON: I have three more on my right to get to, and I will try to get to them in the order I have

noted here. Dr. Yeh.

DR. YEH: I have two very simple questions. One has to do with relapse and efficacy information in relation to relapse. Did you analyze any of your data in relation to the relapses that either patients on placebo or drug experienced?

DR. COHEN: If I could clarify, Dr. Yeh, with respect to specifically--

DR. YEH: I guess the question is, you know, there is going to be worsening and improvement whenever a person with MS has a relapse. My question is did you actually do any subgroup analysis of the people who had relapses or try to take them out of your data to see if it made any difference. It is a very small improvement that you are seeing in walking speed.

DR. COHEN: It sounds like a couple of observations there. With respect to relapse we looked at--if this is what you are asking--the percent of relapses in responders versus non-responders, is that--

DR. YEH: No, actually, I am asking did you analyze, if a person had a relapse, they are presumably going to be doing worse, and there were equal numbers in

each of the groups that had relapses, did you take those people out, and then they will improve? The natural history of the disease, and I just wondered did you take those people out and see if the drug still had an effect?

DR. COHEN: Let me ask Dr. Blight to respond.

DR. BLIGHT: We did not do a separate analysis with taking people out who did not respond. As you saw, we did not see a difference in response rate, for example, between the relapsing, remitting, and the secondary primary progressive populations.

So, our ability to investigate the interactions with relapse is very limited, because we had regular visits in that one trial at four-week intervals and the other at two-week intervals, but they would obviously not be available for a particular examination around relapses.

We don't have any special analyses that would address I think the question you have, which is, is there an effect of the drug perhaps on recovery from relapse. There could be a potential interaction there in terms of the improvement you see with fampridine, that might change the envelope of recovery, if you like.

We certainly don't have any of that information,

and we did not do a separate analysis just taking out all the people that had relapses.

DR. YEH: My second question is a very simple question that has to do with issues that have been raised by many of the clinicians. As a clinician, if I am faced with using this medication, I want to know, if I am going to be provided guidelines as to what constitutes response and what doesn't constitute response, because of the I guess less than clinically exciting effects that is reported.

How am I going to tell, are you going to give guidelines to clinicians I guess is the question.

DR. COHEN: The guidelines that we will emphasize are primarily on safety. But as efficacy relates to the equation, we would certainly guide toward looking for clinical evidence of meaningful walking improvement in patients. How that is assessed in the clinic is very much an individual issue for a given clinician.

Some clinicians, as you have heard, in the field, routinely use timed 25 for walks. But others use other instruments. Many use clinical observation--watching the gait of the patient from the waiting room walking into the examination room, for example. So the determination, as

with any medication, would be to evaluate clinically through history and exam and, possibly, where appropriate, actual objective testing, such as the timed 25 for walk, whether or not the patient is experiencing a benefit on their walking that is clinically meaningful to that patient.

DR. ANDERSON: We have got two more and then I will give us our break here. I am going to get the two who haven't had a chance to ask a question, and then we will take a break, and we can always come back if we need to after the break, but we will have Dr. Fountain first.

DR. FOUNTAIN: My question is in reference to Slide CC-73 and the plasma concentration time curves. In Slide 73, if I understand it correctly, this was obtained at steady state, and so this would represent a population pharmacokinetics from one dose to the next dose.

If that is the case, I am wondering why, at the end of the dose, at 12 hours, is so different from time zero, or maybe there is no time zero, because if this sustained a steady state, I imagine we would expect it to be about the same?

[Slide.]

DR. BLIGHT: These were sparse samples from the

clinical trial itself. So every time the patient came in for evaluation, the sample was obtained, plasma concentrations were measured, so the time from the previous dose was put into bins here. So, the first bin is from zero to one hour post-dose. In most cases, that would be more one hour than fewer by the nature of things.

So, there is no zero time point here in that sense, and I think we see that reflected. This is not a pharmacokinetic study, so the times that we have post-dose are not stopwatch times so there will be some error horizontally, as well as vertically.

DR. FOUNTAIN: I understand that. In reference to Slide 71, those do look like time concentration profiles for individual patients. Is that the same study, or is that a different study?

DR. BLIGHT: This is different. This is a pharmacokinetic study, steady state pharmacokinetics in MS patients.

DR. FOUNTAIN: That is not part of 204?

DR. BLIGHT: No, this is a separate study. It is call AN-751.

DR. ANDERSON: Dr. Brass, you have the last one.

DR. BRASS: I have a question for Dr. Miller. Dr. Miller, you noted that an MS clinician would be able to quickly realize that there is a response to this medication in several weeks and, as an MS physician myself, we often use a 25-foot walk but we don't use the velocity. We actually record the time.

I wondered if you could comment, what do you think is a significant change in the time for a patient from beginning to end on this medication that would be significant in the change in time, because that is actually what we use, and the velocity measurement is more abstract actually.

DR. MILLER: Right. I also am more familiar with using the time. I think that is the way most MS clinicians actually use the test. I want to actually get away from the timed 25-foot walk, because I think actually, in the clinic, in the clinical setting, what I as a clinician would depend on much more than the timed 25-foot walk is my conversation with the patient.

That is why I think I can't really give you an arbitrary time that is going to determine whether a patient is to be a responder. I also really as a clinician don't

care in the final analysis about the time.

What I care about as a clinician is my patient experiencing some improvement in his or her life after taking this drug, and I don't think the company is going to be able to set up sort of arbitrary parameters, because it depends on what an individual's lifestyle is. It depends on how badly their gait is impaired.

It depends on what difference it makes. If a patient is staying at home all the time, it probably doesn't make that much of a difference to cut a few seconds off if they are, let's say, at 20, 25 seconds. But if it's somebody who is walking in the community and they see one of those flashing lights up at the intersection that says you have got 17 seconds to get across the street, then, cutting a few seconds off of that person may make a difference.

I think when I said that I think you can decide early on, I think that is going to be an interaction of your asking functional questions to a particular patient, as well as probably trying to objectify it.

But I would be more inclined to make my treatment decision based on that conversation with the patient than the actual objective measurement on the time, because even

if they speed up, if it doesn't make any difference to them, why would I continue to prescribe the medicine.

DR. ANDERSON: We are about a half an hour behind, so when the FDA does their part, they need to be so clear, there is no need for clarifying questions.

Anyway, we will take out 15-minute break now and reconvene at 11:00.

[Break.]

We are going to reconvene the meeting, which is going to involve the presentation from the FDA. I believe our first presenter is going to be Dr. Illoh.

FDA PRESENTATION

Fampridine Efficacy Issues

[Slide.]

DR. ILLOH: I am Kachi Illoh. I am the medical officer, the Food and Drug Administration, Division of Neurology Products.

I am going to be talking about the efficacy issues as related to fampridine-SR.

[Slide.]

I will just mention briefly the primary response variable that was evaluated for this product and then dwell

more on the additional efficacy considerations that we have considered. These are important questions that physicians are faced with if they are going to be prescribing fampridine, or the important questions that the MS patient will want to know or what to have answers to in terms of getting that treatment.

[Slide.]

We have heard earlier that the fampridine indication or the proposed indication for fampridine is improvement in walking ability in patients with multiple sclerosis.

We have also heard that the primary response variable indicated there was benefit with fampridine treatment in terms of the proportion of people who responded in terms of consistent walking ability.

However, we also noted that the magnitude of improvement in walking speed was indeed small.

In an attempt to examine the clinical significance of the improvement that we have seen, we decided to run additional efficacy analysis.

[Slide.]

There were two pivotal trials that were conducted

as you have heard earlier on the first people to try out MS-F203. Randomized 301 subjects with all the four subtypes of multiple sclerosis in a 3:1 fashion to fampridine 10 mg twice daily or placebo.

I want you to bear in mind for a patient to get into the trial, you had to be able make the 25-foot walk in the time between 8 seconds and 45 seconds.

This first trial was conducted over 21 weeks. They had a two-week placebo run-in period and 14 weeks of double-blind treatment.

[Slide.]

The second people to try out was similarly designed. They had a few differences, though. It randomized 239 subjects in a 1:1 fashion to fampridine or placebo and it was conducted over 14 weeks.

Nine of those 14 weeks was double-blind treatment period, and this is in comparison to 14 weeks in the previous trial.

[Slide.]

The primary analysis was similar for both trials, with interest in efficacy variable of the responder status that was based on consistency of response to making the 25-

foot walk.

The responder was regarded as somebody who was able to walk at least three of the four on-treatment visits faster than the fastest time of any of the off-treatment visits, five of them in number.

[Slide.]

We have also seen this illustrated graphically by earlier presenters, but the proportion of timed walk responders was higher with fampridine treatment. In the first trial, it was 35 percent in the fampridine group compared to 8 percent in the placebo group.

In the second trial, the fampridine group was 43 percent compared to 9 percent in the placebo group.

[Slide.]

So, we conducted additional analyses to examine the clinical significance of the primary results. To maintain the benefits of randomization, we compared whole groups, the whole fampridine group compared to the whole placebo group independent of the responder status and we looked at the various multiple endpoints that were evaluated in the trials.

[Slide.]

The first variable that we looked at, walking speed, in the first trial. Now, walking speed is based on the distance walked in feet per second, and it is based on the time required to complete the 25-foot walk.

In the first trial at baseline, on the table, there are similarities, 2.12 in placebo group and 2.14 for the second in the fampridine group. At the end of double-blind treatment, it was 2.16 feet per second for the placebo group and 2.35 feet per second for the fampridine group with a p value of 0.19. The change from baseline to double-blind in walking speed for the placebo group was 0.05 and, for the fampridine group, it was 0.21 with a nominal p value of 0.03.

[Slide.]

Now, one important question that was raised earlier was in terms of time, how would you put this in perspective in terms of time that was required to complete 25-foot walk. On the graph, the y axis would represent the time needed to complete the 25-foot walk, and on the x axis, the treatment groups.

Three pairs of bars. The pair on the left would represent what they did at baseline, the time that was

required to complete 25-foot walk at baseline; 11.8 for placebo in blue, and 11.7 for the red representing the fampridine group.

The average walking speed during the double-blind treatment, it was similar between both groups. At the end of double-blind treatment, shown in the set of bars to the right, the placebo group, the average was 11.6 second and 10.6 for the fampridine group. The p value between the two groups was 0.17.

If you took into consideration how much time they improved from baseline to the end of double-blind treatment, the fampridine group seemed to have walked faster at the end of treatment by less than the second compared to placebo.

[Slide.]

If you look at the same parameters in the second trial, walking speed similar 2.28 for placebo and 2.21 for fampridine. At the end of double-blind treatment, the numbers were again similar, 2.39 for the placebo group and 2.42. The change in walking speed from baseline to the end of double-blind was 0.1 for placebo, 0.2 for fampridine.

[Slide.]

Again, putting this into perspective in terms of

the time it took to complete the 25-foot walk, similar numbers at baseline, average on treatment, and at the end of double-blind treatment. Baseline to the end of double-blind treatment, the improvement for the fampridine group compared to placebo in walking speed, suggested that the fampridine group walked faster by half a second.

[Slide.]

Then, we looked at the second set of variables, the Multiple Sclerosis Walking Scale in the first trial. Now, MSWS-12, as we heard earlier, is an assessment of how the subjects felt of their walking limitations over the preceding 2 weeks, and there were different domains of walking. It was used as a validation tool in the trials for meaningfulness of responder status, or in this situation, we looked at it and we compared the different treatment groups using the variable.

At baseline for the first trial, it was 67 for placebo, 69 for the fampridine group. At the end of double-blind treatment it was 72, and it was 69 for the fampridine group. Now, realize the smaller numbers here represent an improvement and any negative score on the change would suggest an improvement.

So, the change in MSWS-12 from baseline to the end of double-blind treatment was 5 for placebo group and negative 0.04 for the fampridine group with a nominal p value of 0.06.

[Slide.]

In the second trial, baseline, there seemed to be a difference between the placebo and the fampridine group. In the placebo group it was 67.6 and for the fampridine group it was 73 with a nominal p value of 0.015.

At the end of double-blind treatment, the MSWS-12, it was similar between two groups. It was 68.4 and the placebo group and 70.7 for the fampridine group. The change in the MSWS-12 from baseline to end of double-blind was 0.83 for the placebo group and negative 2.59 for the fampridine group with a nominal p value of 0.04.

So, it would seem that the fampridine group had improved MSWS-12 scores compared to the placebo. But remember that these scores are based on numbers that had been obtained on a scale going from 12 to 48 and subsequently transformed onto the scale of zero to 100.

So, we yet do not know the clinical significance of such an improvement on this transformed scale.

[Slide.]

And then we looked at the third set of variables. The LEMMT, the manual muscle testing is an estimate of the muscle strength, in this situation testing the lower extremities.

In the first trial, F203, baseline, the numbers were similar, 4 for the placebo group and 4 for the fampridine group. At the end of double-blind, again similar, 4 for the placebo group and 4 for the fampridine group, nominal p value of 0.059.

If you look at the change in LEMMT scores from baseline to double-blind treatment, it was 0.04 for the placebo group, 0.13 for the fampridine group, with a p value of 0.003. However, realizing that the scale runs from zero to 5.0, again, we do not know the clinical significance of this small change in leg strength between the two groups.

[Slide.]

If you look at the second trial, F204, baseline, similar strength, 4 for placebo and 4 for fampridine. At end of double-blind, little change, 4 for placebo, 4 for fampridine, and a change from baseline to end of double-blind, 0.07 for the placebo group, 0.1 for the fampridine

group, p value 0.406.

It is giving us an indication that there was no difference in the leg strength between the treatment groups. Baseline to the end of treatment, the trends remain the same, voluntary movement against moderate resistance as applied by the examiner.

[Slide.]

Another variable that we looked at was the Ashworth score. This would be an evaluation of the lower extremities for the degree of spasticity or stiffness.

In both trials, they demonstrated changes or differences between the treatment groups and the change in the Ashworth score.

For the first trial, the change was -0.07 compared to -0.16 for fampridine group. In the second trial, again similar changes.

What is important to remember about this is that on this scale, both the baseline and double-blind end values of both treatments correspond to 1 or slight increase in tone, so we do not know what the significance of the changes that were seen, what they really mean.

[Slide.]

More importantly for the patients, how they felt about their treatment, the subject global impression of change was a record of how the subjects felt on a 7-point scale about the effects of the trial medications, and that is on their well-being over the preceding 7 days.

It will go from feeling terrible about the medication on their well-being to feeling delighted. In the first trial, at baseline, it was 4.7 for the placebo group and 4.6 in the fampridine group.

The average of the SGI scores over the treatment period for the placebo group was 4.5 for the placebo group and for fampridine it was 4.6, p value 0.45. The change in SGI scores from baseline to double-blind period average was -0.2 for the placebo group, -0.01 for the fampridine group with a p value of 0.13.

[Slide.]

The second trial, similar trend in SGI scores. At baseline, similar numbers, and average during double-blind period 4.3 for placebo, 4.4 for fampridine group. The baseline to the average double blind SGI scores, -0.04 for placebo, -0.09 for fampridine, with a p value of 2.48.

So, there was no difference between the treatment

groups in how the subjects perceived the treatment effects on their physical well-being.

On the average, the response of the subjects presented by these averages would represent neutral of mixed feelings about the drug's effect on their physical well-being.

[Slide.]

So, I presented that overall, there is a small improvement in the clinical variables with fampridine given at a dose of 10 mg twice daily.

We do not know the clinical significance of these effects at the given fampridine dose that was tested.

Talking about those, we do know from the earlier presentations here that there does not appear to be any increased efficacy with higher fampridine doses. In addition to that, there is a potential risk of increasing incidence of seizures. I have also heard that there was limited evaluation of doses less than 10 mg twice daily.

[Slide.]

Our Clinical Pharmacology group had conducted some evaluation of the dose-response and they examined the relationship between drug exposure and the percent change

from baseline in walking speed.

They performed a linear regression analysis for the pooled data of three trials: F202, F203, and F204, and this is pooling dose who were on fampridine treatment. These subjects had received 10 mg, 15 mg, or 20 mg twice daily.

The graph that you see is a dose-response analysis for exposure. On the y axis is the percent change in the baseline walking speed, feet per second, and on the x axis, the exposure presented in the AUC or the area under the curve.

Essentially, what we see is a flat line relationship, no relationship between exposure and the change in walking speed, suggesting that we had reached a plateau of effect at 10 mg and that there is a need to determine where doses lower than 10 mg stand.

[Slide.]

So, in conclusion, we have seen that fampridine is associated with a higher proportion of walking speed responders, but improvement in walking speed, even though the clinical variables is of small magnitude, and we do not know the clinical significance of the changes that we have

heard.

Dose-response evaluation suggests that there is a need to look at doses less than 10 mg.

[Slide.]

I will stop at this time.

Fampridine Seizure Risk

[Slide.]

DR. BOEHM: Members of the Committee, during this last scheduled presentation, I will be speaking about the seizure risk of fampridine.

[Slide.]

As we heard this morning, fampridine or 4-aminopyridine causes seizure, and supported by experimental data from animals and reports in humans of seizures from various different exposures including accidental ingestions, overdoses from compounding errors, and use in other experimental settings.

There have been seizures in patients treated with fampridine in clinical trials that used other formulations.

[Slide.]

The SR formulation was developed in part because of seizure risk, and so the information that we have about

MS patients that were exposed to the SR formulation comes from randomized controlled trials, as well as uncontrolled, open-label extension trials.

[Slide.]

This first table summarizes seizures that occurred in three fampridine randomized controlled trials using the SR formulation in MS patients.

If we look at the second column, we see there was 1 seizure in 238 placebo patients or 0.4 percent. The next column includes the pooled data across all dose group in these three randomized controlled trials. Three patients out of 507, or 0.6 percent, experienced a seizure.

For the 10 mg b.i.d. dose group, 1 of the 400 patients, or 0.3 percent, experienced a seizure. None of the 50 patients randomized to 15 mg b.i.d. experienced a seizure. In the last column, 2 patients out of the 57 randomized to the 20 mg b.i.d. dose experienced a seizure.

As was noted earlier this morning, one of those patients had taken a double dose to compensate for a missed dose the night before.

[Slide.]

As I mentioned earlier, we also have open-label

extension data. By the time patients got to the open-label extension, they are a selected population. they had participated in the preceding randomized controlled trials. Any patient with a history of seizure was excluded, and these patients underwent EEG screening.

Then, went through the controlled trial without developing a seizure and then were screened again prior to entering the open-label extension trial.

[Slide.]

This table summarizes the seizures that occurred in open-label extension trials. The last column includes the experience at 10 mg b.i.d. There were 5 patients that experienced seizures and the seizure incidence was 0.41 per 100 person years.

If we look at the second column, it summarizes experience at 15 mg b.i.d. There were 2 patients in this group that experienced seizures and the incidence was 1.7 per 100 person years. I do want to mention that 10 of these patients also had experience at 20 mg b.i.d., but that contributed really less than 2 person years to that total.

[Slide.]

We heard earlier where the company had compared

the seizure incidence in the open-label trials to other sources of data, specifically, to a population-based cohort of MS patients.

[Slide.]

There could be some difficulties when making such comparisons. There were potentially important differences between a population-based cohort and a screened clinical trial population and there may be some uncertainty about which population-based cohort incidence to use.

[Slide.]

The first row summarizes data from the Eriksson study that we heard about earlier, that included 255 MS patients, 20 of those patients experienced seizures, and the reported incidence was 0.35 per 100 person years.

If we look at the second row, that was a cohort of 208 MS patients, 5 of those patients experienced seizure after the diagnosis of MS, and the incidence there was 0.06 per 100 person years.

The authors identified 3 additional patients who experienced seizures after symptoms of MS. But prior to diagnosis, and if you include those 3 patients, the age-adjusted incidence of seizure was 0.08 per 100 person years.

The last two studies looked at a slightly different outcome. They looked at diagnosis of epilepsy. So it was recurring, unprovoked seizures, and a cohort of 188 MS patients, 4 experienced seizure, and the incidence of 0.14 per 100 person years.

The last cohort of 170 MS patients, 4 were diagnosed with epilepsy, the incidence was 0.29, and the age adjusted incidence was 0.15 per 100 person years.

[Slide.]

I am going to skip this since we didn't really talk about other MS drug development programs.

[Slide.]

As we saw earlier, the clinical trial data were limited at higher doses. But we did see some suggestion of an increase in seizure risk in MS patients particularly at the 20 mg b.i.d. dose in the randomized controlled trials. Admittedly one patient had a seizure at that dose and the other patient had taken a double dose.

But one question might come up is whether there is evidence of separation of the Cmax values across the different doses in the randomized controlled trials.

[Slide.]

Plasma levels were collected in randomized controlled trials and our pharmacokineticists identified those plasma levels that were collected between 3 and 5 hours after dosing, which should correspond to the Cmax.

Then, they created a plot of Cmax's across the different doses. What we see in this graph is that there appears to be considerable overlap in terms of Cmax for the different dose groups.

[Slide.]

In summary, we have seen that fampridine can cause seizures. The data from randomized controlled trials, using the SR formulation in MS patients, did not show an increased seizure risk at 10 mg b.i.d.

There is a possible increased seizure risk at higher doses, but we have very limited data and there are difficulties in trying to compare the seizure incidence from the open-label extension trials to other sources of data particularly MS population-based cohorts.

Thank you.

Clarifying Questions

DR. ANDERSON: We now have the opportunity for some clarifying questions for the FDA and their

presentations. I will start with one that I have as sort of my executive privilege.

The demonstration that in the heterogeneous group of treated and untreated patients, the designation as a walking time or walking speed responder predicted an improvement on a subjective rating of sort of wellness or health, or I forget exactly the subjective nature, the patient's own rating suggested that if they were in this category of responder they rated higher statistically significantly than the non-responders.

So, why isn't that sufficient to justify the use of the walking time responder designation as being a surrogate for a clinically meaningful endpoint?

DR. BASTINGS: Well, I think in evaluating the study results, it was important, since this is another endpoint, to look at a good range of endpoint analyzed in the study, to try to gain perspective on what was the meaning and whether it was appropriate in this case to use the MSW-12 to validate the effect on walking speed.

So, that is why in our analyses, we also looked at the direct comparison across these various endpoints. It is really to gain a good understanding of what the drug effect

really was and what it meant to patients.

DR. ANDERSON: I really wasn't asking about the MSW-12. There was this designation of a responder as sort of having 3 out of 4 walking times better than any of the non-treatment walking times and, if you simply categorized the subjects regardless of treatment status based on that designation, and then you looked at their subjective impressions of change, they were significantly better in the group that had been designated as a responder status irrespective of treatment.

So, given that, why isn't that demonstration sufficient to then utilize walking time improvement as an endpoint that has a clinically meaningful impact?

DR. TEMPLE: Rusty can tell this more because he was at more of the meetings--I have only read about them--but we had the same question. Okay, there is a small improvement in walking time, what does that mean?

Therefore, we asked a lot of questions that are not typically asked in a randomized trial. Dr. Illoh showed you the results on some of those numbers, and they are not that impressive. But this is different. This is how do people who are nominally responders by the endpoint in the

study do when you measure them on one of these other scales.

As they showed you, and I don't think we disagree, if you are a responder by walking time, you seem to do well, reasonably well on some of those other scales. So, that was intended to suggest that the walking time might be a reasonable measure, just as you are asking.

I am not sure anybody actively disputes that. But it was important to show that on the 12-point scale, you didn't really see that impressive a thing for the overall population. But, of course, that is everybody in the trial, not just the responders.

We already know that if you look at everybody in the trial, the effect on walking time was modest.

DR. ANDERSON: Dr. Katz.

DR. KATZ: A couple other things. Maybe I missed it, but I don't think we were presented, for example, the subjective global, the patient's global for the responders versus non-responders.

We did see it for the overall and it was not statistically significant. It trended. I actually wanted the sponsor to talk about that. Maybe they did present that and I missed it.

The other thing is this--

DR. ANDERSON: That analysis came in the briefing materials.

DR. KATZ: In the briefing materials, right, but it might be worth just discussing.

The other point that Dr. Illoh made at the beginning of his presentation was one of the reasons we looked at all treatment versus all placebo was because it does preserve randomization. There are questions about what do statistical tests mean when you are comparing responders to non-responders. This is what we asked the company to do. There is no disagreement about that for the reasons you have heard, but those aren't randomized groups really.

So, the question about what do the statistics mean in that case, I think those questions could be asked. So, one of the reasons we did it was purely to look at randomized groups.

But yes, I think that that is what we asked the sponsor to do. We asked the sponsor to look at within responders versus non-responders for these various secondary outcomes. You, of course, could argue that the patient globals and the other measures do validate the responder

definition as being clinically meaningful. That is one of the questions we are asking the Committee to talk about.

DR. ANDERSON: I was asking for clarification of why wouldn't you think that that was a definition of a--that that established clinical meaningfulness, so that I would be able to better evaluate sort of the pro and con arguments.

DR. KATZ: I think we just wanted to look at a whole range of things and see whether or not it all hangs together. You might consider it.

One question perhaps that we can ask the sponsor to talk about at some point is the magnitude of the change, for example. I mean the claim has been made, and we sort of agreed, that the MSWS would be the scale or at least one scale that would measure clinical meaningfulness.

We haven't talked too much about the actual amount of change that was seen on that scale compared to what the baseline values were so, depending upon which analysis you do, it's a few points change between responders and non-responders or drug and placebo against the baseline of somewhere about 65 to 70 as a baseline score.

One thing I would like to hear, at least at some point in the discussion, is yes, the MSWS might be a scale

that looks at clinical utility, but what do changes of that degree mean, drug-induced changes of that degree.

DR. TEMPLE: Can I just comment? There is a reason you worry about these within group comparisons that are not randomized. Imagine, for example, that there is something mysterious going on that is making some people sort of feel better.

Well, it wouldn't surprise you if they felt better on almost everything you could measure. So, the fact that you see a correlation between walking a little better as the study endpoint showed, and feeling better on the MS walking scale, those might be too true and unrelated. You might just be identifying something about the patients that is making them feel better.

I am not saying that is especially likely, but that is why you worry about a comparison that doesn't involve the randomized groups. That said, it certainly is compatible with the idea that one is sort of a clinical measurement that corresponds closely to the thing you are hoping to do with the walking. So, I wouldn't dismiss it, but that is what you worry about when you do that kind of non-randomized comparison. So, you need to worry about it a

little probably.

DR. ANDERSON: Dr. Fountain.

DR. FOUNTAIN: I guess to follow up on that a little bit, there were no differences in the SGI--Dr. Illoh did--but SGI, if I understand it right, asks about well-being. It is not about specific walking. So, I think that it goes back a little bit to does it make you feel better. Apparently not, it doesn't make your well-being better, whereas, the MSW asks do you have some detectable in every-day life difference in walking.

If I understand the analysis right, the whole group analysis, not the responder/non-responder but overall, the placebo compared to treated, there is about a 2-point difference. So, based on those 12 questions, a 2-point difference would seem like it might be clinically meaningful.

I guess the other way to look at that is that for people with chronic diseases that affect their life pervasively a little bit all the time, that a small measurable difference in quality of life often translates to a huge difference over their life.

So, for instance, this is just measuring a 25-foot

walk. But you could extrapolate it to 100 feet or something. So, in reference to the question about quality of life, it seems to me that any improvement that is statistically significant in quality of life is overall probably meaningful, which is, of course, just one-half of the equation about risk/benefit. But. in terms of benefit, that would seem to be true.

So, that analysis that Dr. Illoh did, separating out the responder/non-responder, which has all those inherent problems, is either statistically significant or trends towards statistically significant even though it wasn't powered for that way.

So, in defense of some of the things that aren't significant, you know, the study clearly wasn't powered for that, it was powered for this responder/non-responder difference. That would be my first comment in regard to the SGI.

Just as a point of clarification, then, that is about well-being and not walking really, well-being, or something like that, is that right, Dr. Illoh?

DR. BASTINGS: The SGI, you ask patient how they felt about the effect of the study medication over the past

7 days.

DR. FOUNTAIN: I am sorry?

DR. BASTINGS: The question was how patients felt about the effects of the study medication over the past 7 days.

DR. FOUNTAIN: The SGI?

DR. BASTINGS: That was the SGI. I want to emphasize what you said, that we did not ask that the sponsor show statistically significant differences on any of these endpoints. They were just used to get at both respective on the drug effect, but there was no requirement from us that they met statistical significance for these various end points.

DR. FOUNTAIN: Could I ask a second question? Sort of related to the magnitude of effect, which is another important point, on Slide 12, if we could look at Slide 12, about the overall magnitude of effect, looking at the bar graphs comparing time in the 25-foot walking test, the differences are small or microscopic and not statistically significant.

But I think the assessments we are doing are not really compared to the dotted line of normal, because

people, if I understand it right, had to be performing at a level between 8 and 45 seconds. So the baseline is actually 8 seconds, not at zero or 6 or something else.

So that is a difference starting out, meaning you had to start between 8 and 45. It's the change between 8 and 45 that is most important rather than absolute change over the whole time.

DR. BASTINGS: If you look at the graph, the first two columns show you the baseline. The dotted line is just to give you as a reference what would be the normal time, but the baseline is shown in the first two columns on the left.

DR. FOUNTAIN: Right. So, it shows compared to the whole range of possibilities of how long it takes you to walk 25 feet. There is a microscopic difference for the others, but the possibilities don't go down to zero or up to infinity. They only go between 8 and 45, because that was a requirement of the study, wasn't it?

DR. BASTINGS: Yes, that was an entry criteria.

DR. FOUNTAIN: So, then, you could only vary between that amount. So, contrary to what I said before, I guess looking at the responder/non-responder--I am sorry--

looking at the percent change, it would seem to me a valid way to assess that, since the absolute differences, there is only a tiny range of possibilities that you could have.

So, I think in terms of defending the percent change as opposed to the absolute difference, I think it seems reasonable.

DR. KATZ: Again, that is a question. These were all secondary analyses. They weren't the primary analyses so you could choose to look at percent change from baseline, you could just look at absolute change from baseline, you could look at just the absolute value at the end.

We just wanted to present sort of a range of different ways of looking at the data. The company chose to present percent change from baseline. That is not unreasonable, but they are all after-the-fact analyses, I believe. So, we just wanted to get sort of a different way to look at it. We understand what the company did and why they did it.

DR. TEMPLE: It is also a good idea to remember that for reasons they explained, the company thought that there was a responder/non-responder population and set up their endpoint to reflect that.

This doesn't do that, and that's fine. You need to understand these data, too, but it is a different approach, something like 70 percent or so of the population is not benefitting very much, and everybody agrees on that.

The question is whether the 30 percent benefit enough to make some sort of impression. You have to look at the means also. I mean we would certainly always insist on that. But it is not the only measure, and their primary measure was a very different one, looking at a definition of a responder subset, always a very interesting thing to do.

DR. FOUNTAIN: Just to follow up, I didn't mean to say that there were some problem with it, just in terms of looking at this data for its clinical utility, like the manual muscle testing, again, would only go through 1 point range of possible differences. So a 0.19 change is actually 19 percent change in the possible change because, in order to be in the study, you had to have a 4 or better, you got to be able to walk, so you had to have a 4 or better, that kind of thing.

DR. BASTINGS: Just to add on what Dr. Temple and Katz said, the analyses that we did could be considered traditional kind of analysis that you would do on this sort

of trial, and we tried to contrast that to the analysis that the sponsor did.

DR. KATZ: I just want to emphasize, and it has already been emphasized several times, we refer to the analysis the sponsor did. This is an analysis we agreed with up front. We understood based on the evolution of this project that there were likely to be people who responded, and I think Dr. Cohen explained or someone explained the evolution of how we got to where we did.

I just want to be clear it is not just what the sponsor did. That was the protocol specified analysis, we agreed with it. We are just trying to get a sense of looking at secondary analysis just to see what we have here, but we are very clear about what the protocol said, we agreed with it.

DR. ANDERSON: Dr. Katz had mentioned something about the magnitude of the changes on some of the scales and how people felt about that, and so I was just wondering if some of the people who use walking time and some of the MSWS scales had any comment on whether they have an opinion or a feeling about sort of the magnitude of changes that are being talked about and their relevance as other than

statistical endpoints.

Dr. Goldman.

DR. GOLDMAN: I think that it makes sense to look for a responder subset given what we know about the heterogeneity of multiple sclerosis, and there is certainly a precedent for that in the way we approach treatment of the disease directly, looking at interferons and other therapies. We talk about responders versus non-responders.

So, I think that that makes sense. Then, when you take that group and you look at 25 percent improvement, within what we know about the timed 25-foot walk and the MS functional composite, the consensus is that greater than 20 percent is meaningful, clinically meaningful.

The challenge is that we don't have a gold standard of what clinically meaningful sort of means. In this study, they are using the MS Walking Scale 12, which I think does have recognized value in looking at clinical meaningfulness of walking. And one thing that the sponsor may, if they have a chance to talk about, is a study looking at change in the MS Walking Scale 12 as it is related to accelerometer measures, which is free-living mobility.

So, there is data that that is a useful tool. But

I want to emphasize or comment on more importantly perhaps is the additional data that is out there looking at what is a meaningful change in the timed 25-foot walk and that 20 percent is.

When you look at the data that is out there, it is looking at a variety of measures assessing clinically meaningfulness, not just the MS walking scale. So, when you try to answer that question, I think you have to look at the cohesiveness of studies across several different parameters, because there isn't a gold standard for what that means.

That is just in clinical trials. If you go into practice and try to determine what clinically meaningfulness means, I think that becomes even more challenging.

So, what I feel most impressed by is the idea of a change in the timed 25-foot walk that is greater than 20 percent, knowing what I know about the collective data, not specific to this study. But, in the research in general, what that means in terms of a variety of quality of life and clinically meaningful measures of change for patients.

DR. TEMPLE: Could you comment on the company's Slide 80, CC-80, which gives the distribution of various improvements? So, for your number of 20 percent, the pooled

data and the individual studies were similar, show 31.5 percent of people on drug and 13.1 percent of people on placebo with that effect.

Then, there is a complete distribution, and there is also a showing of even large effects and smaller effects. Do you want to comment on that display? I am trying to see if that is what you had in mind.

DR. GOLDMAN: Yes. So, different studies have tried to capture what is clinically meaningful change using the timed 25-foot walk and, most recently, at the CMSC meeting in Atlanta, there was a group that suggested that a 10 percent change was clinically meaningful using subjective survey measures that are not included here.

So, part of the issue is how you determine what that means. But I think that the general consensus is that 20 percent or greater is meaningful and, if you look at--I mean below that, you still see a difference--I mean greater than zero percent, there is a difference. But the question is where does that impact affect day-to-day function in patients.

I think that if you look at the difference at greater than 20 percent, and you use a variety of subjective

measures, not done in this study specifically but done in the MS research, that difference correlates to differences on several other measures besides the MS Walking Scale 12.

But there is clearly a benefit. Fampridine in this shows even at 1 percent or 5 percent but certainly one could argue that that difference may not be experienced functionally in a patient.

But I think that is hard to capture, I guess that is the point I am getting at, that you have to look at cohesiveness of many measures, and when you do that, greater than 20 percent is where people are looking right now as being clinically meaningful rather than the small difference in the MS Walking Scale in a small population without a powered intent to detect that difference.

DR. ANDERSON: Dr. Brass.

DR. BRASS: Yes, I had a question for Dr. Goldman. Does the data on the 20 percent apply to the change in walking speed or the change in time and does that make a difference because we are looking at speed here, we are not looking at time, because from the published data that I have seen, the 20 percent applies to time, and whether that is equivalent once you make it into speed or time, whether it's

the same or not.

DR. GOLDMAN: Right. I think that that is a fair point, that there are different ways that it has been looked at. I don't know whether the company can comment on if they assessed that data. It is certainly available to break it down that way.

So, I think that that is a fair comment. But I don't know. I couldn't say specifically about how that would translate from a statistical standpoint. I don't know if other people have a thought about that.

DR. ANDERSON: We have a lot of time for discussion of the questions and things, which we can do more of this about, but I guess we are supposed to be focusing on sort of clarifying issues for the FDA--and I started this, so I am the reason we have gotten derailed, but I want to bring us back and then resume some of this in the afternoon.

So questions for the FDA to clarify either their presentation or sort of the nature of their interest, and then we will be able to break for lunch and come back and resume these at greater length.

Are there other questions? I am going to go in the order of my list, so I will get you, Dr. Wolfe, in a

moment. But we will start with Dr. van Belle, who had a question a while ago.

DR. VAN BELLE: I believe my question was actually answered. My question dealt with what was the agreement between the FDA and the sponsor in terms of the endpoints, and I think Dr. Katz clarified that, and I think we are all agreed on that. So what we are talking about the clinical interpretation of the evidence and the potential side effects. They are really the two issues that we should be dealing with, in my opinion at least.

DR. ANDERSON: Dr. Wolfe.

DR. WOLFE: There seems to be a tug between that slide that we have seen several times. It says that a minority of people, but better with the drug than with placebo, have at least a 20 percent improvement in walking speed.

But that sort of runs head up against the statement--this is in our briefing package from the FDA--the walking speed at the end of the double-blind treatment was not different between the treatment group, 2.37 feet per second, versus 2.30, suggesting that the magnitude of change is small.

Certainly, it is reasonable to look at some of these other measures aside from walking speed although as was pointed out by Dr. Illoh, a number of them aren't really statistically significant at the end.

For the neurology clinicians as opposed to the general clinician that I am, I wonder what comments that could be offered to the FDA, the comments on the fact that there isn't any difference at the end of this trial or the average during the trial in the walking speed between the placebo and the drug group.

That seems itself to be reasonably dispositive even if the agreement for this analysis included, but was not limited to, just the percent of responders. I mean as the FDA pointed out in its briefing document, 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. This seems to be a conflict to say the least. I would like comments by the FDA on that.

DR. BASTINGS: I think that the site shown by a quota about the different proportion of patients with various percentages of improvement provide some additional

meaning to the drug endpoints. So the fact that they show the higher proportion of patients receiving fampridine having more than 20 percent, 30 percent, 40 percent improvement gives some perspective to the average data that was shown by Dr. Illoh, so it is just different ways to look at the same data.

You can look at the data using mean values and by doing that, there is not much difference for many endpoints between the drug group and placebo, or you can look at various responder definitions and, as you have seen, the one used as the primary endpoint was a positive one, others looking at these proportion of patients with 20, 30, 40 percent change in walking speed, also in favor of fampridine.

So the whole point of the discussion here is to get your opinion as to whether these differences are sufficient to balance the risk of seizures that has been described by the sponsor and by Dr. Boehm.

DR. ANDERSON: So, if we have a fixed difference of 25 meters, whatever it is, feet, then, it doesn't really matter.

I mean we only have really that the speed and the

time are sort of interchangeable if we have only one distance to look at. But when you change from speed to time, you change sort of the nature of the distribution and, when you use time, which is what most of the FDA measures seem to be using, 11.57 seconds versus 10.64 seconds, you are looking at a highly skewed distribution with a long rightward tail and a large number of outliers.

So, I would like to know why the FDA chose to do analyses on means for this sort of distribution as opposed to medians or something else, or to not use the transformed data in terms of speeds where you would expect it to be sort of more of a unimodal, sort of Gaussian-like shape.

DR. BASTINGS: Our analyses were based on speed, you know. You had a display of time, because this was an easier way graphically to compare the groups. But our analyses were based on speed, not time.

DR. ANDERSON: But when you show the slide that says this is the time on the walking test, and you have a little line between the two that says p equals 0.17, you didn't do the p test on the raw data of times. You just plotted it over the times, but you calculated it on the speeds.

DR. BASTINGS: I think that is correct.

DR. ANDERSON: Dr. Temple.

DR. TEMPLE: It is worth remembering that if you have a nice response in a small fraction of the population, the average response will look very small. I mean that is why people look for responder subsets.

So, by my quick calculation, if you had a 50 percent improvement in 10 percent of the population, that would be something like a 5 percent of improvement overall. Dr. van Belle can correct me if I did that wrong.

You see this in oncology all the time and, nowadays, now that we know that there are genetic predictors of response, we adjust for it. But in one of my favorites from a long time ago when I had responsibility for these, the drug Tarceva had an overall benefit of about 1.5 months survival in the entire population.

When you looked at the responder subset with the right receptor, they had a six-month overall survival so the 1.5 months could be considered trivial. Nobody would think the 6 months was trivial.

That is why people look at responders. And then it seems to me the question has to be well, overall, those

seem like a good deal to treat. But it is worth looking at the people who respond especially if you think you can get rid of the others after they don't respond.

I mean whether you can really do that clinically, you know, is not known to me because I don't treat these people, but people seem to think you can. But you can expect that an effect will be diluted is there is a significant fraction of people who don't have much effect. That always happens. We just don't look at it very much.

DR. ANDERSON: We will get Dr. Katz. Then, we will solicit Dr. Stuve, and then we will break for lunch.

DR. KATZ: Just to remind people, the reason we wanted to look at the question of clinical meaningfulness was because, as I said, we have no doubt about the robustness of the finding on the primary outcome. It is a very big difference. It's in both studies, the proportion of responders as defined, but the definition of responder involved having to be faster on drug basically than the fastest off drug but timed walking test. But it didn't mandate any particular difference.

You could have been 0.01 seconds faster on your 3 out of 4 on-treatment measures compared to the fastest off

treatment. So, even though the difference in the primary outcome is large and indisputable, it could have been based on extraordinarily, extraordinarily minor differences on timed walking test.

So, that is why we tried to look at whether or not it meant anything, and that is why all these other measures, that is why we have looked at all these other measures in the responder category even though one could argue that it is really not amenable to inferential statistics. So that is why we are doing this.

Walking speed overall is one thing. But walking speed on responders versus non-responders is of great interest to us, as are the other outcomes.

DR. ANDERSON: Dr. Stuve, do you have any clarifying questions for the FDA or other comment you want to make at this time?

DR. STUVE: I think most of my questions have been answered. One question I had earlier to the sponsor, but maybe the FDA knows this, too. Earlier this morning it was stated that there was no association between the use of other disease-modifying therapies and response or non-response to fampridine.

I wasn't sure, I saw data on whether patients switched from one disease-modifying therapy to others during the trial and, if that is true, whether there was a difference between the different groups, the responders, the non-responders, and the placebo group. Was that clear?

DR. ANDERSON: It wasn't clear to me. Could you repeat your question again?

DR. STUVE: The patients, they were all under these modifying therapies, on interferon beta, Copaxone, and I think on some other therapies. It was stated earlier that there was no correlation between treatment response to fampridine and the use of any other disease-modifying therapies.

I was wondering whether there was a difference between the different groups of responders and the non-responders or the placebo group with regard to whether disease-modifying therapies were changed during the course of any of the clinical trials, or whether the disease-modifying therapies were continued from beginning to end of the trials, in other words, somebody was started on interferon beta, whether that drug was continued throughout the trial or not.

DR. ANDERSON: That sounds more like a sponsor question and we will make this the last one, and then I will announce our break for lunch.

Do we know if there was a difference in the proportion of patients, either fampridine versus placebo, or responder versus non-responder in terms of the proportion that had their other disease-modifying treatments altered?

DR. COHEN: The requirement of all the studies was that any patient taking disease modifiers needed to have been on stable therapy I believe for two months at least prior to the trial and then to continue on stable therapy throughout the study.

So, to my knowledge, we did not have people switching from one immunomodulator to the other, and about 70 percent of the overall study group was taking one immunomodulator or another.

DR. ANDERSON: Did that address it, Dr. Stuve?

DR. STUVE: Yes, yes.

DR. ANDERSON: At this point, we will take a one-hour break for lunch. For the members of the Committee, we have a lunch set up for us in the President's room. Others are left to their own resources, and there are a couple of

restaurants in the hotel conference center available.

[Luncheon recess taken at 12:04 p.m.]

AFTERNOON SESSION

(1:04 p.m.]

Open Public Hearing

DR. ANDERSON: Good afternoon. We will go ahead and commence the afternoon's session for the meeting here. I have some messages that I need to read at the beginning of this which is going to be the open comment section.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing Session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationships that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or

other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, please speak only when recognized by the Chair. Thank you for cooperation.

In order to have as many speakers as possible for this session, I have been told that the assignments have

been limited to four minutes. So, if you are a speaker, there is supposed to be some sort of warning sign that will occur on the podium at three minutes to let you know that you are getting close and then, at four minutes, the microphone gets muted. I apologize, but we are not seeking to cause any offense, we are just trying to give as many people a chance to speak to the Committee as possible.

Our first presenter today will be Nicholas G. LaRocca, Ph.D., representing the National Multiple Sclerosis Society.

DR. LaROCCA: Thank you. I have no financial relationship with the sponsor. The National Multiple Sclerosis Society does have a financial relationship with the sponsor.

I represent the National Multiple Sclerosis Society, the foremost advocacy group for people with MS in the United States with more than 300,000 people self identified as having MS as part of our organization. I am here today because I wish to provide evidence for the unmet need for symptomatic therapies that can improve walking for

persons with MS.

I have been involved in MS research, clinical care, and education for over 30 years, originally tutored, like Dr. Miller, by the late Labe Scheinberg. As vice president of health care delivery and policy research at the National MS Society, I lead the Society's research efforts in symptom management, rehabilitation, patient care, and health policy studies.

Because MS slows nerve conduction in the central nervous system, it has profound effects on quality of life for both patients and families, making it difficult for those affected to run, walk, pick up a child, tend to everyday needs or activities and even store and retrieve memories.

We do not know the cause of MS and there is no cure at present. While there are six FDA-approved medications that are at least partially effective against some forms of the disease and, although we have rehabilitation and symptomatic treatments for many MS symptoms, there is at present no pharmacologic treatment

available for MS-related walking difficulties. This in spite of the fact that difficulty walking has wide-ranging effects on people's lives, even in its milder manifestations.

Recently I was involved in developing and conducting a Harris interactive survey among more than 1,000 individuals with MS and many of their family members. This was one of the first studies to examine in depth the impact that difficulty walking can have on quality of life among patients with MS and their families. I would like to provide you with some of the important and perhaps surprising findings from this research.

Two-thirds of the patients polled reported difficulty walking and of these, 70 percent reported that such difficulty was THE most challenging part of their MS and most reported that difficulty walking restricts their daily activities significantly, including their ability to travel.

More than half reported that difficulty walking interfered with socializing outside the home and caused them

to miss or cancel significant life events such as weddings, birthday parties and vacation plans.

The vast majority reported that walking difficulty affected their emotional health, self-esteem, and intimate relationships with a spouse or dating partner.

Half reported that expenses increased when difficulty walking began. Among those still working in spite of walking difficulties, half lost days from work and one-third had to reduce their working hours due to walking difficulties.

One in five even changed plans for having children due to difficulty walking.

Among those with difficulty walking, three-quarters reported that family members had to take on more household responsibilities because of their problems with walking, two-thirds reported that getting around could be dangerous, and close to half reported that difficulty walking had increased the cost of their care.

Although we might think of difficulty walking as an isolated symptom of MS, this is far from the truth.

Difficulty walking is related both functionally and neurologically to a wide range of everyday functions and activities including standing and balance, running, stair climbing, bathing and showering, toileting, and sitting and rising from a sitting position.

It can even affects levels of fatigue. There is thus an important unmet need for symptomatic treatments that could improve walking for persons with MS and thereby enhance quality of life for them and for family members who care for them.

Given the wide-ranging effects of walking difficulty in MS, even a modest improvement could translate into a significant boost to quality of life by enhancing an individual's ability to participate in important life activities - navigating in the workplace, accompanying one's children on a visit to Disney World, shopping, exercising, getting to the bathroom in time, and many others.

Difficulty walking is no simple matter.

Thank you.

DR. ANDERSON: Thank you, Dr. LaRocca.

The next speaker is June Halper.

MS. HALPER: Good afternoon. I represent the Consortium of MS Centers and the International Organization of MS Nurses, who both have business with the Acorda. I personally do not.

Thank you so much for inviting me to present at this session. I am an adult nurse practitioner who has specialized in MS since 1978.

I have watched the world of MS change in terms of prognosis, disease modifying treatments, and the widespread availability of specialty MS center. I believe it is extremely important that fampridine is approved as a symptomatic treatment for MS, since I believe it will positively affect MS patients' quality of life.

It has a far-reaching and life-long impact on the patient who is diagnosed and his or her circle of support, family, friends, co-workers, and community at large.

MS has acquired unfortunately a widespread reputation of hopelessness, severe disability, disappointments, and alterations in one's quality of life.

What is quality of life? It has been defined as a state of complete well-being, not merely the absence of disease or infirmity. It is one's perception of the impact of the disease subjectively and culturally. Dr. Richard Rudick of the Mellen Center has stated that MS has a greater impact on quality of life than inflammatory bowel disease or rheumatoid arthritis.

Research has shown there are specific issues related to health-related quality of life. That is cost, alterations in the social environment, role reversals, social and emotional isolation, restricted range of opportunities and, high on the list, impaired mobility.

Improvement in strength and walking can lead to enhanced employment, social interaction and activities, and emotional behavior. Walking and mobility is indirectly related with improved depression, fatigue, pain, social support, and self-efficacy in those affected by MS.

Therefore, any therapy that results in an enhanced ability to move and navigate through one's environment is a vital component of living with MS.

Many years ago, Dr. Labe Scheinberg asked patients what mattered most to them related to losses. Walking was rated very, very high; the ability to navigate their environment through the ability to be mobile and independent.

For many years, treatment of MS was limited to acute management of relapses and symptoms were managed by pharmacotherapies that we offered our patients but not specifically indicated for MS.

Since 1993, with the advent of injectable and one infusible therapy for MS, our options increased for disease modification. The disease itself is treatable and its prognosis has changed. But symptoms persist and continue to affect quality of life. Fampridine will be the first symptomatic medication approved specifically for an MS symptom. It will treat the important life-altering symptom of impaired mobility.

The late Linda Morgante. an internationally recognized nursing expert in MS, was a proponent of the importance of hope. She stated that hope embodies our

vision of the future, our opinion of ourselves and others, and our sense of control over the direction of the events in our lives.

The experience of hope for someone with chronic illness can provide the energy necessary to promote health and enhance quality of life.

I thank you for this opportunity and urge you to approve fampridine, a treatment that will add to the hope chest in MS care.

Thank you.

DR. ANDERSON: Thank you very much.

The next speaker is Susan Zurndorfer.

MS. ZURNDORFER: I have no financial relationship with Acorda. Good afternoon. My name is Susan Zurndorfer and I was diagnosed with primary progressive multiple sclerosis in November of 2000.

I cannot say that I didn't know anything about MS since my brother had it, as well. He was diagnosed in the 1960s when he was in his early 20s and at that time there were no treatments, not even MRIs.

Unfortunately, he had a chronic progressive form of MS and his condition deteriorated rapidly, and he went from using a cane to crutches, to a scooter and, finally, to an electronic wheelchair. By the time he passed away in 1996, at the age of 53, from complications related to the MS, he was quadriplegic.

Fortunately, for me, by the time I was diagnosed, it was a different ball game. And then, even in spite of my family history, it took a long time to diagnose. My symptoms started about four years prior to being diagnosed and was basically a weakness in my left side, mostly in my leg.

I first noticed it when spending summers on Fire Island and taking long walks on the beach. My left leg would tire and start to drag. However, after resting for a while, it seemed to improve, but the symptoms did persist and over time I did start to trip and fall quite a bit.

At the time, I was an account manager for a legal services company in New York City and would visit law firms all over Manhattan. This required a lot of walking in and

out of subways, up and down stairs, and usually carrying presentation materials and a laptop computer. Just to get to my office, I had to walk three blocks, take two subways that required walking upstairs, and then another two blocks.

There were many times when I fell while on the job. My supervisor and my colleagues knew there was a problem, but I had not told anyone about the MS. It had gotten very difficult getting around and it became unsafe for me to continue in my job and, in August of 2002, I went out on disability.

I have always lived in Manhattan where everybody walks. But my walking was becoming more difficult and I had to be careful of every step I took. A day without falling was a good day for me.

I did eventually start using a cane. The cane did work for a while but I became limited to walking short distances. I had to decide if I would go to the drugstore or the bank since I could not do both.

Then I overcame another psychological hurdle and started using a walker. In the meantime, during one of my

routine visits in 2004, my neurologist told me about a new drug that was being developed that she thought would help my walking.

I was told that it was as pill taken twice day, that there were few, if no, side effects, that it would not interfere with my other MS therapy and that I should notice an improvement in my walking right away.

I began Phase 1 of the clinical trial in July of 2004. I had a feeling I was getting the placebo since I did not notice any difference in my walking. As soon as I started Phase 2, and was actually receiving the drug, I saw an improvement immediately. My legs felt stronger and I could walk better and for longer distances.

I have now been on fampridine for over 3.5 years and I am still walking, and I no longer have to decide if I should go to the drugstore or the bank because I can do both.

I would imagine that most people take walking for granted. I know that I did. But when one has a walking disability, one has to make decisions all the time. My life

revolves around getting from A to B. My life revolves around making decisions based on what is easiest and what is most important. I just can't do everything.

I have to pace myself and I have to plan, but I did adjust and the bottom line is I just want to keep on walking. I am delighted to be here today, nine years after being diagnosed with MS, to say that the world is a different place than it was in the 1960s when my brother was diagnosed. Thanks to drugs such as fampridine, I am still walking.

DR. ANDERSON: Thank you very much.

MS. ZURNDORFER: Thank you.

DR. ANDERSON: Our next speaker is Karen Jackson.

MS. JACKSON: My name is Karen Knable Jackson. I am a person living and working with MS.

My interest in speaking to you today about fampridine is based on the fact that I have a progressive form of multiple sclerosis, which means I am in a long distance marathon with this disease. MS has required me to make a number of physical and mental adjustments, typically

far more than those that are demanded of the ordinary adult.

My adjustments include having to plan out every move of my day to ensure that I have the energy and stamina to complete my objectives.

MS also requires that I use a number of mobility aids, such as a scooter, walker, or cane to assist me in my movements. These mobility aids provide me with the ability to get around and do the things I need to accomplish, while helping me to conserve my energy to complete my tasks.

My mobility has been severely compromised by MS and is a system that requires the most effort and expenditure of energy on my part. I often joke that by the time I get to work in the morning, I have put in a full day. This is because MS demands so much from me as an individual to get and stay moving.

My typical day begins at 5:15 and as I said, I have to plan every step I take. For instance, in my home I use a chair lift to get up and down steps but there are three steps that I must traverse to get to the chair. To accomplish this, I have to raise my feet 1.5 inches to clear

each step.

The possibilities that this drug could hold for me are very exciting. If it can improve my nerve conduction for me, it can improve my walking, which could improve my overall stamina, which would improve my quality of life since I might not have to plan out every step I take every waking moment, and it's an oral drug.

If this drug is deemed safe and effective, it would greatly benefit not only me but others like me who endure and continue to fight this debilitating disease. The mere promise of this drug's potential benefits brings hope to me and I am sure to many others.

As a participant in several clinical trials for other MS therapies, I believe that once a therapy has demonstrated beneficial effect and safety, it should be made available to all those who could benefit from its use as soon as possible.

If you find that this drug has demonstrated positive outcomes, I hope you will give it prompt favorable consideration for its use as a MS treatment.

I would like to take this opportunity to thank the Peripheral and Central Nervous System Drugs Advisory Committee for this opportunity to share with you how important the therapy could be to people with MS, like me, who have mobility challenges.

On a personal note, Dr. Miller, I thank you. Your clinical observations are 100 percent on target especially for people like me.

DR. ANDERSON: Thank you very much.

Our next speaker is Elissa Levy.

MS. LEVY: Hi. I am Elissa Levy and I own a very tiny bit of Acorda stock, and I also am the founder and president of a not-for-profit organization that raises money for MS research and programs, and Acorda has been kind enough to support some of our events.

That said--that's not why I am here--I am here because I have secondary progressive MS. I did just jog over here and three and a half years ago I would not have been able to do that. My father would have rolled me in, in a wheelchair, and I would have used a cane to get up here,

and I probably would be sitting, speaking to you because I would have been so tired.

I am sorry, this is more emotional than I thought it would be.

I had written something that I was going to read to you today. But after listening to the comments today, I have a few things I just wanted to stress.

Mainly, what Dr. Miller said, that this isn't about a 25-foot walk, it's about quality of life. It's about the fact, when I was 33 years old, I was diagnosed with this disease and I had to stop working. I had to sell my apartment because it was a second floor walk-up, and I couldn't get up the stairs.

I had to move into my parents' apartment building so they could take care of me. My mom came down every day to help me get dressed and get out of bed, get me my food. My social life ceased to exist, and I had been a very social and active person prior to the diagnosis.

At 35, I thought my life was over. I had tried all the disease-modifying drugs, gone through all the

miserable flu-like symptoms and side effects, and nothing was working. I really went in about 18 months from limping to, you know, using a wheelchair and a cane full time.

Things were so bad that I even decided that the risk was there for me to try the Novantrone, the chemotherapy, which made me very, very sick, and still I seemed to be getting worse and worse.

Then, I found out about the 4-aminopyridine trial. And I actually failed the 4-amino trial. I guess you don't fail, but I didn't qualify to get in because I can limp faster than any other girl living in New York City can limp. I had to get across the street, so I would swing my leg way out to the right because I had a weak hip flexor, but it kind of worked this way. So, when I did the timed walk, I did it too quickly, and I couldn't get in.

Luckily, my doctor knew that I was desperate to find something that worked and we decided to try the compounding pharmacy. In the past three years, I started an organization, as I mentioned, that raises money. We raised $2 million in two years for research, and I wouldn't have

done that without the fampridine. I wouldn't have my life without fampridine really right now.

I guess the other thing I want to stress. Compounding pharmacy is working for me now. But, you know, if we are worried about seizure, which after listening to everybody talk this morning, it seems like at the new recommended dose, there is no increased risk of seizure, so I am not quite sure what that is but, as an adult, I want to be able to take that risk myself.

When I decided to go on the 4-aminopyridine, my doctor sat down and discussed with me the risks, and he asked me not to drive for the first few months in case of seizure. I did the test to make sure I wasn't prone to seizures. Those were things that I was willing to do to be able to have the opportunity to get my life back and get to work.

MS is this incredibly miserable, unpredictable disease, and nothing works for everybody. None of the other drugs worked for me, and I am lucky that 4-AP is my miracle pill and that I take it twice a day, and I have my life

back.

But I think as like a medical community, all we can do is give. You know, maybe there is only 30 percent of us out there this is going to affect, but it is my life and another 100,000 people's lives that it is going to affect, I mean I think that is significant and I think it is worth taking the risk to make this drug available to people so they have every opportunity to get their lives back.

Thank you.

DR. ANDERSON: Thank you very much.

The next speaker is Robert Engel.

MR. ENGEL: I know this is a formal process, but how do you follow that? I would just like to know. How do you follow that?

My name is Rob Engel. I came to tell you one thing, and that's if this product or a product comes on the market that can improve mobility even for a smallest amount, it will change the quality of my life.

I was diagnosed with MS seven years ago. It was relapsing/remitting form, and the effects were significant

on me. Right off I had trouble with balance, I had trouble walking, and it led to nothing but falls and consistent falls, and led to lots of broken bones, and it is consistent with the case today.

Today, I have become progressive in nature. Now, if it continues to progress on the same track that it's on, which means the disease was on my left side, now, it's on my left and my right side, there is no doubt in my mind and no doubt that I will be wheelchair bound.

So, I do everything I can do every day because that is my responsibility. Okay? I get up, I ride a stationary bike for 20 minutes. I basically stretch and do strengthening exercises for 60 minutes and, after that I walk three-quarters of a mile dragging myself around a track.

Now, here is the story. I can continue to do that, but the fight has still got me because I am not getting any better and the bottom line is I am progressing at a faster pace.

So, all right. Here is what I know. If there is

a drug that can be into the market that is like this, I say let's give it a try. It's not only going to help me but it is going to help thousands of other people who have the same symptoms that I do.

Now, listen, on top of that, on top of the disease, I have an 8-year-old son. And you know what I like to do? I like to play catch, I like to go walking with him, I like to do all the things that a young father should do. The way that I look at it is you folks here, the FDA, you are the only hope that I have.

The bottom line is if you think this drug is worth it, and you think this drug can be helpful, my only suggestion is don't wait. Bring it to market and bring it to market as quickly as you can, because here is the situation with me.

I need your help, I need the help of this drug. I need your hope. I need the hope that this drug can give, and I need the time with my son. That is what my focus of my life is.

I say thank you. I thank you for your time and

allowing me to speak.

DR. ANDERSON: Thank you, Mr. Engel.

Our next speaker is Jacqueline Havener.

MS. HAVENER: I am delighted to be here today to share my fampridine experience and the way it has improved my life.

I have been on the drug for 15 years. Prior to that, walking had really gone downhill. I could walk very little and I needed help even to do that. I was diagnosed in 1965. That is almost 45 years ago. I have three wheelchairs, many canes and a stairclimber.

In 1993, when my late husband had cancer surgery, I had to use my electric wheelchair scooter to go back and forth to his room. Then, I went on fampridine in early February of '94, only a few months later. Fortunately, for me I was already seeing a physical therapist and had been for years.

Incidentally, I strongly recommend seeing a physical therapist for anybody going on fampridine, as he was able, not only to strengthen my legs but re-teach me how

to walk properly and climb stairs.

The next time my husband was in the hospital, not only did I walk to his room, but I was able to carry those heavy envelopes of scans. What a difference.

Everyone in this room should have to use a wheelchair part of the time and experience real trouble walking to be able to feel and understand the difference this made for me.

My attending doctors and physical therapists were thrilled at my terrific improvement. My therapist had been working with me on walking and climbing stairs after I had started fampridine since the premise of the drug is nerve conduction.

My husband and I took a number of trips throughout the years. I wore out the soles on a pair of shoes walking in Greece. Those were in the early days of MS. By the next and subsequent trips, I had to take a folding wheelchair.

I walked a little when I could using a chair as a walker, but pretty much had to be in it. Fast forward to the beginning of this summer. I spent two weeks in Italy

where I did a huge amount of walking using only a cane or another person for balance, something I could not have done without fampridine.

Only months after starting the fampridine, I was able to get down, pick something up off the floor or out of the cabinet and get back up, something I had not been able to do for years. I would just simply fall over.

In fact, on neurological exams for years, I had not been able to raise the upper part of my legs even so much as one inch. Now, not only can I raise them, I can resist pressure being exerted on them.

The combination of the drug and the physical therapy clearly allowed me to strengthen the upper legs.

Something which perhaps says it best is a To Whom It May Concern letter written by my physical therapist Charlie Kibbe. He said, and I quote, "I have taken her up to the brick wall. Fampridine has taken her over it, and now I have taken her far beyond." I think this is a wonderful analogy.

To summarize, you can see my life as vastly

improved. Would I be standing here today without the drug? Probably not. I sincerely hope it will help others as much as it has helped me.

I would be glad to answer any questions. Thank you.

DR. ANDERSON: Thank you very much.

The next speaker is Dr. Bever, Dr. Christopher Bever.

DR. BEVER: Good afternoon. Thank you for allowing me to testify.

I am an academic neurologist and MS practitioner with more than 20 years of experience with the use of aminopyridines in MS. I am the local site investigator on ongoing Acorda studies of fampridine. I am not a consultant to Acorda or in any other way receiving financial compensation from them or from any other company involved in the development of fampridine or their competitors.

I should say that I am an employee of the Department of Veterans Affairs but I am on annual leave and my testimony in no way represents the Federal Government or

the VA.

I wanted to address the specific questions that the Committee has been given by the FDA.

Firstly, has the sponsor demonstrated substantial evidence of effectiveness? A review of the company's filings shows that fampridine treatment improves walking speed in a subset of MS patients. This is entirely consistent with my experience and that of many other practitioners with aminopyridines in MS, both in published Phase 1 and Phase 2 studies and in individual patients.

In clinical practice, patients are able to determine within a matter of days, whether treatment is beneficial and either continue or stop treatment.

I have concerns about the fact that after agreeing to the responder analysis, the FDA, in their briefing materials, have introduced a re-analysis of the entire treatment cohort. Basically, they showed no significant effect, which is the whole reason that the responder analysis was done.

The second issue was has the sponsor shown the

effect to be clinically meaningful. The results using the 12 item walking scale, the prospectively defined subjective outcome, clearly show the change is clinically meaningful, and this is entirely consistent with my experience in practice.

I would discount the value of the patient subjective measures as a secondary measure that would be influenced by many factors other than walking and would therefore have a large amount of background noise.

Should the sponsor be required to evaluate the effects of lower doses? The primary issue is safety here, I think, and the primary safety issue is seizure induction. I think it has been shown this morning that seizures are not increased at the current dose that is being used and further studies would not be valuable here.

Finally, if a clinically meaningful effect has been demonstrated, under what conditions should fampridine be considered safe?

Both approved disease modifying and symptomatic medications used in MS are associated with increased

seizures. Prudence suggests that MS patients with a history of seizures not be treated with such drugs. My recommendation would be that this issue be included in the product labeling and addressed by prescribing providers with their patient in developing the treatment plan.

I would like to close by saying that MS providers have little to offer their patients with impaired ambulation. Fampridine-SR represents an important treatment that will benefit a significant subset of MS patients. Seizure risk will limit its use but should not prevent its use in those patients who can benefit from it.

Thank you.

DR. ANDERSON: Thank you, Dr. Bever.

Our next speaker is Serena Lowe.

MS. LOWE: Good afternoon. I would like to begin by thanking Acorda for drug evaluation and research for affording the National Disability Institute the opportunity to present its views today during today's Advisory Committee meeting. Although NDI in the past has received financial support from Acorda, I personally have no financial

relationship or obligations to Acorda Therapeutics.

We are here today to talk about the New Drug Application 22-250 submitted by Acorda Therapeutics, and we are delighted to have the opportunity to address the Advisory Committee.

My comments today will focus solely on the importance of therapeutic interventions aimed at improving mobility for individuals with MS and the connection between improved mobility and increased opportunities for an individual to actively engage in the workforce and the economy.

Enduring poverty and chronic underemployment for persons with disabilities mandates new strategies for building economic empowerment options for 20 million families who have at least one member with a disability.

According to the 2000 census data, 20 percent of people between the ages of 5 and 64 have a disability; 38 percent of working age adults with disabilities live in households with annual incomes of under $15,000, and 30 percent do not have either checking or savings accounts.

They are unbanked or underbanked, as we refer to it, and are in poor physical health.

The National Disability Institute is a national research and development organization with a mission to promote income preservation and asset development for persons with disabilities, and to build healthy financial futures for Americans with disabilities and their families.

The real economic impact towards one of NDI's signature programs aimed at creating a national public/private initiative assisting low-income persons with disabilities with asset-building strategies, free tax preparation, and financial assistance.

One of the outcomes is for low-income families with a member with the disability to receive earned income tax credits. We know from our research that approximately $1 billion of unclaimed EITC credits is left on the table every year by 1 million people with disabilities. In the 2009 filing season, we worked to prepare over 180,000 tax returns in 84 cities, resulting in over $176 million in refunds for people with disabilities.

We are submitting testimony today because we work a lot with the MS community. MS represents a chronic degeneration of the central nervous system and approximately 400,000 Americans have MS. Every week an estimated additional 200 people are diagnosed.

Problems with gaits and difficulty in walking are among the most common mobility limitations experienced by people with MS. Limited mobility affects the ability of individuals to accomplish daily tasks at home, work, school, and in the community, and significantly limits their independence.

Furthermore, NDI has researched the significant barriers that limited mobility can cause in terms of preventing an individual from engaging in a meaningful way in the workforce, economy or a community. You have heard several examples today, I can't do that justice.

What I can tell you is that research conducted by the Burton Blatt Institute affiliated with Syracuse University has demonstrated that lack of mobility and other challenges related to disabilities results in major

obstacles to an individual's ability to work, earn, save, and contribute back into the economic system through taxes, investments, and consumption.

Because there are currently no therapies indicated specifically to improve walking ability for those with MS, this aspect of the disease has not been adequately treated and clinicians and patients alike, many of whom you have heard from today, are frustrated by the lack of viable therapeutic interventions.

Furthermore, the BBI research demonstrates that even the most incremental benefit in an individual's mobility can make the difference between that person not being able to actively engage in the workforce and the ability of that person to earn, save, and sustain-- [microphone muted].

DR. ANDERSON: Thank you very much.

The next speaker is Diane Edquist Dorman.

MS. DORMAN: Good afternoon. My name is Diane Dorman. I am Vice President for Public Policy for the National Organization for Rare Disorders. I have no

personal financial relationship with the company in question. However, NORD does run Acorda's patient assistance program for Zanaflex, a product that treats spasticity in MS. This program provides free product for patients who cannot afford therapies.

I am here today, not on behalf of any one pharmaceutical company or any one particular product, but on behalf of the millions of men, women, and children in the United States affected by one of the 7,000 known rare diseases that, in the aggregate, affect approximately 30 million people.

Since 1983, NORD has been dedicated to helping patients with rare diseases and assisting the organizations that serve them. A rare disease is defined by the Orphan Drug Act as a disease that affects fewer than 200,000 people in the United States, and we serve as the primary, nongovernmental clearinghouse for information on rare disorders. We are committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

Today, there are 340 orphan products and biologics that treat only 200 rare diseases. Given that there are thousands more rare diseases without any specific treatment, it is easy to understand that there are millions of people who can only hope that one day someone will take on the significant financial risk to develop a therapy for their condition.

It may appear to some that walking a few extra feet unaided is insignificant but, for MS patients, those few extra feet may feel like a mile. As you deliberate today, I ask only that you keep in mind that patients affected by rare diseases are willing to take on a far greater degree of risk than those affected by more widely characterized diseases affecting larger populations.

Thank you.

DR. ANDERSON: Thank you.

Our next two speakers are Jonathan and Mimi Mosher.

MRS. MOSHER: Hi. My name is Mimi Mosher. I have had MS for 24 years and I unfortunately now am confined to a

wheelchair. The first part of my disease was very gradual. I didn't have any disability for the first nine years, but I have to say that I have gone through I think every possible piece of adaptive equipment that is out there.

MR. MOSHER: I am Jonathan. I am the carepartner and husband. In addition to loss of mobility, Mimi is also legally blind so she is not working from comments like all of us are. I would like to say that Mimi's first sign of mobility loss was a loss of energy and then one foot dragging way back in the '80s when she worked for the science museum. Her vision had been declining for some years so, as a carepartner, I became very scared. I didn't know what this would mean.

Some days she would be better, some days I think she would be paralyzed, all kinds of questions raced through my head, would I be able to earn enough money to take care of her, would our insurance cover her.

As time went by, Mimi became what we call a wall walker, someone who needs to hold onto the wall to maintain balance and, with some reluctance, we went through canes and

walkers and all sorts of adaptive equipment.

Acceptance would come later. But I must tell you it was very hard to see our friends live vital lives, going on beach trips, biking, and more, while we were settling for a living space that was growing smaller with time.

Eventually, Mimi had to stop working and, of course, that affected our finances. Because it hit her right after college, she never had a full-time job. So the Social Security disability income was very, very small. We live on a 1.2 income family with lots of different expenses, but we do have some help from family, which we are very grateful for.

Another thing that impacts us is the lost productivity. A lot of families can divide their labor, the husband go to the grocery store, the wife goes to the veterinarian. Mimi and I go together wherever we go. Because I drive, so we don't divide as easily. So, I am the driver as well as the lifter, the cook, the lawn guy, the reader, the artist assistant. Mimi is a wonderful artist, by the way, despite her visual loss.

MRS. MOSHER: Normally, I do most of the talking, but I am all choked up, so here we go.

MR. MOSHER: There were times when I wanted to break out of the confines of MS and go away for a weekend to the mountains or the beach, but it is not that simple. Feelings of guilt and selfishness get into my head. Even early on, when Mimi's mobility was better, I felt obligated to be nearby just in case she needed me. It is a struggle that I can overcome with the help of friends but I feel uneasy being away from her and having fun all by myself. But that is something that I do struggle with.

Financially, I am very grateful to have the job I have. I love my job but, unfortunately, I can't go to another job because, if I go to another job, I won't be able to get health insurance. I am very lucky to have the job I have.

I would like to say that loss of mobility is a three-word phrase that seems so neat and tidy and yet for us it is a definition that grows and grows. It is very messy and very unruly but, with 27 seconds left, I would like to

say that Mimi is a smart, funny, sexy woman, and we love each other very much, and we live a very, very full life, lots of fun, despite MS. But we are here to share our experience about how loss of mobility affects Mimi, how it affects me. It is a lot more than you would think when you just look at it from the outside.

Thank you for letting us share.

MRS. MOSHER: Thank you.

DR. ANDERSON: Thank you very much.

I would like to thank all of the speakers who took their time out to come and address our committee today.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee as well as the public comments.

At this point, I think we have the opportunity to resume sort of general clarification questions that people didn't feel like they got addressed from this morning, and then we will proceed to reading the specific questions and

working through them on an item-by-item basis, anyone who has holdovers from this morning. We will start with Dr. Rudnicki.

Clarifying Questions (Continued)

DR. RUDNICKI: This is a question for Acorda, and it has to do with the open-label extension. With 660 patients in it, that means that non-responders opted to continue, as well as responders.

So, I am curious, was there any difference between how many people in those two groups opted to extend, and then was there any difference between those two groups in terms of how long they continued on the drug?

DR. COHEN: We had a very high rate of opting into the extension studies from the double-blind. Well over 90 percent of the patients from the double-blind studies, whether they were on placebo or fampridine, or whether they had been classified as responders or non-responders, opted to go into the extension studies, so it is not possible to see a meaningful difference. There was no meaningful difference between or among those groups electing to go in.

We have data on the behavior of the different groups as they migrated from the double-blind study into the open label. Slide up.

[Slide.]

Here we are looking at the 203 extension study where everyone has been taking 10 mg b.i.d. On the left you see the double-blind treatment period. The white boxes in each case are off-drug treatment, first, the 4 visits leading up to randomization and the double-blind.

Then, you see, in gold and blue, for the original fampridine responders and non-responders respectively, the change from baseline speed during the double-blind treatment. Then, when they came off drug, you can see that there was a rapid return to baseline.

Then, there were follow-up visits off drug and screening visits prior to entering into the extension study, and then they got into the extension study again, and you can see again an uptake or an increase in the walking speed as a group.

Now, a couple of observations here. The non-

responder group, you will recall in all of the studies, as the placebo group, had some mean increase in walking speed of approximately 7 percent whereas, as you have seen, the responder groups had mean increases of 25 percent or so over baseline.

So, you see that behavior repeated here in the extension study where you put them back on drug and you get the same behavior or similar behavior.

Now, this is looking at the course over about two years of extension study, and what you see is that over a two-year course, as one would expect from a mostly progressive population of people with MS, that there is a gradual decline in mean walking improvement over the original baseline prior.

But you still see a continued maintenance of a gap between the original fampridine responders versus the original non-responders, where the non-responders eventually actually progressed below baseline as a group, whereas, even after two years, the original responders continued to be above their original baseline.

Was that responsive to your question?

DR. RUDNICKI: Could you put that slide back up?

DR. COHEN: Please. Slide up.

[Slide.]

DR. RUDNICKI: Just looking at the N, I was kind of interested in whether or not non-responders continued on the open label.

DR. COHEN: They do.

DR. RUDNICKI: And they did. So do you have any idea of why they did?

DR. COHEN: We have discussed that with our investigators. We, too, had the question, and I will actually ask Dr. Miller or Dr. Goodman rather if he could share some of his observations.

DR. GOODMAN: I am Andrew Goodman from the University of Rochester.

People continue on in studies for lots of reasons. I would say among them--and this is not an all-inclusive list--among them are a sense of loyalty to the study center and the nurses, I think a sense of altruism that they are

participating in MS research. In our center, they get free parking, that is an advantage. So, I think that is part of it.

The other part of it may be that, in fact, there are other aspects of MS that the patients may sense as improvement. That may be bladder control. That may be a sense of stamina that isn't necessarily reflected in a walking speed. Stamina to do other things other than walking may be reflected in increase in strength, so non-responders on the timed 25-foot walk over a short period of time doesn't necessarily encompass the entire spectrum of effects that patients may experience.

DR. ANDERSON: Ms. Sitcov.

MS. SITCOV: Yes, I have two quick questions.

One, just out of curiosity, will 4-AP, if this drug is not approved, continue to be compounded by pharmacies? It seems as though there is a tremendous risk of seizures if that is the case. I don't know if you want to address that.

DR. ANDERSON: That is probably a better question

for our FDA colleagues.

What are the rules that would limit or permit continued compounding of this drug as it has been if there is a decision not to approve this version?

DR. TEMPLE: We would probably need to ask our Office of Regulation about what the rules of compounding are. I believe that if we were to determine that there was a real hazard from compounding a particular thing, we could intervene. But I am not knowledgeable about this, so I don't know. Ordinarily, compounding is allowed.

MS. SITCOV: Thank you. My other question has to do with a point that Dr. Bever just made and something I have thought about in reading some of this material.

That has to do with his concern about to the FDA of introducing a re-analysis of the responder, agreeing to the responder analysis, and then introducing a re-analysis of that 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.

I guess I am wondering, if one has a treatment

regimen that has significant benefit for 35 percent of the people who take it, how would the FDA want to design the study and treat the data in a way that would demonstrate benefit and be acceptable.

Thank you.

DR. ANDERSON: Any of you that you feel is the best one to speak on this one?

DR. KATZ: Not the best one, we absolutely did agree with the company about looking at responder rates. Again, we talked about how we got there, and we think it is a perfectly reasonable thing to do, as long as the criteria prospectively designated and that sort of thing, which of course they were in these studies.

The fact that we have done other analyses doesn't mean that we think the responder rate is in an inappropriate analysis. We are just trying to get a sense of all aspects of the data.

It is not uncommon at all to do additional secondary analyses or sensitivity analyses in addition to what has been agreed with the company is going to be the

primary analysis.

It is just relatively standard, we are just trying to get a handle on what we think all of the data mean. But we have not in any way backed off from our agreement to look primarily at the responder rate and the other analyses that the protocol dictated.

We are just trying to look at the data in multiple different ways. As I say, one of the aspects of looking at both groups in total as opposed to just the responders has to do in part with preserving randomization and doing analyses that preserve randomization.

So, there are lots of reasons why we do other ancillary analyses. But we have not backed off from our agreement that the primary analysis is what the protocol said it was.

DR. BASTINGS: An additional reason is that we have to balance the efficacy data with the safety issue, which is seizure. In order to do that, you want to have as much an understanding as you can of what the study results were and what efficacy was. That is why we did the other

analyses.

DR. TEMPLE: We are actually perfectly enthusiastic about discovering that a drug works in only a subset. We have a variety of things that we have written, that I have written about trying to identify who the responders are and perhaps even studying the drug primarily in those people, so-called enrichment designs.

We are not remotely against that but, as Eric said, if you can't identify those people at the outset you need to have some idea of what the overall effect is so you can make overall judgments. But that absolutely does not mean that we think a drug has to work in everybody, because no drug does.

MS. SITCOV: Thank you.

DR. ANDERSON: Dr. Green.

DR. GREEN: I have a question, that since this drug has such a narrow safety window, is there any anticipated dose adjustment for renal disease, and it looked like it wasn't investigated in hepatic disease because it wasn't presumably metabolized that way?

DR. COHEN: The drug is excreted over 90 percent unchanged in the urine. There is minimal hepatic metabolism, and we have done an extensive range of metabolic studies showing that there is minor metabolic component that is mediated by CYP2E1, which in fact is one of the rarer CYP enzymes.

So, there is no anticipation, nor is there any suggestion in the safety data of liver interactions or effects, or indeed significant drug-drug interactions.

On the other hand, because the drug is excreted in the urine and, in fact, concentrated in the urine, there is a concern with respect to renal insufficiency and what implications that has on dosing in those patients.

In our studies, based on the expected pharmacokinetics and, indeed, a renal insufficiency study we did on pharmacokinetic study, we excluded patients with severe renal insufficiency defined as a creatinine clearance of 30 ml per minute or less.

Others were not excluded specifically because we wanted to have data with respect to those patients at the 10

mg dose. It turned out that we had quite a few patients with renal insufficiency who were entered into the study. Almost all of them with one exception was mild meaning a clearance rate of between 50 and 80 ml per minute. There was only one who qualified as a moderate, so we really have no substantial data to speak of.

However, we had 86 patients, as I said--I don't know if I said that--but we had 86 patients with renal insufficiency who received fampridine-SR at 10 mg b.i.d., and we had 39 in the placebo group, so we were able to look at that.

In terms of response status, that was essentially the same. There was no significant difference in the increase in responders that we saw in the renal patient.

DR. GREEN: I am more interested in the Cmax.

DR. COHEN: In the Cmax? I was going to address the safety profile, but I can go--

DR. GREEN: No, I am sorry.

DR. COHEN: So, I can do that and then we can go to the PK.

Slide up, please.

[Slide.]

DR. COHEN: If we look at the AE profile in those patients who were receiving 10 mg b.i.d., there was not a substantial difference. This looks at the placebo patients versus the fampridine patients, and the top half, that is people with normal renal function, and in the lower half, it is separated out by those who had the abnormal function.

For those with abnormal renal function, you see that if we look all the way to the right, there were about 89.5 percent of patients who experienced at least 1 AE versus 83.4 of those without renal insufficiency, and if you look at the severities, they were not much different.

In fact when we looked at the specific AE profiles, we did see three types of AEs that appeared to be more frequent but not others.

[Slide.]

Those specifically being balance disorder, dizziness, and insomnia. Those generally, when we looked, were mild to moderate, and did not result in discontinuation

so, overall, the mildly renally impaired patients in the studies appeared to do about the same as the non-renally impaired.

Now, with respect to the specific PK, I would like to ask Dr. Weir to address that.

DR. WEIR: As Dr. Cohen had mentioned, a pharmacokinetics study was conducted in patients with mild, moderate, and severe renal impairment. Under the definitions that Dr. Cohen described, mild impairment patients, 80 to 50, 50 to 30, and below 30 for the severest.

This was a single-dose, pharmacokinetic study where the SR tablet was administered as a 10 mg dose. In mild renal impairment patients, Cmax was increased 67 percent, AUC increase 75 percent.

In the moderate patients, Cmax was increased 75 percent, area under the curve 100 percent, and with the severe renal impairment patients, the area under the curve was increased 300 percent.

DR. GREEN: So, does that mean you would not anticipate any labeling changes in those settings?

DR. COHEN: At this point, we feel that there is enough--let me rephrase that. I don't think you ever have enough data. Based on the data we have, it would appear that it may be reasonable to allow mildly renally insufficient patients access to the drug with appropriate cautionary notes to alert physicians to monitor the situation even more carefully.

With severe, it is very clear that you would exclude those patients, you would just have to. With moderate insufficiency, we just don't have the information, and that would have to be developed in the future to make reasonable judgment.

DR. BASTINGS: Just to continue on this topic, could you give us a perspective on how Cmax in a patient with marginal impairment compares to Cmax, let's say, at the 20 mg dose that we have some concerns about?

DR. COHEN: At the 20 mg b.i.d. dose level?

DR. BASTINGS: 20 mg b.i.d. compared to patients with marginal impairment.

DR. COHEN: Dr. Weir.

DR. WEIR: The Cmax associated with 20 mg dose--slide up, please.

[Slide.]

From the population pharmacokinetic analyses, you will see this slide summarizes the Cmax and Cmin concentrations, and again this was an analyses performed on a dataset including 580 MS patients, healthy volunteer, as well as renal impairment patients.

You will see that the population-based model predicts that the Cmax values for a 10 mg b.i.d. dosage regimen would be approximately 25 nanograms per ml. With 20, you will be at 49 nanograms per ml. Again, as we described, in mild renal impairment patients, you would observe a 67 percent increase above the 25 nanogram per ml observed in healthy volunteers.

DR. ANDERSON: That was the data you were looking for?

DR. BASTINGS: Yes.

DR. ANDERSON: Okay. This is related to the renal? Okay, we have got a couple more on this side.

Let me make sure that I don't forget our telephone speaker. Dr. Stuve, do you have a question you would like to make? I have a couple others here if you don't.

DR. STUVE: I have no question at this time.

DR. ANDERSON: Dr. Fountain.

DR. FOUNTAIN: I have a brief question. The power analysis suggests that you are going to enroll 240 patients in the 203 study. But you enrolled 301. I am surprised there is such a relatively large difference between the two. Was it the way it worked out logistically or was it to increase the power of the study?

DR. COHEN: It was an operational issue, if you will, that we just learned as we went along in the multicenter context. In that study, we had 33 centers, so we had 33 centers, and there is always a time lag in between the time patients are screened or scheduled for screening, and then brought in.

What we discovered is in the early going in the trial, enrollment would sort of be in fits and starts, and then as the centers came on line and were sort of into the

groove, it would accelerate.

So, by the time we got close to the 240 number and looked to set a date to stop enrollment, what we discovered is many patients had already been scheduled for screening visits or had already come in, and the decision was made not to disappoint them since they had already raised their hands and volunteered. They were brought in and we had an overshoot.

DR. ANDERSON: Dr. van Belle.

DR. VAN BELLE: One question and one comment. Could you put up Slide CC-74? I thought I understood it, but now I don't.

DR. COHEN: Slide up.

[Slide.]

DR. VAN BELLE: If I add up the N's, roughly, I come to 450 or so. So, clearly, and this is the MS-204 study with about 120 patients on active treatment--so clearly, people are being counted more than once. So, could you tell me what is really going on in this slide?

DR. COHEN: Dr. Blight.

DR. BLIGHT: Yes. We collected plasma concentrations at every visit in the double-blind treatment period, and so all visits are represented here. These patients are counted more than once because they had more than one visit in which samples were taken. That is why you see a larger number.

DR. VAN BELLE: But the change from walking speed, those subjects would have the same baseline value basically.

DR. BLIGHT: Each sample was related to the walking speed change at that time point for that patient compared to their own baseline visit. So the vertical axis is percent change in walking speed.

We bin the data by the fampridine concentration and then within that bin, we incorporated all of the walking speed improvements for all the patients based upon the change from baseline for each individual patient.

DR. VAN BELLE: It is becoming more complicated rather than less. I will just take that for information.

My second question or comment relates to the concept of responder. Now, responder, we sort of take it as

if there are people who respond and don't. In point of fact, that is not how it is done. The responder is defined operationally as a person who scores higher on three visits than the maximum of the baseline visit.

Now, I think from the point of view of the pharmacology, it could be possible that some people are, in fact, harmed by the drug, as well.

So, I could also define the responder as a person who does worse on the drug, and one possibility would be to do something like the following: define the three lowest values at baseline and then see how many people do worse than that on three visits during the active trial. That would be then the responders who were responding in the opposite direction.

I don't think there is any reason to believe that that wouldn't be the case, because we are dealing with something that is pharmacologically fairly active, and the dose may, in fact, be too high for some of these people and may cause other effects.

I don't think that has been analyzed, and I am not

sure that you could analyze that. But I worry about this because it could be that some people are going to be harmed by the drug just in terms of their walking ability.

As we have seen, there are quite a few that actually the change from baseline is actually negative, and so I was wondering among those, are there people that are, in fact, significantly lower in terms of their walking than the other component where we claim that there is a response.

DR. BLIGHT: We did have the same thought, and when we began looking at the responder criterion, we were quite interested in whether or not they were negative responders similar to the positive responders.

We were quite satisfied, when you look at the placebo group, you see an equal number of negative responders as you see positive responders, which goes along with there being a fairly random process underlying people changing in the placebo group.

In the fampridine group, you actually see less negative responders than you do in the placebo group, which again is consistent with the fact that when you look at the

average change in walking speed, the fampridine group gets less worse.

So, as you saw in one of the plots we had this morning--slide up, please.

[Slide.]

If you look at the average walking speed in the left graph here, there is no point in the population where the fampridine group goes below the placebo group, which means that there are no patients who seem to get worse than the placebo group.

Sometimes with plots like this you see a crossover so that there are some patients who benefit, some patients who get worse but, in this case, it seems with regard to walking at least, that there are no cases where fampridine-treated patients show a worse walking outcome than you would expect from the placebo change.

DR. ANDERSON: Dr. Rudnicki.

DR. RUDNICKI: No.

DR. ANDERSON: No? It has been addressed? Okay. Dr. Yeh.

DR. YEH: Just a quick question. Do you anticipate offering or suggesting blood level monitoring for patients with mild renal deficiency particularly for clinicians that are wary of using the medication in that case?

DR. COHEN: It is not clear what instruction we would give in that case with respect to levels. We do have a reasonable characterization of what the increase in Cmax and AUC looks like in mildly renally impaired patients.

We also have those 86 patients who we were able to follow, and most of them did go into the extension studies. I think it was about 77 who went into the extension studies. We have been following most of them for several years, as well, so it is not clear what instruction we would give with respect to a plasma level and what do you do with the information when you get it.

Within the range of plasma levels that exist in that situation, we don't appear to see a substantial increase in AEs or severe AEs. Now, granted we have limited information. It is based on 86 patients. We have followed

many of them for a long time.

This is one of the liabilities in any preclinical program. We can only get so much data and then develop, hopefully, more data when more people are taking the drug, hopefully, in the after market, but, at this point, it is not clear what we would be able to say about the meaning of a plasma level in these patients.

DR. YEH: I guess the reason for my question is that if you push the patients that were on 10 mg b.i.d. up 67 percent, you get very close to the 20 b.i.d. level that you would obtain because it seems to increase linearly.

That is why I asked the question.

DR. COHEN: Quite so. Specifically, based on the 67 percent increase in Cmax that you see in the mildly renally impaired, you would expect it to be the equivalent because the kinetics are so linear. You would expect it to be the equivalent of 16.7 mg, if you will. So, it is somewhere between 15 and 20.

As we have seen, we don't have enough exposure at this point. I wish we did, but there is only so much that

is feasible at this stage. We don't have enough exposure between doses of, say, 15 and 25 mg b.i.d. really to have a handle on what is the actual increased incidence or increased risk of seizure.

What we can say at this point is that at 10, you know, it looks pretty good, it looks like a low risk. There may be some increase when you get to larger numbers. We will have to monitor that and gather those data but, as you can see, so far it looks like the expected rate of background.

Between 15 and 25, there is a suggestion that maybe the risk does go up, and maybe at 20 it goes up, maybe at 15 it goes up, but we really don't have a good handle on that. The closest, in fact, that we have to that is the renal patients in our studies.

So, if they are, in fact, taking the equivalent of 15 or 16 mg on average, which pharmacokinetically would be the case, we at least have 86 on drug and 39 on placebo where we can begin to make some judgments, and so far we are not seeing a signal.

That doesn't mean we wouldn't see one later, and it absolutely would need to be monitored and more data developed, but so far we don't.

DR. ANDERSON: Dr. Twyman.

DR. TWYMAN: Could I have Slide 65?

Could you remind me what the y axis is before I ask my question on this?

DR. COHEN: That is percent walking speed improvement over baseline.

DR. TWYMAN: Great. So, it looks like on the graph on the right, that the error bars are pretty tight, and getting at the question of identifying a responder, it seems to me that it might actually be done relatively early because the definition of a treatment responder is having 3 of those 4 measures better than the baseline itself.

Do you have data that shows how many subjects fail by visit 2, visit 3, visit 4 from the responder definition, because it seems to me that if those error bars are indeed as tight as they are, it should be by the second visit you will have a pretty good idea of who is responding and who is

not.

DR. COHEN: I will put a slide up in a moment to address your question.

The short answer is we have come to a similar conclusion with respect to needing about two visits to get there. By way of illustration, if you look at the responder analysis formula by way of illustration, and you look at a baseline visit, you measure them or assess them, you then give the patient drug and look over the next two visits to see how they do, you can see a potential.

It is not really a formula, it is really an illustration. Slide up.

[Slide.]

You can see how that might translate. Now, again, I need to emphasize that this is not a recipe, rather, it is an illustrative way of looking at the data to get a sense of what you are asking about, which is clinically, how long does it take to figure out that someone is responding or not.

So, if you went back to the 203/204 data and just

set as a rule in our studies, that if you didn't see an improvement over baseline in the first two visits, both visits--one is not enough--both visits, and you discontinued everyone who didn't have an improvement in the first two visits, which could be, in our studies, within a four-week period, then, you would be able successfully to separate responders from non-responders at about a 75 to 80 percent level based on the data in this study.

Now, again, clearly, clinical practice is not quite so tight and mathematical, but I think it does give an impression, and a correct one, that echoes what you have heard from Drs. Miller, Dr. Goodman, Dr. Short, that, indeed, the effect of the drug is rapid, it happens within the first few weeks certainly, and it is clinically discernible.

DR. ANDERSON: Dr. Temple.

DR. TEMPLE: In dealing with so-called narrow therapeutic drugs, it is common practice to adjust the dose based on the effect of abnormal renal function usually. But I won't say always, without asking for further studies. If

you know the blood levels are doubled, you give half the dose as long as you know it's reasonably dose proportional.

Do you have any thoughts about making a smaller tablet size?

DR. COHEN: Yes. The challenge we have had as part of the program is in the early going, as Dr. Blight mentioned, based on the literature, we expected that the dosing would be closer to 20 or 25.

In fact, in our earlier program, which focused on spinal cord injury, we started out with doses of 25 to 40 mg b.i.d. based on the literature and based on compounding practices and translating those levels.

As we developed the program, it became clear that that impression was mistaken and that, in fact, the true effective doses were lower and furthermore, that there was a threshold and above that threshold, the further above it you got, the more AEs you got, the more risk of seizure you got without a corresponding benefit in return.

So, that pushed us down the curve. At the point at which the program developed in MS, we had developed 10 mg

formulations and above.

We collaborate with Elan Pharmaceuticals who does the formulating by the original agreement where we got the right to develop it, and for whatever reason, the original 5 mg formulation that was made did not have the stability that would make it viable as a commercial product.

So, we have been working with Elan diligently over the last couple of years to develop such a formulation, and that is in process now. We do not have all the data on it yet. But we are working on it.

DR. ANDERSON: Dr. Brass.

DR. BRASS: Was there any calculation done of numbers needed to treat or numbers needed to harm in this study?

DR. COHEN: The number needed to treat is fairly straightforward by either responder analysis that we do, so if you take a 35 to 40 percent rate of response on the prespecified responder analysis, or if you look in alternate analysis that you saw and that we have discussed, just taking a 20 percent improvement threshold where about 31, 32

percent respond, so you are in the same ballpark. It equates to about 3:1, so 3:3 to get one who responds.

DR. ANDERSON: Dr. Morrato.

DR. MORRATO: I wanted to follow up a little bit more around compounding practice right now, just so we understand sort of current state of care.

Do you have any data that talks about the prevalence, so what percent of practitioners seeing MS patients are already using compounded, what is their dosing experience? It sounds like you said based on the literature, that it is at 20 to 25.

What are sort of discontinuation rates that are seen in practice, and is there dose titration that is occurring? Do you have any data on current utilization?

DR. COHEN: We have studied as best we could. Because of its nature, which is not an FDA-approved activity, there is very limited data, and one actually has to go and poll every compounded pharmacy and try to sort of triangulate pieces of data that are out there.

We have done that to the extent that we can. So,

subject to those variables, it appears that there are certainly several thousand patients taking compounded drug. I believe that FDA itself had an estimate about 10 years ago in the range of 10,000. I can't verify it, nor do I know where that came from, but our own work would suggest that that is entirely possible.

It is certainly in the thousands but, as to how many thousands, it is very hard. We have seen estimates based on our own work as low as 4- or 5,000 and as high as 20,000. So it is probably somewhere in that range but we can't say for sure.

In terms of the practice, it is very individual by its very nature. When we started the program, the dosing was probably higher than it is now, and our sense has been that, in part, in response to the data that we have published, practice has accommodated that.

Remember also that the compounded drug is frequently given three or four times a day so a not atypical dose might be 10 mg 3 or 4 times a day for a total of 30 or 40 mg a day. But patients are highly individual and

treatment regimens are highly individual, so it is really not possible to describe a specific level of practice.

DR. MORRATO: In clinical practice, are people titrating up if they don't see effect?

DR. COHEN: It is my understanding that at times they do.

DR. MORRATO: Thank you.

DR. ANDERSON: Dr. Goldman.

DR. GOLDMAN: Just as an opening thought about that, I think the sustained demand for compounded 4-AP over greater than a decade may speak something to the clinical significance, at least perceived by the patients, but I am wondering if you could comment, or someone from your group, could expand on what we know about a 7-point change in the MS Walking Scale 12 and its meaningfulness in the responder population.

DR. COHEN: We selected the instrument based on what appeared to be its face validity and also literature of several studies that had been done with it, validating it against other measures.

We have here Dr. Jeremy Hobart, who is one of the co-developers of the instrument, and also an expert psychometric scientist who has also consulted with FDA. So I would like to ask him to address that.

DR. HOBART: Slide MS-32, please.

[Slide.]

In addressing the issue of whether 7-point change is clinically significant, I would like to come at this question from three different perspectives.

The first one is to say exactly what does a mean change of 7 points mean for an individual person. Then, what I will do is answer the question to what extent does a 6.9 change satisfy criteria for minimal clinical significance. Thirdly, I will add in some clinical reasoning and clinical context.

The slide we have here addresses this issue of exactly what does it mean to an individual person. I think in looking at this, we have to understand that the changes that people get are person specific, and they are also specific to the start point that they are on the scale.

If you evaluate the MSWS-12 with sophisticated modern psychometric methods, you can come to two conclusions. The first one is that people with MS can reliably and consistently distinguish between the five different levels for each of the items.

Secondly, it allows us to predict very accurately what will happen to any one person from that baseline score should they be a responder.

Next slide, please.

[Slide.]

So, what we have done here is we have taken the mean person entering the study in terms of their MS Walking Scale score at baseline, and we have predicted exactly what will happen to them should they be a mean responder.

These are not anecdotal reports, these are predictions based on mathematical modeling. What we see is that a person with a start point of 7, who is a mean responder, will change 6 items of the scale in terms of their category, they will improve on 6 items.

They will not only notice that, but they will

report it back through the scale. What they will report is that their overall walking ability is improved, their ability to climb stairs has improved, their balance has improved, their effort required to walk has improved, that the amount of support they need to walk indoors has improved, and the speed of their walking has improved.

Now, it is important to note that people who lie at the mean score in this sample are actually towards the upper end of the scale, and they are actually in the area of the scale, which is not its maximum area of response.

If you take people in the middle region of the scale, they will change 9 of these items in a positive direction. So, that is a qualitative indicator of what will happen to any one person, and this can be predicted for any person at any point of their start point on the scale.

Slide MS-22, please.

The next way to look at this question is to ask the question to what extent does the 6.9 point change satisfy current criteria as clinically significant.

Slide up, please.

[Slide.]

You will all appreciate from this morning's discussion that this is a complex issue for which there is no consensus, and that leads us to a triangulation of evidence. But an important statement came out last year from the IMMPACT group. IMMPACT stands for the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.

They put out a consensus statement and recommendations for determining clinically significant change. It is notable that this group of 40 included a senior member from the FDA's Study Endpoint in Labeling Committee.

Next slide, please. MS-23, please.

[Slide.]

This is the framework that this consensus group produced about determining important changes for individuals. They stated that these can be considered in two main areas, anchor based and distribution based.

Within each of those two areas, they could be

considered as within patient, between patient for anchor based and effect size and standard error of measurement for distribution based.

Their recommendation is that for a change to be considered as clinically significant, these should be satisfied in at least two of these areas, one of which should be anchor based and one should be distribution based.

Next slide, please. MS-24, please.

[Slide.]

What we have is evidence in all four areas, that a change of 6.9 points satisfies all these criteria. So we actually meet every part of their framework, and the two ticks means that there are multiple bits of evidence for each one.

If we just look at one of those, if we go to Slide MS-30, please.

[Slide.]

This is called the standard error of measurement for a scale, and what it relates is the standard deviation to the reliability and the calculation thereof.

Essentially, multiple studies across multiple different disorders have shown that one standard error of measurement is considered equivalent to a meaningful change in the scale.

What we have done here is computed the standard error of measurement across 9 different samples from independent studies on both sides of the Atlantic. The mean standard error of measurement from both samples is 5 points. That means that 5 points on this scale can be considered as clinically significant difference or change.

The range of those was 4.23 to 6.03. Now, a mean change in fampridine responders of 6.9 points comfortable exceeds the mean of those 9 independent studies and also comfortably exceeds the range.

The final way of looking at this question I think is to look at some clinical reasoning, and can we go to Slide MS-31, please.

[Slide.]

The scale measures walking ability and by definition, a person who ticks not at all limited for all 12

questions is unlimited in their running. By definition, a person who ticks 5 for all 12 questions has severe limitations in their walking ability indoors, and our understanding of this is usually people who scored the bottom end of the scale can walk very, very short distances and require aids to do that. By short distances, we often mean a few feet or a few meters.

So, the range covered by this scale is massive and therefore a 7-point change on that almost by clinical reasoning has to be meaningful.

Now, if we anchor that and say that if we have 7 percent changes, that is 15 different gradations within the scale that might be clinically meaningful. That means if we take someone at the top end who is unlimited in their ability to run, and we take someone at the bottom end who can only walk very short distances with aids, then, we have 13 different gradations in there to mean it will be clinically significant. I think that is strong evidence that a 6.9 change is very clinically meaningful.

DR. ANDERSON: Dr. Fountain.

DR. FOUNTAIN: I guess I want to change gears a little bit to the seizure risk. In particular, I am trying to understand what the seizure risk is.

I think we have seen two kinds of data, the data that was prepared by Acorda, that has the seizure rates for a number of different dose levels in which there was only, for instance, one seizure in the 40 mg a day dose. That would be Slide CC-110.

On the other hand, we have the information prepared by the FDA that looks only at information from 202, 203, and 204, in which 2 seizures occurred in fampridine 20 mg b.i.d. out of 57 patients.

I am trying to get a handle on what is the rate above 10 mg b.i.d., because the N is large for 10 mg b.i.d., and is moderately large for--I guess really only for 10 mg b.i.d.-- I am trying to figure out what is the total N across all studies that were exposed above 10 mg b.i.d. and the rate of seizure for each one of those.

Do we have a compound analysis across all exposures by dose?

DR. COHEN: Dr. Fountain, could you repeat the question?

DR. FOUNTAIN: Sure. I took a long way to get there. What I meant to ask was do you have a single slide or piece of data that represents the rate of convulsion by dose across all doses for all indications across all studies?

It might be easiest by illustrating in Slide CC-110.

DR. COHEN: Slide up.

[Slide.]

I am not sure if this is the slide you wanted. This is for the spinal cord injury program only, and this is the controlled trials only rather than the open label because here we have a placebo comparator, and the same was true in--well, we have this one.

In the controlled studies, you can see the numbers. The largest numbers are at 15 and 25 mg, and as I said, in those studies we were focusing more on the 25 and indeed the 40 until we realized we should back off the 25.

DR. FOUNTAIN: Right. I understand that for spinal cord injury. Do you have it across all your studies in controlled trials like combining spinal cord injury?

DR. COHEN: I don't believe we have it in this form. You are including all of the seizures you mean?

DR. FOUNTAIN: Right.

DR. COHEN: I don't think we have it in this form. We do have the listing of all of the seizures, the 22 seizures. We can start with this.

Slide up.

[Slide.]

We can start with this, but then we need to go to the dosing that shows each case and ordered by dose. This covers the seizures that were mentioned in the FDA briefing document and with which we agreed in terms of over the last 15 years or so of the program we had 22 seizures, 19 were listed as convulsions, and 3 were complex partial. Then, you see the breakdown across indications. The next slide.

Slide up.

[Slide.]

This looks at those cases. This looks at the cases for fampridine-SR. The other slide also included 5 cases using other formulations at the very, very beginning when Elan was developing the formulation.

If you look at the fampridine-SR cases, they are all listed here. Now this doesn't give you rates. I don't believe we have it by rates except in the double-blind, but it gives you by rate and dose here.

DR. FOUNTAIN: My comment is just that the N is so low at the upper range that it is difficult to get an understanding of the magnitude of the problem.

DR. COHEN: We agree. The difficulty that we are all grappling with, the FDA, the sponsor, and everyone, is that we have a reasonably good handle at 10. At 30 and above, it is possible to say that even with small numbers, that the rate jumps so much, to the 4 percent range and higher consistently.

Even in spinal cord and MS, once you get to 30 and above b.i.d., you begin to see those sorts of rates even with small numbers, 4 percent and so on, so it seems like a

very strong signal even with small numbers that that is certainly at least a threshold.

The difficulty is between 15 and 25 mg b.i.d., we don't have enough data to draw conclusions, and that is just the reality of it. The closest we come is, as I mentioned earlier, extrapolating from those renal patients who effectively could be said to be taking a dose somewhere between 15 and 20.

DR. FOUNTAIN: And that is exactly the point I was getting at, is that I suppose that the question is you are going to do a study at 40, after it is available and people take twice as much at 20 b.i.d., so that is the rate, trying to understand--so your answer addressed that.

The second comment I would make I guess is just that I am not sure that looking at seizure incidence per person year is exactly what we are after because we would expect somebody to have a seizure or not, and so those people that are susceptible probably have one relatively early, whereas, over time, if you don't have in the first period of time.

In other words, if someone is on Wellbutrin, and they have been on it for 3 years and they have a seizure, we don't typically say oh, it must have been the Wellbutrin you have been on for 3 years, whereas, if they started it last week, and they have a seizure, then, we blame it on that.

I guess I would find more value in the rates instead of the person years in terms of the data.

DR. COHEN: Are you referring to a presentation showing the relationship to time on drug, because we have that if that is of interest.

DR. FOUNTAIN: It is more of a general comment, in particular, looking at the rates, trying to get an understanding of the rates that particularly from the FDA presentation, it was presented as in terms of per person year of exposure.

I am suggesting that the person years of exposure may not be so meaningful as it is just the rate of who had a seizure and who didn't.

DR. KATZ: I just don't think we know that really. Things change all the time. One day your plasma level is a

little bit higher than it typically is. MS patients continue over the course of their life to get additional lesions in their brain, which may increase their risk or susceptibility to a given plasma level.

So, I don't think we have enough events really to know whether the hazard is all early or not at whatever dose they are currently on.

DR. COHEN: We can, with the few events we have, we have looked at least at that relationship because we also were concerned to see whether most or many of the seizures were occurring closer to the time when the patient was actually on drug.

Slide up.

[Slide.]

In fact, that was not the case. But, again, we have a very few events to work with at 10 mg although for a number of the events, at 30, 35, and 40, they did occur within a month or 6 weeks or 2 months of dosing.

Here, of these 5 events, in the extension studies, 4 of them occurred no earlier than 11 months after exposure,

and the one that you see on the far left actually was an interesting and special case.

This was a patient who had successfully taken fampridine for 3 months in the double-blind study without incident, and had a seizure 9 days into the extension study. That was coincident with her having just taken the day before a very high, unusually high dose of tolterodine for bladder control, 12 mg.

She had a seizure the next morning and we actually had a plasma level of fampridine 4 hours later that was 4.6 nanogram per ml, so it was below trough. She was taken off the study and a year later she again took tolterodine at that dose and promptly had another seizure. So, the investigator concluded that both seizures were very likely related to the tolterodine.

Those are the sorts of variables that we deal with. But, other than that case, the cases not only occurred at 11 months or more, but they were spaced out in a way that would suggest, but by no means prove, that it looks like a background rate over time.

DR. ANDERSON: Dr. Twyman.

DR. TWYMAN: Back to the functional area, I know the studies are only 9 weeks and 14 weeks long, and just curious. The EDSS is collected at baseline and I know there are issues at the scale, variability and non-linearity.

But was EDSS, by chance, collected also at the end of double-blind? If you have, I would be curious to see it.

DR. COHEN: I will ask Dr. Blight to answer.

DR. BLIGHT: We collected EDSS at baseline primarily to classify the patients by their disability on that scale because everyone is so familiar with it. We did not use it again in the double-blind studies.

Within the extension studies, we collected a new EDSS two years after going into the extension study. So, those are the two time points that we have. What we see in the extension study is that there is some progression on EDSS at two years, about 0.3 points.

That was for the original timed walk non-responders, and that is what you saw in that walking profile that you saw earlier. For the timed walk responders at two

years, there was really no change in the EDSS score. But those are the only data points that we have.

DR. ANDERSON: Dr. Brass.

DR. BRASS: In the literature, there is some data that fampridine has been used to treat MS fatigue, and I was wondering, as an off-label use, have you collected any data on the MS fatigue severity score in this trial, and do you think that fatigue could be a confounder for any of the data?

DR. COHEN: We specifically looked at fatigue among other outcome measures in Phase 2 studies when we were exploring the optimal design for future studies and also potential indications for the drug.

In our 202 study, in particular, which was the dose comparison study against placebo, we used three different fatigue scales among other outcome measures, one of them being the Krupp Fatigue Inventory and then two other well-used and known fatigue scales.

We did not see a difference with fampridine. Now, that is against a background of placebo rates of response on

those fatigue measures that were in excess of 70 percent at times so it would have been very difficult to show a difference.

It is quite true that there is a sense from those who use compounded drug that perhaps fatigue can be affected, there are anecdotal reports. We were not able to verify that in our studies, nor was there any evidence that the walking effect was an adventitial byproduct of fatigue.

DR. ANDERSON: Does anyone have any difficulty if we move on to consider the questions before us at this point? Are there more critical details people would like to explore from FDA or the sponsor at this point?

[No response.]

Panel Discussion/Questions

DR. ANDERSON: I was going to suggest that we handle the first question, see how lengthy our discussion is and then decide whether to simply push on or if it's getting lengthy, we can take a break at that point. Is that acceptable to everybody pretty much? Okay.

At this point, let's go ahead and we will now

proceed with the questions to the Committee and the panel discussions. I would like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate at this time except at the specific request of the panel.

Although we can certainly add questions or secondarily consider rephrased versions, I am asked that we specifically vote and deliberate on the questions as written before us. Let me read the first question for you.

Question 1. Has the sponsor demonstrated substantial evidence of effectiveness of fampridine as a treatment to improve walking in patients with multiple sclerosis?

Is there anybody in particular who would like to sort of open up our discussion as to whether they feel convinced or they are convinced they are not convinced on this issue? Dr. Wolfe.

DR. WOLFE: Given that there were different ways in which that question was raised, I mean when FDA agreed to allow this responder/non-responder analysis, it did say,

quote: "Even though they are doing that, as usual the Division will evaluate the risk and benefit of the treatment to determine approvability."

Part of the analysis that was done independent of responder status was to get more information. So, my problem with answering this question is if it is limited just to the responder analysis as in were more people who took the drug responding by improving their walking speed compared with the pre-trial, the answer would be yes.

But on the other hand, FDA showed that at the end of the study or during the study, there was no difference in the walking speed, no statistically significant difference between the walking speed of the placebo or the other, that answer would be no, and neither of those really take into account the clinical significance at all I suppose.

So, I am just saying that you could answer the question two different ways as a function of whether you are limiting it to just the responder analysis or whether you are instead looking at FDA's much more critical analysis saying there is no difference.

So, I would like maybe from FDA discussion as to which of those two, or should it be some melange of the two that we use to answer this 1(a).

DR. ANDERSON: I think we are sort of going to vote on 1 before we vote on 1(a). The reason I bring it up is because 1(a) says if you believe that this effect has been demonstrated, is it clinically meaningful.

DR. WOLFE: But I am saying forget the clinically meaningful for the second. Just has it been demonstrated. It would be demonstrated if you use the responder analysis, it would not be demonstrated if you look at the fact that there is no difference in the walking speed at the end of the study with the placebo or the drug group.

So, that is my question, before we get to 1(a). How do we answer this question, using both of them, using just one of them, what?

DR. ANDERSON: The way you stated it before, I felt you intertwined these issues a little bit. So I think in one sense, there is a question related to sort of objective demonstration of walking.

There is a secondary question of whether this is of clinical relevance, and I think the idea of how benefit in walking is defined regardless of its clinical significance is in a sense what we, as clinicians and experts, are being asked to take a stand on.

The FDA could and may choose to adopt any definition they so choose, but I think they are leaving it somewhat open ended so that they can hear from us.

For example, it sounds to me--and I hope you will clarify this--that you are sort of in favor of using a more sort of the FDA's form of analysis, and that would lead you to reach a decision in terms of clinical efficacy, while for myself, I mean I feel like the responder definition, which was defined in advance based on evidence from earlier clinical trials provides to me an objective measure by which to make a designation of improved walking.

I, for one, would be willing to accept that there is a demonstration of improvement in walking from these trials.

DR. WOLFE: Again, maybe I wasn't as clear as I

should be. I am limiting it just to statistical significance in the responder analysis, we agree it is statistically significant.

Before getting to the clinical things, just in looking at was there a difference in the walking speed at the end of the experiment, there wasn't any. So those are two different ways before even getting to the clinical issue that one could answer that question.

DR. ANDERSON: But this doesn't say an improvement in walking speed. This says an improvement in walking. Is an improvement in walking, walking speed across a randomized cohort of drug and non-drug patients?

Is an improvement in walking the proportion of individuals who will show a predefined measure in walking speed? Is an improvement in walking the Multiple Sclerosis Walking Scale?

DR. WOLFE: I think what you are saying is that we could interpret this question in whatever way we want and answer whether we think there is an improvement in walking.

DR. ANDERSON: Right, and the interpretation you

give should be enunciated as to the basis of what you chose and why you chose it. That will help them understand it, and Dr. Temple can expand on that.

DR. TEMPLE: What you are saying is right. You can looking at another measure and say I hate this one, I hate this one. Do not interpret what we presented, however, as a statement of preference.

We went by the responder analysis so fast because it had already been presented. We haven't said we think that is wrong or stupid, and it is the one we agreed with the company to do.

We did think you ought to see what the whole patient population analyses looked like. That is not an assertion of preference, but we would like your views on all this.

DR. ANDERSON: Dr. Goldman, please.

DR. GOLDMAN: Is it too late for an additional question or clarification about a statistical issue?

DR. ANDERSON: It is not too late. Was that your question?

DR. GOLDMAN: Thank you very much.

Just to clarify, the study was powered based on the anticipated responder. Is it correct if I am understanding this, power based on a responder model, and not powered to detect a difference for all comers, and is that sample size different?

What I mean to say is based on the number available, can you expect to detect a difference in all comers, and is that a fair way to look at the data based on the sample size that we have?

DR. KATZ: I believe they were powered to look at the proportion of responders. That was the primary outcome. Whether it was powered sufficiently to look overall or at the change in walking speed, of course, depends on what that effect was overall.

But I believe these studies were powered to look at the responder rate although, as we discussed, I guess it was Study 203 maybe, it was originally supposed to be 240, I think, and it went up to 300, so there is that little twist, but I believe the studies were powered by protocol to look

at the responder rate.

Again, all the other variables that were assessed could be assessed in many different ways, change from baseline, absolute value at baseline, percent change from baseline, and these various analyses were done, but the study was powered to look at the primary outcome. Correct me if I am wrong.

DR. TEMPLE: Also, as you saw in the 203 study, if you look at end values of walking speed, there isn't any difference. If you look at change from baseline in walking speed, there is a nominally significant difference. These are at the margin.

All of those things determine how much variance there is and a whole bunch of complicated stuff that I can't begin to explain, but Dr. van Belle can, that would determine whether you are likely to make it.

DR. GOLDMAN: Right. I guess my question is would you need 600 or 1,000 people to show a statistically significant difference taking all comers?

DR. TEMPLE: Well, the all comers 203 analysis on

change in walking speed was nominally significant in 203 and was not quite in 204 so, obviously, fairly close if you buy that measurement.

But you are looking at a small change on top of a larger number. So to see a difference in the larger number, I can't even begin to say how many people you would need, but it would be very large.

DR. GOLDMAN: [Comment off mike.]

DR. ANDERSON: Can you turn on your microphone when you speak, Dr. Goldman, so everyone can hear?

DR. GOLDMAN: Sorry. I guess it wasn't really a question, was it. I guess that is what I am getting at, which is why I am looking it that way may be problematic, I don't know if Dr. van Belle has other thoughts.

DR. TEMPLE: That is a different debate. Some people would say well, I want to see if it changed in the direction I want. That is my measurement, and you can see they are fairly close to being able to show that, whatever you think that means in the whole population. But focusing on just the responders, obviously gave them a much better p

value, so lucky for them that is what they planned initially. That usually helps, but you could still ask whether it means anything.

DR. BASTINGS: Besides p values the other way is look at the effect size on these various measures. You can get some sense even if it's not powered to show significance, you still can look at the effect size and try to make sense of it.

DR. ANDERSON: Dr. van Belle.

DR. VAN BELLE: Well, the claim was made that there was no treatment effect if you look at the average speed. That is not quite true. It is only if you look at visit 6. If you looked at the average across the clinical trial, the active trial, there was a significant treatment effect in fairness to the sponsor.

So, if you go to Table 2 of the FDA, at least if I interpret it correctly, the walking speed change on drug average versus baseline, that's about 8 lines from the top, it is 0.17 for placebo and 0.29 for fampridine, and that is significant at the 0.0089 level.

So, I think the average change is significant. Am I wrong?

DR. BASTINGS: I think that the p value for the average change is 0.02 in Study 204.

DR. VAN BELLE: Is this for responders only?

DR. BASTINGS: No, that is the other group. For the entire fampridine group compared to placebo.

DR. ANDERSON: Which slide are you looking at there, Dr. van Belle?

DR. VAN BELLE: I am looking at Table 2 that was sent out, revised table. This is of Study 204, although Study 203 shows exactly the same thing. Can we get that table up?

DR. BASTINGS: I don't think we have it up. I don't think it's on the slide. We used the visit 6 data because the change in walking speed compared visit 6 to visit 2, so we thought a fair comparison was to compare.

DR. VAN BELLE: Right, but again in fairness to the sponsor, they had observations across the whole trial, so taking the last observation clearly increases the

variability and would lead to a nonsignificant effect.

But if you look at the average over the trial period, that turns out to be significant. That could have been asked whether there is a linear trend or not. That could have been done.

DR. ANDERSON: I would like all of us to be able to follow the discussion here. You are looking at the two-page addenda that came to us?

DR. VAN BELLE: Right, and I just picked F204.

DR. ANDERSON: We are looking at the second page?

DR. VAN BELLE: That's fine.

DR. ANDERSON: No, I am asking, I am not telling you.

DR. VAN BELLE: I was looking at page 2.

DR. ANDERSON: And which table on page 2?

DR. VAN BELLE: Look at Table 2, the bottom table which is the revised table. Go six lines down. Walking speed change on drug, average versus baseline.

So, I interpret that as the average during the blind piece of the trial. That turns out to be significant

at the 0.0089 level, 0.17 versus 0.29, and one could argue, and that is what we are here for, is this clinically meaningful or not, and I think that's fine, But in terms of statistical significance, I think they have shown that there is an average change, significantly higher in the treatment group than in the control group.

DR. BASTINGS: In that study, it is even true if you compare visit 6 versus baseline. You also have a nominal p value under 05.

DR. TEMPLE: In all those things, it all depends how many values you take. If you just take the last baseline value, it's a highly variable number. If you take all four, it's narrower, so maybe you win on some of those. There is a lot of possible analyses. But you are right, it's not all negative.

DR. ANDERSON: Could you sort of summarize for me, Dr. van Belle, the point you were making by illustration of the table?

DR. VAN BELLE: The point I was making, that the claim was made that there is no change when you look at the

average across the whole trial, across all subjects, and that is not quite correct.

There is a change if you look at the average over the blind period, and not just visit 6, so visit 6 represents only one small piece of the whole trial, and it would seem to me that if you want to look at the whole trial, you take the average of the median--I don't care which it is, but you take some kind of a summary statistic for the whole period, not just one particular visit.

So, that is the only point I was trying to make.

DR. ANDERSON: You have something related to this?

DR. WOLFE: Just on that point. The same Table 2. What I was referring to is walking speed on drug average, which is the average across the whole study, and there the placebo was 2.37 and the fampridine was 2.41. This is what I was referring to, not the change again, the absolute walking speed over the whole study for the two groups, not different at all.

DR. TEMPLE: I had addressed that before. If you look at change from baseline, you get one set of values. If

you look at absolute walking speed, you get quite a different value, and it is hard to change a number in the 6 and 7. It is easier to reduce it a little bit and show the difference.

DR. VAN BELLE: Let me just add one point of clarification. This is one reason that I asked the FDA to tell me earlier, a couple weeks ago, what was the primary endpoint because the primary endpoint is the one that presumably the FDA and the sponsor agreed to, and I was told that there were really three primary endpoints. But the primary primary endpoint was the change in walking speed from baseline. It was not the average walking speed on treatment.

So, I think that from the point of view for settling here whether or not there is a treatment effect, I think the appropriate measure is the change in walking speed from baseline.

DR. ANDERSON: That is not really the primary primary, right?

DR. KATZ: The primary outcome was the responder

rate. The responder rate, it is a complicated definition but it depends upon the differences between on treatment, walking test, and the fastest off treatment.

It is clearly dependent upon the results of the walking speed, but the primary endpoint is the responder rate as it has been defined.

DR. VAN BELLE: You are right. Thanks.

DR. ANDERSON: Since we have heard at least some discussion as to what constitutes an improvement in walking between Dr. Wolfe and myself, those who are most directly involved in the care of MS patients with us today, and I think they do but I don't want to omit anyone on this side, maybe you would offer an opinion--I am sort of thinking out loud--on this question of whether you feel sort of the issue of a substantial evidence of effectiveness as in a treatment to improve walking, what your thoughts are.

Dr. Brass, how about you?

DR. BRASS: Overall, there are a lot of medications that we use in MS that may not respond in every single case. Even for the disease-modifying therapies, there

is a large percentage of patients who don't respond, and we still have them available to our patients, and we still use them.

What I was looking at is for the first question, whether there was evidence of effectiveness, and based on the response rate, I would say yes, the answer is yes.

In terms of the clinically meaningful response, looking more towards the responder, the group who did respond, the sponsor did show evidence that there was a response in the responder group.

When you are looking, however, at the absolute value for the whole study, there was not a significant change in the absolute walking speed prior in the baseline versus the follow up.

It is a little conflicting, but when you focus in just on the responder rate, there is a little more meat there.

DR. ANDERSON: Dr. Yeh, do you want to weigh in on this?

DR. YEH: I feel that grouping the patients into

responders and non-responders is a helpful way as a clinician for me to understand these data because, as Dr. Brass said, we have many patients, and it seems like in anything that we do, a third will respond and two-thirds won't.

Having that as part of the definition, as a clinician evaluating these studies, it is helpful to me because I then understand that there are some patients that I can say--and I would define that as effective--that the medication is effective for, so I would be prepared to look at the data in the way that the company has produced the data in evaluating the responders as a special subgroup.

DR. ANDERSON: Thank you. Dr. Goldman, how about this issue that Dr. Wolfe raises, as an MS person, do you have any opinion on this fact that there is no significant difference between walking speed on drug average between placebo and fampridine?

DR. GOLDMAN: Yes. I think that what we know about multiple sclerosis is that the underlying pathology varies from person to person, and some patients have a

demyelinating predominance and some patients have axonal injury, and, of course, there is a lot of overlap.

But the drug requires a substrate of axonal integrity. So. for patients with axonal injury or loss, you know, permanent axonal loss, it makes sense that there would be some percentage of the population that wouldn't respond because they don't have the substrate necessary for the drug to be effective.

I think that it doesn't surprise me that when you take the population as a whole, you may not see an average benefit because that population includes people who don't actually have the substrate required for the drug to be effective, meaning axonal integrity. That is taken on a microscopic level but, conceptually, that is how I would think about it.

I wanted to add as a clinician, my experience, which was touched on in the testimonies, which is that understanding the cognitive clinical meaningfulness is I think difficult and somewhat elusive, although I think that Dr. Hobart did an excellent job defining it, using the MS

Walking Scale.

But I think that one thing to bring forward and think about is what is the risk tolerance, what is the tradeoff here, and the relative risk, although we have identified it, I think is small relative to the potential benefit for a subset of the people, and how do we weigh that in thinking about our decision. I just wanted to bring that forward, as well.

DR. ANDERSON: Dr. Morrato, do you want to enter in on this?

DR. MORRATO: I very much appreciate the clinical view. I guess I just wanted to add that as I am interpreting substantial, that is sort of the operative word for me. Substantial evidence would be if we had seen strong effect in both the responder and non-responder group, as well as in the drug versus placebo, and that you are looking at the totality of evidence, and that they all hang together very strongly and clearly.

So, my vote is going to reflect that, not necessarily that it is not statistically significant in

areas, or that it is not having a significant response in some subpopulations, but that substantial is sort of reflecting the totality of evidence.

DR. ANDERSON: Dr. Fountain, did you still have a comment you wanted to enter in here?

DR. FOUNTAIN: I was just going to reflect what Dr. van Belle said, that statistically, a lot of the other measures, the post hoc analyses were actually statistically significant among ways that at least I would typically think about in terms of change from baseline as opposed to change in absolute value.

DR. ANDERSON: Dr. Katz.

DR. KATZ: I just want one clarifying point about the word substantial. We use the word substantial because substantial evidence of effectiveness is the standard in law as articulated in the statute, the federal Food, Drug, and Cosmetic Act, of what is necessary for determining effectiveness, or it's the sine qua non for drug approval.

So, substantial in this context isn't intended necessarily to mean the preponderance of the data, in fact,

it specifically isn't the preponderance, and it doesn't really speak necessarily to treatment effect size. It is defined as evidence from adequate and well-controlled clinical investigations.

So, that is what that word means. You can I guess interpret it how you like, but the word is there, not specifically to talk about or describe preponderance of the evidence, it is a term of law, and it is defined as evidence from adequate and well-controlled clinical investigations.

DR. TEMPLE: It doesn't refer to the effect size and whether you think it is large enough. We have questions that follow on that. It is also in legal terms not a particularly high standard. But that is another story.

But it really means do you think that there are two studies that show an effect. That is really how we translate it. Then, you get to whether you think the effect is worth it. Different question.

DR. ANDERSON: Before we vote on this first question, are there others who would like to weigh in with a comment or an argument? Dr. Stuve?

DR. STUVE: Yes. I would say yes, I think the sponsor has shown evidence --

DR. ANDERSON: I want to make sure you are just offering a comment, you are not voting at this point.

DR. STUVE: No, no, I know, I wasn't saying yes. I think the responder rate was higher in the treatment group than in the placebo group. In clinical practice, I think all patients are going to be treated with this drug, and I think that is what we do with all other drugs that are currently approved. We treat responders and non-responders.

I think as a clinician who sees them as patients, obviously, I think I would feel more comfortable if there was some sort of algorithm that very early on identifies people who respond to this drug versus people who don't respond to this drug, so that I don't have to treat 65 percent of my patients who really will only be exposed to the side effects of this drug.

So, I think that is how I feel about it. The word substantial, I think that is obviously very hard to grasp with the data I think that we have available.

DR. ANDERSON: Thank you. If there are no further comments on this question, we will vote and everyone is required to vote. You will have to vote Yes, No, or you have to actually hit the Abstain button if you feel that you can't reach a Yes or No question on this.

Because we have a remote attendee, those of us who are present will in a moment push our buttons for Yes, No, or Abstain. Once all of those have been logged in, we will have Dr. Stuve verbally state his vote, and then our manually entered votes, the summary will be displayed on the screen, and then we have to go around the table and each confirm that our vote was accurately reflected and pass around.

At this point, let me re-read the question and then at that point, if everyone would please enter in their response.

Has the sponsor demonstrated substantial evidence of effectiveness of fampridine as a treatment to improve walking in patients with multiple sclerosis?

[Electronic voting.]

DR. ANDERSON: We are waiting on two more votes.

LCDR NGO: Dr. Stuve, can you please state your vote?

DR. STUVE: Yes.

DR. ANDERSON: The voting results are 12 Yes, 1 No, and zero abstentions.

Now, we will just go around in the same order we did before. Our first voting member is Dr. Todd. Basically, you just state your vote so they make sure it is entered correct. Your name and your vote, please.

DR. TODD: Dr. Todd. Yes, that is correct.

DR. FOUNTAIN: Nathan Fountain. Yes.

DR. VAN BELLE: Gerald van Belle. Yes.

DR. GOLDMAN: Myla Goldman. Yes.

DR. YEH: Ann Yeh. Yes.

DR. BRASS: Steven Brass. Yes.

DR. ANDERSON: Britt Anderson. Yes.

DR. GREEN: Mark Green. Yes.

MS. SITCOV: Cynthia Sitcov. Yes.

DR. WOLFE: Sid Wolfe. No.

DR. MORRATO: Elaine Morrato. Yes.

DR. RUDNICKI: Stacy Rudnicki: Yes.

DR. ANDERSON: Since we did vote Yes on that question, we move on to consideration of Question 1(a), which reads: If yes, has the sponsor demonstrated that this effect is clinically meaningful, either in the group of fampridine-treated patients as a whole, or in a specific subset?

Is there anyone who would like to weigh in whether the effect that they voted Yes for is actually a clinically meaningful effect?

DR. BRASS: Clarify the question. If we thought it was only clinically meaningful in the subset, but not as a whole, how would you approach that?

DR. ANDERSON: The way I would read this is since it is an "or," is if either one of those two clauses is something that you would Yes for, then, you would vote Yes.

I will take a stand on this. My own opinion is an argument that I tried to state before, but I guess I didn't do it clearly, and I haven't really heard enunciated

extensively, which is that if I had any measure regardless of what it was, that I showed in the heterogeneous group of patients correlated with their personal estimate of subjective doing better or doing well, then, I could use that measure as a proxy in a subsequent trial for clinically meaningful effectiveness, if it was something that the patients themselves rated as having given them subjective improvement.

Although the way it was intertwined together in the study, it seems to me like the responder definition has that benefit because, if you take all responders regardless of whether they are placebo patients or treatment patients, and you look at those who meet this classification of responder, you see a significantly better subjective SGCI global clinical impression than you do in the non-responder category.

So, to me that says that if you are a responder, you feel like you are doing better, therefore, that designation asserts to something that is clinically meaningful, and then as a subsequent observation, you see

that there is a greater proportion of those subjects in or participants in the treated group. So, for me personally, that establishes clinically meaningfulness more directly than some of the other discussions we have had today.

But I would actively solicit a rejection of that point of view. I mean you didn't feel that it had any effectiveness, so maybe you could rebut that.

DR. WOLFE: Well, I am really going with FDA's own interpretation of these other ancillary studies, and where they said that the effect size was very small, whether they were talking about the MSWS score or the LAMMT or the subject global impression.

I mean in each of those cases there was a change, but it was very, very small when compared with the size of the scale, so that, aside from the vote on the first thing, 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 it.

Again, this is tempered by the fact that over the course of the study, there was no difference in the walking

speed and, in all, maybe but one of these other measures, there was a very, very small effect size.

So, those are my thoughts as to why I wouldn't think that there is--it's clinically important to say nothing of the risk issue, because it is clinically important isn't limited just to efficacy. I mean the focus has been--and the FDA's discussion this morning was just on the seizures, but there are a number of fairly commonly occurring and in most cases, statistically significant higher rates of balance disorder, insomnia, dizziness, and other things that can be very troubling to patients.

So, ever if those don't rise to the level of a seizure, those are on the down side, and they are things that would presumably be experienced by people including the two-thirds who don't benefit at all, and we do have this problem of not being able to evaluate at the beginning of the study who are going to be the responders and if one looks at the average walking speed, not even into the study.

I mean the definition of responder can be made as the company showed in their slide. But from the clinician's

perspective, unless you have done four measurements before the drug, and so forth, it is not going to easily be able to determine. So, these average effects take on even greater proportion since two-thirds of the people who get them are not going to have any benefit.

So that to me is the larger clinical picture that brings in adverse effects and brings in the fact that aside from no difference in the walking speed, at the end or on the average during the study, you don't have other patient-oriented measures that seem to be importantly in the right direction in terms of clinical improvement.

DR. ANDERSON: Ms. Sitcov.

MS. SITCOV: In that regard, in terms of the two-thirds that don't respond versus the third that does respond, the interferons, and some of the other MS drugs, we are seeing the same kind of response rate, which is maybe a third, yet, there is a great need that is being met.

As one of the folks testifying pointed out, said something very important, and that was--I believe she said she was not seeing any results with any of the approved

disease modifiers, yet, she was seeing great results with this drug. So, I think the fact that it is only a third, that shouldn't be discounted.

DR. ANDERSON: We will get the dynamic duo over there, we will get first Dr. van Belle and then Dr. Fountain.

DR. VAN BELLE: If I had to vote on clinical effectiveness, I would either abstain or vote No for the same reason that Dr. Wolfe said.

DR. FOUNTAIN: I think the way we would present this to patients, if I interpret it right, which is very difficult to interpret, that I would say, well, do you want to try to taking this drug. You have a 1 in 3 chance of improving your walking speed by 30 percent, and you have got some small chance if you take too much of it, of having a seizure.

I think that is probably the ultimate risk/benefit that each person would have to decide about, and I suppose ours is the larger perspective as is it appropriate for us to present the patient with that risk/benefit ratio, if I

interpret it right.

Or if you don't like the responder rate, you would say, well, then, you have got a chance of an average improvement of 21 percent increase in your speed, and you can decide if that is important or not.

I think for the patients I have with MS anyway, if I said you had a 1 in 3 chance of improving your walking speed by 30 percent, or if I said, well, some people respond, some don't, and the average improvement is 21 percent increase in walking speed. I think they would all say yes, and I think if I projected myself to that situation, I would probably say yes, all presupposed on the idea that the risk of seizure doesn't appear to be substantially increased when you take it properly.

DR. ANDERSON: Dr. Katz.

DR. KATZ: Just one clarification. Our documents were intended to make certain observations and to raise questions that we think are important to answer. No one should read them to mean that we have reached a conclusion about how small the effect is or anything like that.

People can certainly take into consideration the questions we have raised, the data we have presented and the way we presented it, but it shouldn't be taken to mean that we have in any way taken a position on what the answers should be.

DR. ANDERSON: Duly noted and I would say you got some good questions from your analyses.

Dr. Temple.

DR. TEMPLE: As I indicated before, I like dichotomized data and I was interested in what Dr. van Belle said. If you look at their Slide No. 80, the company slide 80, that is the distribution of walking speed effects.

If you look at the greater than 20 percent, which I guess most people seem to think, I mean I have no knowledge of this, most people seem to think is a meaningful thing. It is 31 percent versus 13 percent. That's another way of looking at the overall data.

I just wondered if people had views on that. You know, to the person who knows very little about MS, that doesn't look so bad. Is that meaningless? That's the

fraction of people that had a 20 percent improvement in walking. It's not the same as the average in the whole group. It's different.

DR. TEMPLE: You can do the same thing on 30 percent.

DR. ANDERSON: If you can see this, Dr. Stuve, maybe you could give us your impression as to that. Looking at the greater than 20 percent column, there is a 31.5 percent versus 13.1 percent difference between the fampridine and placebo. Is that something you think is clinically meaningful?

DR. STUVE: To me, it certainly does look meaningful in that subgroup of patients. I think I would refer to Dr. Goldman. I think she is really probably the world expert on this outcome measure, and she stated earlier that if it is greater than 20 percent improvement that this is significant. It looks very significant to me.

DR. ANDERSON: Dr. Goldman.

DR. GOLDMAN: I wanted to expand on that because actually I think that Dr. Brass's point was important. I

was thinking about this, and I think this speaks to his issue directly, which is that I think about timed 25-foot walk as time and that is how I do it every day.

But the data that I was speaking about is the preponderance of it, and I don't have all the articles available here, but it is in time. My opinion about whether or not this is meaningful is different from some of the data that would be available as regards to its meaning specifically with a cutoff point of 20 percent.

That was the point that you were making, and I was hoping--mathematically, I tried to sort of extrapolate what that would be time versus speed. And we know that they are related, but they are not directly proportional, and the change in time is probably different looking at the population.

You have got a wide range of time here. So, I am not sure. I think that this is sort of a spin on how we traditionally think about it. That makes it a little bit more challenging.

DR. ANDERSON: If you have exactly this data for

time, then, we would like to see it. But if we are going to get another mini-presentation, then, you can just tell us you don't have it.

DR. BLIGHT: Hopefully, not a mini-presentation. But people do get very tangled up and, even having worked with it for a long time, I get tangled up with speed and time changes.

The issue is that most of the literature on 20 percent has been derived from progression of disease gecause no one has something that improves walking speed up to this point. Most of the literature deals with time.

The curiosity is that a 20 percent reduction, I would say increase in time, which is disease getting worse, is equivalent to a 20 percent improvement in someone who is getting better. But a 20 percent worsening in time is actually like a 16.6 percent worsening in speed. But most of the literature relates to worsening. Ours relates to improvement.

In that case, they are both 20 percent because, if your time goes up by 20 percent, then, if you go back to

where you started, your speed has improved by 20 percent. So, it's very confusing, but it's very symmetrical in that way.

DR. GOLDMAN: It is confusing and my math during the break--and I am not a mathematician by any measure--was a little different, it wasn't 16.6 percent depending on how you look at it. But I think that the other important thing about 20 percent is not worsening but it's figuring out what is noise in the measure and what is clinically meaningful.

I think that was where I was trying to go with that cutoff in terms of how we think about it, and I think that is what we as a community are struggling with in using the measure in terms of time is what is noise and what is really changed in progression. I see your point here in regard to improvement.

But I think that is clinically meaningful, I mean based on the other data, as well. So I don't want to challenge that point.

DR. ANDERSON: Dr. Morrato.

DR. MORRATO: I am envisioning that that graph

might make it on advertising material and so, with that in mind, I think it would be useful to also be quoting absolute rates, and not just the relative rates, so that people can say these are patients that were starting at about 10 to 11 seconds taking to do the 25-foot walk and, therefore, these kinds of benefits you can expect to carve off maybe 2 to 3 seconds from that so that we are not all just focusing on the percentile.

DR. ANDERSON: You can just ask a procedural question.

DR. GOLDMAN: Do we have time data?

DR. ANDERSON: Does that same exact slide exist with absolute time as opposed to percentage?

DR. BLIGHT: The problem with using absolute values of time or speed is that the baselines differ, so people are different at baseline. So what is important to somebody who walks the timed 25-foot walk in 8 seconds is not the same as what is important if somebody walks at 45 seconds.

However, the effects appear to be similar in

percentage terms across that range of disability, which makes it reasonable to talk about percent because, if I say 2 seconds, you don't know whether that is someone who takes 8 seconds or 45 seconds. So, it is very difficult to do it that way, which is why we stayed away as much as possible from presenting absolute values because they are not referenced to the baseline.

DR. ANDERSON: Yes, please.

DR. MORRATO: I just wanted to add I mean it would be useful. I understand your point, but you could stratify based on where the baseline risk is, such that there you are grouping 8 to 10 second people together or whatever is the right clinical cut points versus the upper and then looking at the response in those I think might be helpful.

DR. ANDERSON: Can I call the question? Okay. We are going to vote on this question and then we will take a break. Let me re-read the question. Oh, this is not a voting question so, basically, I am going to give a summary of the discussion.

Those who did not feel that there was

demonstration of effectiveness, didn't feel that there was a clinical meaningful effect, and the basis for that put a great deal of emphasis on looking at treated and untreated groups as a whole, and using the omnibus measure of walking speed and the lack of difference between walking speed on drug and off drug as the basis for that decision.

Some people used the proportion of responders and prior demonstration of responder subjective impressions and others put a great deal of emphasis on the proportion changes in walking speed or walking time and trying to reach their conclusion as to the clinical meaningfulness of the effect.

Do people feel their opinions were misstated? Okay. In that case, we will take a 15-minute break at this point and then reconvene for the remaining questions.

[Break.]

DR. ANDERSON: We will begin our discussion of the next question, which is a voting question, so let me read it to begin and then we will go from there.

Question No. 2 reads: If yes to Question No. 1,

should the sponsor be required to evaluate the effects of doses lower than 10 mg twice daily (b.i.d.)? Dr. Green.

DR. GREEN: Again, as I said earlier, I am concerned about the renal disease issue because, fundamentally, the doses that people obtain even with mild renal insufficiency approximate the dose that even the sponsor discarded as a trial dose.

So, I think that a 5 b.i.d. should be available at some point or at least be studied very closely.

DR. ANDERSON: Dr. Wolfe.

DR. WOLFE: I think the question means--you are talking about the availability of a 5 mg pill, and the company said--I don't know what the reasons are, they probably do--that there was a formulation problem where you weren't able to get 5 mg in the pill, so that it was available. I don't know what it was, but that is a different issue.

I think what we are being asked, and it is important, too, that we are being asked should the sponsor be required to show that it actually works at a lower dose.

Just repeating a little bit what I said this morning, there were comments by a number of FDA people that because there was really a flat dose-response curve in the dosages of 10, 15, and 20, they thought that since there is a very sharp dose-response curve in terms of adverse effects, that you should go down lower.

The answer from the sponsor was that curve showing that when you started getting down to 15, 17, whatever it was, nanograms, blood concentration, there was a fallout, but those 15, 17 nanograms correspond to a dose much lower than just 10 mg.

So it may be if there is an effect, again, I have questioned that enough times, it may be that the effect doesn't start going down until 5 or below, and the company agreed we have no data, no randomized controlled trials looking at 5 mg.

I think to the extent that both the seizure risk goes down (a) and (b), these common adverse effects, which can be very troubling particularly to people who have multiple sclerosis, are also going to go down because they

all appear to be very dose related.

So, I think that from the standpoint of increasing the benefit/risk ratio by, for instance, having a dose that is just as effective, 5 as 10, but reducing the risk in half, that really is necessary, and I think the FDA hinted that that would be a good idea to have before approval a trial on 5 mg b.i.d.

DR. ANDERSON: Dr. Katz.

DR. KATZ: Again, just to clarify. I think largely we agree with Dr. Wolfe's formulation of the issue. I think what we are trying to get at here is whether or not the group thinks that the 10 mg--let me back up--first of all, it's pretty clear there is no dose-response at doses higher than 10, so it, of course, begs the question what about doses lower.

The underpinnings for this question are the risks. One clarification. I am not sure that anywhere have we intimated or concluded that if this is to be done, it should be done prior to approval. Again, we are just raising the question.

I will tell you what I am particularly interested in, and it has been sort of stated already. If we look at the experience at 15 mg b.i.d., which, of course, is not much greater than 10, at 15 mg b.i.d., the percent of seizures is I think 1.4 percent, more or less, the way we calculated, and the rate is somewhere around 1.7 per 100,000 per 100 patient years.

If you compare it to the estimates of the background seizure rate in MS patients, which I am not sure one can make this comparison. But it has been discussed. I think the highest rate per 100 patient years in the literature is about 0.3 something.

So, at 1.7 per 100 patient years, at 15 mg b.i.d., that is about 5 times the highest background rate. Again, these are patients who were screened with EEG as opposed to the patients who were described in the literature who as far as we know weren't.

So, it appears to us that at 15 mg b.i.d., which is not that much higher than 10 b.i.d., there is a possibility that there is an increased seizure rate.

We have already heard that with mild renal impairment, and we don't really know in the population how many patients would qualify, in the background population of MS patients how many would qualify as meeting those criteria.

There are about 80 or so patients of mild, moderate, and severe in the database, but with mild renal impairment. The Cmax's that you would get at 10 b.i.d., we have already heard, is about 15 or maybe somewhere between 15 and 20 b.i.d.

The question really is one of what we really want discussion about do people think that we either know enough to say that there is or isn't likely to be significant overlap at 10 b.i.d. in many patients with levels that you achieve at 15 b.i.d., which looks like there is an increased rate of seizures.

That is the issue we are trying to get at here. So, therefore, do we really need to know whether or not the drug works at lower levels so that there is a greater distance between the exposures that might be effective and

the exposures associated with seizure. That is really the background for this question.

DR. TEMPLE: I just wanted to add one thing, that the single problem of what to do with people with poor renal function, we would ordinarily--I don't know whether there would be an exception here--we would ordinarily just cut the dose for those people without further data.

So, Rusty's question is really the rest of the population, which is closer than he would like to the 15 mg level.

DR. ANDERSON: Dr. Fountain.

DR. FOUNTAIN: I was thinking about it just that way, about the levels, and I believe what we saw is that not only were the mean levels different, but that Cmax and Cmins across the dose levels we saw didn't overlap. Sort of surprising; the confidence intervals didn't overlap at all.

But, of course, they are wide enough that they are well within the rates at which we think maybe there is some increased possibility of seizure risk.

So, I would just say it only sort of makes sense

to study at a lower dose in hopes you would avoid the possibility of seizure risk for those who intentionally or accidentally took higher doses than you would intend.

So, it seems to me it only makes sense to study it at a lower dose since we don't know what the lower dose--maybe it's linear between 1 and 10 mg, and so 5 is good. Maybe 1 is good because it is an absolute effect possibly.

It seems like that makes sense to me, whether or not it is before or after approval I think is a separate question.

DR. ANDERSON: I am going to go ahead and make a comment, and then I will get you, Dr. Wolfe.

DR. WOLFE: Just responding to what Dr. Katz just said, in this figure 6 in the FDA presentation about distribution of Cmax, the reason they put that in there is there clearly is an overlap in the Cmax between the 10 and the 15, and one of the seizures occurred at a level that isn't out of the range of possibility for the 10.

I think that is one of the reasons you put it in there, but your own reviewer said explicitly why aren't

there studies at a lower dose. I mean they are two different things that are being raised here.

Again, yes, they didn't say whether it should be before or after approval. But, in at least two or three times in the documents that were mailed to us, they said, given that there is a flat dose-response curve, given that the risk goes down, they don't understand why hasn't it been studied at a lower dose.

DR. KATZ: I was specifically referring to the conclusion that it should be studied before or after. I mean that was the question. But yes, the question, you look at the means, there is no overlap in the means, but there clearly is a distribution, and there are going to be some people at 10, whether it is because they have mild renal impairment or just because they do, they are going to have Cmax's that get into the range of what you would see with 15 or maybe 20. And the question is do you think we have enough comfort at 10 given all of those vagaries to say 10 is okay at least for the moment.

DR. ANDERSON: It would seem that although you

keep saying whether it is done before or after doesn't matter. But, since 2(a) says if yes, should this be required prior to approval, there seems to be an explicit statement that it should be debated whether it should come before or after if it's necessary.

I guess when I looked at the 10, 15, 20 sort of flat lined in terms of the responder ratio--but we know that the serum levels are going up across that, it wasn't clear that there was a very predictable relationship between the serum level and the proportion of the responder population, and therefore, it seemed a little bit optimistic to assume that if you went in the lower direction, that the fact that serum levels were falling would mean that you would lose therapeutic efficacy.

So, it certainly seems reasonable to suppose that there may be a dose less than 10, which provides clinical therapeutic effectiveness by the responder definition and which presumably would offer greater safety from seizures, and that would be a good thing to know about, I think.

DR. TEMPLE: The population PK data they showed

suggested that if you go low enough, you will maybe lose some effectiveness. But another question is whether you really have to be effective for the whole dosing interval. It might be that in return for a lower risk, you might be willing to have it not be as effective for the last hour or so. You won't know that until you study it.

DR. ANDERSON: You don't necessarily need to have a great deal of benefit when you are sleeping either. There may be terms in terms of dosing frequency and times and things that would also be relevant questions for how you might be able to get by with less and get similar therapeutic effectiveness and things that seem like they would be good to know.

Ms. Sitcov?

MS. SITCOV: I guess I wasn't certain whether it would be possible to vote Yes on this, but that it could be approved at 10, but that the FDA, if you were to approve it, would then take it up at a lower dose at another time. I just needed a clarification on that.

DR. KATZ: If you think it should be studied,

then, the answer to the first question is yes, and if you do, yes, that is what 2(a) is.

MS. SITCOV: I didn't see 2(a) before.

DR. TEMPLE: Just to be clear, it is not uncommon to approve drugs with a requirement that further doses be studied. That happens all the time.

DR. ANDERSON: A person could vote that they think lower doses should be studied. They could then make an independent decision as to whether that should be required pre- or post-approval, and as a matter of history, it is not infrequently done or it is done that drugs are approved with a requirement for additional studies at lower doses.

With that as background, Dr. Goldman.

DR. GOLDMAN: In anticipation of having to answer Question 2(a), would it be possible to just get a brief idea of what the logistical barriers would be to doing this, and what the timeline would be to delaying it if it was contingent on approval?

DR. ANDERSON: I guess I just want to make the logistical barrier question more concrete.

DR. GOLDMAN: There was a comment about some issues with the sustained release being difficult for smaller doses, I mean actually making the tablets, if I understood the issue.

DR. ANDERSON: We would want to know that if a lower dose study were required, would it even be technically possible to do so in terms of having an available medication.

DR. GOLDMAN: Correct, and how long would it take before we had that information if the approval of the 10 mg dose became contingent on doing lower dose studies, is it going to be another year, another 3 years? What are we looking at?

DR. ANDERSON: Dr. Cohen, could you tell us if it were possible at the present time to do studies at lower doses, and if not, what your best estimate is for when it might be possible to do such, to have a formulation available?

DR. COHEN: We have been working with Elan on a 5 mg formulation. We have not yet begun work on a 7.5, for

example. That certainly could be done. Once a formulation is developed and initial testing is done to ensure that it has a chance of being approvable, commercially viable, that has to be put up on stability testing.

Typically, you like to see a minimum of 2 year stability for something that will be commercially viable, that you can sort of put out there within the system and makes sure it isn't going bad on the shelf on a regular basis. So, you need to do those tests.

There is an accelerated stability phase which takes the first cut at that is at 6 months, and then every several months after that there are additional cuts. But, ultimately, you need to get the 2 year, and then hopefully, beyond that, 3 year, but a minimum of 2 years.

We have a current, I am told--I just checked yesterday with our manufacturing group--we have a current formulation that has just gone up on stability testing.

What that implies is that we won't know for sure for two years. We could begin to do testing within the next six months to a year. But then, if it failed along the way,

we would pretty much be back at square one. So, there are unknowns, but that is just drug development.

The bottom line I guess is that optimistically, let's say 2, 3 years we could test it and have it submitted. You are out at about 3 years if everything goes well.

DR. TEMPLE: But that all depends on how different it is from the current formulation and a whole bunch of other things like that. It doesn't always take that long.

The other thing is you can start doing testing well before the two years of stability have elapsed, or even 6 months. People do that all the time.

DR. COHEN: I think I mentioned that, but I want to make sure that everyone heard it or that I said it correctly. Absolutely, we can begin to test as early as 6 months. The issue then becomes just hoping that everything turns out well with that formulation so that we don't have to go back and tweak it later.

DR. TEMPLE: There are also, I should note, various ways to do the studies we are talking about. We were shnoozing about this a little at lunch, a kind of study

design I like is to take the people who have responded and then randomize them to the dose they were on and the two lower doses and placebo, a randomized withdrawal study.

It is done in responders. So you expect to not need as many patients as you might have otherwise, and they show data that show that responders drop down to where they were before. That is a very efficient study design, and the patients already exist, they are all the people on the follow-on exam.

So, we would have to talk about that, but it might not take so long.

DR. ANDERSON: Do other people have comments, questions or statements they want to make regarding Question 2 before we vote on it?

How about Dr. Stuve, would you like to weigh in at all before we vote?

DR. STUVE: I don't have really any very significant additional comments. I think the PK data, as others have said, I think they suggested a lower dose may work. As a clinician, you know, you are always a little bit

nervous with a drug that has a very narrow therapeutic index.

I think many patients, when they perceive that a drug works for them, don't necessarily adhere to the dose that they are being prescribed. So I think, for those reasons, I think it would make sense to test lower doses as others have said.

At this point, I will read the question one more time and then everyone will have to push their Yes, No, or Abstain button, and then we will solicit after that, we will ask for Dr. Stuve's verbal vote, and then we will go around the table.

At this point, please vote Yes, No, or Abstain to the following question: If yes, to Question No. 1, should the sponsor be required to evaluate the effects of doses lower than 10 mg twice daily b.i.d.?

[Electronic voting.]

LCDR NGO: Dr. Stuve?

DR. STUVE: For Question 2, Yes, and Question 2(a) Yes.

LCDR NGO: We are not voting on Question 2(a) yet, sir.

DR. STUVE: Okay. Then, just Yes.

DR. ANDERSON: The results are 12 voting Yes, 1 voting No, zero abstentions.

I guess we go to the display, and if we could have people go around and confirm their vote starting with Dr. Todd.

DR. TODD: Jason Todd. Yes.

DR. FOUNTAIN: Nathan Fountain. Yes.

DR. VAN BELLE: Gerald van Belle. Yes.

DR. GOLDMAN: Myla Goldman. Yes.

DR. YEH: Ann Yeh. Yes.

DR. BRASS: Steven Brass. Yes.

DR. ANDERSON: Britt Anderson. Yes.

DR. GREEN: Mark Green. Yes.

MS. SITCOV: Cynthia Sitcov. No.

DR. WOLFE: Sid Wolfe. Yes.

DR. MORRATO: Elaine Morrato. Yes.

DR. RUDNICKI: Stacy Rudnicki. Yes.

DR. ANDERSON: Okay. Following Dr. Stuve's lead, do we need further discussion in order for people to feel comfortable voting to Question 2(a)? Dr. Morrato.

DR. MORRATO: I guess since I am considering this, I think one of the public speakers was mentioning that there is an inherent risk with the active, and there is data that suggest that risk goes up on seizure--for example, as you go to higher doses. But we are kind of assuming if you go to lower, therefore, the seizure risk will go less.

As I am weighing, do you wait a couple of years or a year or what have you, six months, whatever the right time is? We don't really have good evidence that would suggest that by waiting, you are necessarily going to get a benefit by that waiting and the development of a lower dose.

I think that hasn't been discussed, that there is an inherent risk in the active and we know people are going to be using higher doses out there, and while it might be nice to have a lower dose, I don't know if it's needed to be marketed.

DR. ANDERSON: Does anyone else want to weigh in

on this question or respond?

[No response.]

DR. ANDERSON: We will move to the voting on Question 2(a), which you will have to enter Yes, No, or Abstain to the following question: If Yes, should this be required prior to approval?

[Electronic voting.]

LCDR NGO: Dr. Stuve, your vote, please.

DR. STUVE: Yes.

LCDR NGO: Was that a yes, sir?

DR. STUVE: Yes.

LCDR NGO: If you can vote for Yes, No, or Abstain?

DR. STUVE: I vote Yes.

LCDR NGO: Thank you, sir.

DR. ANDERSON: The results are 2 voting Yes, 10 voting No, zero abstentions.

Dr. Todd, can you lead us off again, please.

DR. TODD: Jason Todd. No.

DR. FOUNTAIN: Nathan Fountain. No.

DR. VAN BELLE: Gerald van Belle. No.

DR. GOLDMAN: Myla Goldman. No.

DR. YEH: Ann Yeh. No.

DR. BRASS: Steven Brass. No.

DR. ANDERSON: Britt Anderson. No.

DR. GREEN: Mark Green. No.

MS. SITCOV: No.

DR. WOLFE: Sid Wolfe. Yes.

DR. MORRATO: Elaine Morrato. No.

DR. RUDNICKI: Stacy Rudnicki: No.

DR. ANDERSON: So, that is Question No. 2. So, now we are down to Question No. 3, which has two parts, a voting part and a discussion portion.

The first portion of Question 3 reads: If substantial evidence of a clinically meaningful effect has been demonstrated, do you conclude that there are conditions under which fampridine could be considered safe in use for this indication?

This is the issue of risk versus benefit. Thank you, Dr. Wolfe.

DR. WOLFE: This is from a paper published about two weeks ago in something called Expert Opinion in Pharmacotherapy. The author is one of the investigators for the company, and said, in the disclosure that he is a consultant. I just want to read two sentences from here because I think they bear very greatly on this issue.

"There will probably be an enthusiastic swell of new prescriptions for fampridine-SR after its licensing. Depending on how the indication approved by the FDA is written, it is probable that much of the drug's prescriptions will be written for ostensibly off-label uses."

It goes on to say that it is only realistic to predict a significant amount of off-label experimentation, and in his own clinic, UFC, he would estimate that three-quarters of the people in his clinic would want this drug.

What they are discussing is uses other than the one approved, and then in the same paper, they discuss the idea that many patients may be used to judging whether they are getting better on their own, which is sort of patient

oriented off-label use, and it says, "A perceived direct dose-related effect benefit of fampridine in ameliorating MS symptom increases the potential for toxicity. Patients will do self-adjustment. Patients may sneak one of two extra pills."

Again, this drug has a very narrow therapeutic index whether one is talking about seizures or the other adverse effects. So I am very concerned about one of the investigators, a consultant to the company, basically saying there is going to be a massive amount of off-label use.

An off-label use for a drug means that people will be using it either at doses or for conditions for which we don't have substantial evidence of benefit outweighing the risk.

I am just throwing this out. This is not my words, it's one of the investigators for this company.

DR. ANDERSON: I guess it might be good if we had sort of the exact reference so that others--if they wanted to refer to this.

DR. WOLFE: It is Expert Opinion in

Pharmacotherapy 2009, Volume 10, pages 2025 through 2036, and the author is Norman Kachuck. Is that how you pronounce his name?

DR. ANDERSON: They may or may not know, but let me ask you a question. As important as off-label use is, and the misuse of medicines is, is it really directly--let me rephrase that.

How does that influence your opinion for somebody who, like myself, feels that there is a clinical benefit for this, about whether it should be considered there is an indication for which it should be considered safe for use?

I have knowledge that people may misuse the drug. People missed a dose, they took a double dose, and they had a seizure. We heard about that. Or I may have someone who for whatever reason wants to get it for resale or something. So that is a concern, but that seems to me slightly different from whether I believe there is an indication for which there is a risk/benefit benefit for its use.

Do you feel that that is--I mean as important an issue as it is--really directly addresses what we are asked

here?

DR. WOLFE: I mean the question as is are there conditions under which it could be considered safe, and the only point I am making is that even if you think that there may be these conditions, the real world at least as articulated by this person, and I suspect other people, is that people will self-administer higher doses within narrow therapeutic indexes. Doctors will prescribe off-label. It sounds like this person thinks that most of the prescribing is going to be off-label.

That is sort of the reality. I mean we know that for a lot of drugs, there is off-label prescription, in some cases it is 10 percent of the prescriptions; for neurontin, it was 90 percent of the prescriptions were off-label for things for which there wasn't evidence of benefit outweighing risk.

So, this is a concern I am raising in terms of a discussion about conditions for safe use.

DR. ANDERSON: Dr. Temple.

DR. TEMPLE: Sid, apart from people taking excess

doses, did you get any sense of what other off-label uses he had in mind? We can read this eventually, but--

DR. WOLFE: I mean they were talking about it for other conditions. Amongst the other things described, there were things other than walking. The idea might be that if it improves this, it might improve something else.

The self-administering a higher dose because it didn't work was at the patient level, but the off-label use discussion was really at the doctor level. Doctors would be willing to try it for different kinds of things in addition to just the amelioration of walking problems.

DR. TEMPLE: Just to follow up on your thought, I think you are suggesting that if this were to be approved, it should, in messages to both patients and doctors, say there is just no evidence that using a larger dose does any good, don't even think about it, and also I guess if you miss one dose, don't double up the next one.

DR. WOLFE: That is at the patient level, but there was a discussion before of what a risk management program would be, and it would seem to me that if this is

going to come on the market, that there needs to be a lot of attention paid to reducing the chance that there is going to be off-label use. This is true of any drug that has a narrow therapeutic index, and this one is amongst the top of those, yes.

DR. ANDERSON: Let's go with Dr. Katz next.

DR. KATZ: I think that is a discussion that is pertinent to 3(a). The way we have worded 3, it says can you imagine any conditions under which it could be considered safe in use for this indication. So, I think that is mostly what we are interested in getting the Committee's opinion on.

If you think that, for example, there should be considerable attention paid to limiting off-label use or any other sort of restrictions, I think that comes under 3(a) when we get to it.

DR. WOLFE: I was merging the discussion to 2 because I assumed people will come with conditions, and I was just saying that those are the concerns I have.

DR. ANDERSON: Dr. Morrato.

DR. MORRATO: I was interested in what others thought. Given the novel design here, that it is a responder/non-responder, what implications that might have for how the indication is worded as opposed to saying use for treatment in all patients with MS for improvement in walking whether or not there will be reference to the effect was largely seen in people, more of a responder.

There is no precedence, so I didn't know if there is any discussion around how that might be handled in the indication I guess.

DR. ANDERSON: Dr. Katz.

DR. KATZ: I think when we wrote this question we were just considering the indication to improve walking ability in patients with MS. I don't think we were--because I don't think we know how to identify responders--I don't think we were anticipating that the indication itself would try to direct prescribe as to use this drug in only people who were responders.

Again, there is precedent for labeling, indicating a drug for a larger population and then saying things in

labeling like look, you can usually tell if this drug works within a month. If your patient isn't getting any better, stop it.

I mean labeling itself can take into account that sort of thing.

DR. MORRATO: I think that would just be important. I know it may not be in the indication because that relates to we may find subsets of patients where we see this is demonstrated value. But if the labeling is written where it doesn't clearly direct that and it implies it is everyone, I think you are sending mixed messages.

DR. ANDERSON: I think off-label use is a component of active clinical practice and that if we waited always for a definitive double-blind, controlled study, we wouldn't actually always provide the best clinical care. So I don't think off-label us, in and of itself, constitutes a misuse of a medication.

I think off-label use can be a misuse, and it is something that you should be aware of. But I don't think that it should preclude us from recommending or approving in

a particular indication what we think is best practice for something.

When I read the materials for this, I thought a lot about tacrine, which was the first, as far as I know, the first approved treatment for Alzheimer's disease, which was a real pain because the patients had to take it like four times a day, and you had to do liver tests all the time, and the benefit was modest, and yet there was a great clinical desire, and I don't know, there could have been, in theory, off-label use for people who thought it was a cognitive enhancer and might have wanted to take it.

I personally think something that has a narrow therapeutic window for causing seizures is not something that most physicians are going to really be interested in widely prescribing to their patients as opposed to something like the neurontin that you gave an example where you could use low dose and have a relative expectation of safety.

While I appreciate those issues, I don't see them as eliminating the prospect for an indication for which it would be considered on balance safe.

How about the issues of seizures and screening with EEGs, and some of those things that we heard about this morning for this drug, and how you would weigh in on some of this risk/benefit stuff?

DR. FOUNTAIN: Maybe that is part of 3(a) instead of 3, but --

DR. ANDERSON: Following Dr. Wolfe's lead of sort of considering them as a joint question.

DR. FOUNTAIN: I think the comments we heard about EEG were right on the mark. There is no clinical context in which we would consider EEG for screening in any context because, remember the positive predictive value of a test--let's say finding a spike on the EEG is dependent on disease in the population, and epilepsy is uncommon in MS, more common in the general population but still uncommon. So finding a spike would still be unlikely to predict that someone would have a seizure.

That is based on a number of different ideas. So I think that statistically it just doesn't make any sense and I don't think we have any data to suggest from other

contexts that it would be useful.

So, I think all we are left with is that that is what they did, and so they eliminated people and we don't know if they made a difference if they hadn't done that, but I don't think there is any other context or precedent for knowing that.

So, really, I don't see why you would get screening EEGs. I suppose if we backtracked just a little, I suppose this could be another opportunity for looking at a clinical trial. If you didn't get EEGs to see if there was an increased risk, or if you obtained EEGs but didn't exclude people on that basis, you would find out the importance of the EEG because I think that you would probably do more disservice than service by obtaining the EEGs because it will send people down inappropriate diagnostic evaluations and treatment.

DR. ANDERSON: Dr. Goldman, did you have anything?

DR. GOLDMAN: I was just going to make some comments, I don't know if we want to do that or continue. I think in terms of--I mean two things.

One is agreed that there is a sort of a culture among patients and potentially in medicine that more is always better, and I think that meaning that they are going to take more and potentially get more benefit.

That is an issue all the time when we prescribe medication. But, in this instance, there is actually a mechanism to help protect against that, which is the REMS program, which is not something that is common to other medications that are approved and that we commonly use in everyday medicine and specifically in multiple sclerosis.

Also, my other thought was about the issue about recognizing responders versus non-responders and what that means, and I think in this study, it is relevant because there is a potential substrate to explain the mechanism for non-responders.

But in clinical practice we do this all the time every day. So, if you have a headache, we give you one medicine, and if you keep getting headaches on that medicine, we stop it and we give you a different medicine, and we say you didn't respond to the first. But we don't

prospectively collect data or try to quantify or anticipate which headache medicine you are going to respond to or in epilepsy we give seizure medicine and if you still have seizures, we stop it and we give a different medicine.

So, I think we use this cause of the responder versus non-responder every day in clinical practice, and don't try to sort of capture it.

I think that that discrepancy is important in my thinking about this.

DR. WOLFE: This, I think gets back to the other question about the dose because I think the reason why most people thought that there should be a trial at a lower dose, that is sort of a condition. You are saying yes by the definition agreed upon.

It seems to improve walking ability, but we haven't yet gotten to the right or safest part of the curve. So, I would throw that back in because it is one of the conditions that might make safer use of this drug.

Again, I think it should have been done before the drug was put on the market whether it takes 6 months or

whether the FDA is going to crack a whip on this I don't know, but I think that the comfort level of anyone including myself about this drug would increase enormously if it turned out that it worked at 5 and you got this linear, which is what these data look like, decrease in adverse effects. That is a safer condition of use.

DR. ANDERSON: Dr. Rudnicki.

DR. RUDNICKI: I agree that we do all the time switch things because people aren't having a response, but this is a little bit more nebulous to me in terms of a response, and all those people who were on the open-label extension, who continued drug, although they were non-responders, when it is nebulous it is harder to know you are not responding, and so, you know, the MS drugs, you have an exacerbation. The MRI gets worse.

It is very clear you are not responding. But this is not so clear when you are not responding. So you continue to be at risk for the side effects, yet you are really not having any benefit, and I think part of it is also we don't have another alternative, we have other

modulating drugs.

Just a general question about the question. As I read it, it assumes we agree it is clinically meaningful, and we never voted on that.

DR. ANDERSON: Right. We did not vote, but Question 1(a) said--yes, we did not vote because the question was written as a discussion question.

DR. KATZ: We wanted to get a sense--I suppose we could have asked for a vote--but we really just wanted to get a sense of if people thought it was clinically meaningful. I think we got that sense.

DR. ANDERSON: I guess I would assume that if you didn't feel there was a clinically meaningful effect, then, the consistent thing would be to vote No on this question.

Dr. Goldman.

DR. GOLDMAN: I just wanted to respond to your comment. I think if I understand what you are saying, you are assuming that people who stayed in the study, who were non-responders, stayed because they didn't know they were non-responders.

But if you look at the MSWS-12 data, they knew they were non-responders because they responded to the survey in such a way that they weren't having a change in their walking function. As Dr. Goodman mentioned, there are lots of other reasons and motivations to stay on the study despite a lack of benefit.

I am not sure that you can make that assumption that non-responders continued on the trial meant that they didn't know they were not responding. Certainly, placebo-controlled trials and benefit on placebo would suggest that that is not always the case either.

DR. ANDERSON: I have a question that maybe our Patient Representative and others could address, which is how much does a patient's willingness to accept risk, how much did that factor into our consideration in terms of whether there is sort of this clinically meaningful condition for which it is considered safe.

That doesn't seem to me to be an absolute level, and so I would be interested from the perspective of someone with multiple sclerosis of how we should weigh that

deference to the potential risk of seizure.

MS. SITCOV: Well, I think people with MS are willing to take risks. If I was told that I would 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 don't think that I am--I really think I am reflecting the population.

I have had MS for many years and know many people with MS, so I think--you know, I also weigh it against what I find sort of disturbing is this, you know, having pharmacies just formulating this stuff.

To me that has tremendous potential for damage, partly in that it seems so terribly unregulated. If I were to take the drug under those circumstances and have a seizure, does anybody--you know, if a tree falls in the wilderness, does anybody hear it fall? Who would know that? I suppose I would call my doctor, but who beyond that person would know that for statistical purposes?

Yes, I think there is a great willingness to take

a certain degree of risk. Now, if you are talking about the seizure risk at 20 mg of the drug or 30 mg of the drug, I don't know, I think there is less of a willingness. But the seizure risk on placebo and drug are fairly equivalent, I guess are equivalent, in the studies.

Did I answer your question?

DR. ANDERSON: Yes, I found your answer very helpful. Thank you.

Dr. Goldman.

DR. GOLDMAN: I just wanted to rephrase your comment because I think it just struck me in terms of what is the risk of seizures in the MS population if this drug is not approved based on what we know is happening, which is that people are getting it from compound pharmacies and they are taking it at higher doses, which is another way to sort of think about--

MS. SITCOV: I think that's right and combine that with the fact that there is a risk of seizure among the MS population. I know people who will go and try to have this drug given to them from a pharmacy, and that to me is not

prudent.

I mean the prudent thing to do is there is plenty of evidence here, plenty enough for me to see that there is some benefit. It doesn't benefit everyone. Avonex doesn't benefit everyone, Tysabri doesn't benefit everyone. There are epilepsy drugs that work for some people but don't work for others.

DR. ANDERSON: Dr. Bastings.

DR. BASTINGS: A point I would like to make about the EEG is that even though it may have no predictive value in the general population for the risk of seizure, we really have no idea in the specific population of MS patients taking a drug which is known to induce seizure at some dosages, if it actually has any value and what there is would be in that population. That is information we just do not have at this point.

I don't think you can entirely discount it just by the fact that in the general population it has not been shown to have a good value.

DR. FOUNTAIN: I think that is right. All we are

left with is the observation that they did EEGs and exclude on that basis. But there would be no reason from any other context to think that would be true.

So, for example, if we did EEGs in the normal population, which has been done in Air Force pilots, it is routine that all Air Force pilots have to have EEGs obtained. So, from the United States Air Force, the Royal Air Force, the Dutch Air Force, somewhere between 0.7 and 1.4 percent of people have an abnormal EEG. But, if you look at the risk of subsequently having a seizure after that, it is infinitesimally small. Sohe positive predictive value is low because the incidence of disease in that population is infinitesimally small.

If we go to the population of patients with epilepsy, in an epilepsy clinic, who are referred to the EEG lab, and, say, 50 percent of the people have epilepsy who are referred for EEGs, then, finding an abnormality on the EEG, a spike, an epileptiform discharge predicts that there is about a 60 percent chance or better that they will have epilepsy.

So, the problem is the incidence of disease in the MS population, we think is probably the lifetime instance of a seizure is probably about 4 percent. So, whether you do it on a per-person year basis or an annual incidence risk over the course of their life, which would kind of give you the largest proportion, it is probably about 4 or 5 percent. That is still so little to find an abnormality it is unlikely to predict that they are going to have a seizure.

So, I take your point exactly. We don't know. It could be the case but, in every other context it has been looked at as far as EEGs go, it hasn't played out that it has been useful in predicting who will have a subsequent seizure.

So, you are right, we can't discount it because it is what they did, and so we don't know. I would absolutely agree with that, but it is just in terms of trying to generalize it for the whole population that adds a whole another level of complexity.

I would be very concerned that if you get EEGs in these people and find abnormalities, they are going to get

additional tests and treated in ways that are more likely to do them more harm than good.

In that context, that is supposition because I don't know that. But I know that that is true in the general population.

DR. MORRATO: I just wanted to add on to Dr. Goldman's point about the REMS. I know the point here is not to design it. But it was clear that we heard from the sponsor that it is in a state of development and I would hope that there is pre-testing of the educational materials before they are put into place.

So, what you actually have here on the REMS, medication guides are important. But we also know that patients don't always get them from their pharmacy. We know that labeling and Dear Prescriber letters are important, but we are not always so certain as to their level of communication and actually getting across the key, the goals that you have in terms of promoting informed prescribing in that.

I am not sure what is meant by the ongoing health

care provider education route outreach. That can be as simple as launching and an all sales forces detailing, or whether or not this is added kind of education.

So, I think as that gets developed, the only way to really assure that the REMS is helping towards the things that I know Dr. Goldman was mentioning, is to make sure that they are effective in communicating and that that work is done among a representative sample of prescribers and patients before you actually launch.

DR. ANDERSON: Dr. Stuve, do you want to weigh in with any comments on this before we vote?

DR. STUVE: Perhaps I should have asked this earlier, but it appears that the number of side effects were more prevalent in the treatment groups and the placebo groups.

Some of the things that were mentioned were also anxiety, insomnia, but there wasn't a good description on was that just a patient complaint or how severe were these side effects, did they require pharmacotherapy or any other sort of intervention.

I think some of that data would also help to determine if the safety profile of fampridine is favorable or not favorable in the patient population.

DR. ANDERSON: Thank you.

I am going to try to rephrase your comments because we had somebody here asking about them. If I get it wrong, please chime in after me, which is that you had said that we had to spend a lot of time on the seizures, but we had not necessarily emphasized some of the other CNS-like side effects, anxiety, imbalance disorders, and those sorts of things, and that that also should influence our considerations of the risk/benefit of the medicine.

Is that somewhat close, Dr. Stuve?

DR. STUVE: Yes, I think that is correct.

DR. ANDERSON: At this point, we have another vote on Question 3. So it's Yes, No, or Abstain, please. I will read it again and then after we have all entered, we will get Dr. Stuve to verbally register his vote.

If substantial evidence of a clinically meaningful effect has been demonstrated, do you conclude that there are

conditions under which fampridine could be considered safe in use for this indication?

[Electronic voting.]

LCDR NGO: Dr. Stuve, what is your vote?

DR. STUVE: Yes.

DR. ANDERSON: The votes are 10 Yes, 2 No, 1 Abstention.

For variety, we will start with Rudnicki this time and go around the other way.

DR. RUDNICKI: Stacy Rudnicki. No.

DR. MORRATO: Elaine Morrato. Yes.

DR. WOLFE: Sid Wolfe. No.

MS. SITCOV: Cynthia Sitcov. Yes.

DR. GREEN: Mark Green. Yes.

DR. ANDERSON: Britt Anderson. Yes.

DR. BRASS: Steven Brass. Yes.

DR. YEH: Ann Yeh. Yes.

DR. GOLDMAN: Myla Goldman. Yes.

DR. VAN BELLE: Gerald van Belle. I abstain.

DR. FOUNTAIN: Nathan Fountain. Yes.

DR. TODD: Jason Todd. Yes.

DR. ANDERSON: Now, we have our remaining question which is primarily a discussion question, and we have sort of blended them a little bit. So I guess we will just sort of open it up and then maybe we can do a brief roundtable to see sort of a final word from everyone, and then that will sort of conclude things.

If yes, what are those conditions, for example, specific enrollment criteria, specific monitoring, et cetera?

How about you, Dr. Todd, do you want to weigh in on what you think would be sort of the appropriate person for whom this condition applies, what sort of enrollment criteria or monitoring should apply?

DR. TODD: I have one question. Is there a way to put the seizure risk in context with other medications at increased seizure risk like tricyclic antidepressants or antipsychotic agents just for comparison?

DR. ANDERSON: I can't do that. But does anyone on our panel here feel like they have the expertise to

relate the 10 mg b.i.d. dose numbers that we have seen to any of the other common medications we might use or give us a benchmark? Dr. Fountain?

DR. FOUNTAIN: First, I think we would have to go back to the day that there is no increased risk at 10 mg b.i.d., isn't that true? There is one in each group of the placebo and the treated at 10 mg b.i.d. So, we have all talked about the seizure risk. But the seizure risk isn't increased at 10 mg b.i.d.; isn't that right? One in each group of equal numbers.

So, I think that is the place it starts, above those levels, and so that is I guess was my question before is how do we put this in context. So, the answer is I don't know. But I can tell you that when tricyclic antidepressants originally were thought to increase risk of seizures in patients who received them, in subsequent retrospective analysis, the increase in seizure risk is not nearly as high as it was anticipated.

So, I think your question--I don't know the answer, but your question I think is exactly on, what is the

context to put it in.

DR. ANDERSON: Dr. Green.

DR. GREEN: I have no argument with Dr. Fountain's position on EEG, but isn't it customary if there is an exclusion in the trial like excluding people for epilepsy, that that be reflected in the labeling?

DR. KATZ: It depends on how important you think that is. By the way, there is a difference between saying patients who had an abnormal EEG or history of seizures were excluded in terms of ascribing the patients who were on the trial, that is one thing, and then requiring that therefore patients be screened with an EEG before they get this drug once it is marketed. Those are two very different things.

We typically describe the patient population in labeling but, again, there are many things that are true about patients enrolled in trials. We don't describe everything. We describe what we think is important.

We describe, of course, some exclusions, but not others. But I want to make a distinction between describing it and requiring that patients be screened with an EEG

before they get this.

DR. GREEN: No, no, and I understand that. I don't think anyone here would say that. It just seems to me that--forget about the EEG part, that epileptics were excluded, therefore, shouldn't there be some reflection in the labeling.

DR. KATZ: Well, very possibly, yes.

DR. TEMPLE: It is extremely typical when people with moderate to severe liver disease are excluded, which they are for many drugs, to take note of that, and sometimes to contraindicate the drug, its use in those.

But as Rusty says, here, it is certainly something that will be thought about, needs to be thought about.

DR. ANDERSON: I am going to come back to make sure Dr. Todd finished his chance, and then I will come back over here and resume this discussion.

DR. TODD: Well, in terms of seizure risk, it seems that patients with active epilepsy shouldn't take this drug. There are some patients that are somewhere between active epilepsy and population or MS population risk of

seizures. A patient had childhood epilepsy, outgrew it, and has not needed treatment for a decade or two or three.

For a patient who had a single seizure that might have been related to benzodiazepine withdrawal, for patients like that, would it make sense to screen that subgroup with EEG but still maintain eligibility for the drug?

DR. ANDERSON: I will get Dr. Morrato first.

DR. MORRATO: This is real quick. The sponsors in their materials say that they propose contraindicating the use of the drug in patients with a history of seizure, so I think that probably that is their intent.

They also mentioned that they propose a contraindication in patients with severe renal impairment. So, I think, you know, they are at least acknowledging that. I guess the question is whether or not there are warnings for mild or moderate, not just the severe given what we saw in the Cmax. Others have more expertise there.

DR. ANDERSON: Dr. Bastings.

DR. BASTINGS: A couple of things. In terms of EEG, I think, you know, we would like to have some idea from

the panel as whether they think an EEG should be mandated before patients start treatment or not.

Regarding the renal impairment, I think we also would like to have some idea as to whether a metabolic profile should be mandated before starting treatment and maybe estimation of creatinine clearance to ascertain whether patients has a mild renal impairment and whether treatment should be initiated in these patients.

DR. ANDERSON: So, it is not necessarily an official thing, but maybe we could take a quick poll to specifically address your question.

If you believed that you were going to start a patient on a 10 mg b.i.d. dosage, who had no history of epilepsy and normal renal function, would you choose to do an EEG before finalizing your decision to initiate medication?

Dr. Todd.

DR. TODD: No.

DR. ANDERSON: Dr. Fountain.

DR. FOUNTAIN: No.

DR. ANDERSON: Dr. van Belle.

DR. VAN BELLE: Abstain.

DR. GOLDMAN: No.

DR. YEH: No.

DR. BRASS: No.

DR. ANDERSON: I would not.

DR. GREEN: No.

MS. SITCOV: No.

DR. WOLFE: Abstain.

DR. MORRATO: Abstain.

DR. RUDNICKI: No.

DR. ANDERSON: Dr. Stuve, how about you?

DR. STUVE: No.

DR. ANDERSON: The renal issue is something that people have mentioned a couple of times. There is a statement that severe renal insufficiency should not get the drug. A statement that moderate--this is as I recall the company stating it--moderate may be and mild is probably okay.

You have waited on this a couple times, Dr. Green,

what do you thing?

DR. GREEN: Particularly since there is not the availability of a 5 mg tablet at this point, therefore, we don't have the ability to make a dosage estimate or at the point of marketing, therefore, I think the only solution would be to make it a contraindication, a moderate to severe renal insufficiency.

DR. ANDERSON: Does anyone else want to weigh in on this? Dr. Goldman.

DR. GOLDMAN: I just actually have a question about that. Since the issue, if I understand it, is that in the renally impaired individual, their peak dose might approach that where the seizure risk becomes more meaningful.

So, I guess the question would be--and perhaps Dr. Fountain or someone else could clarify--you know, we use seizure precautions all the time in terms of no bathing, no swimming, no climbing up a ladder, in patients where we are transitioning our anti-epileptics, is there a role for that in patients with moderate or mild to moderate renal

impairment where we don't know what that is going to be, and is that useful in general, and what is the endpoint for that, and could we come up with some paradigm where you could use it in that population after a certain point.

DR. ANDERSON: You are on the spot again, Dr. Fountain.

DR. FOUNTAIN: I guess if you thought they were going to have a seizure, you wouldn't give it to them. It's problematic in presenting people with seizure precautions who haven't had a seizure.

I think I would agree with Dr. Green that if there is no way to give them a smaller dose, we don't know anything about the safety of the higher doses except extrapolate from other--I mean higher serum levels--except extrapolate from higher doses. I would think it would be contraindicated.

I am not sure if that means it requires obtaining a creatinine, or determine a creatinine clearance before you do it, but it certainly, I guess by implication would, since you are going to say you would exclude it.

Certainly, for severe renal failure. Moderate I am not so sure about. And I guess the only other pharmacokinetic thing to consider is that if really it is just their elimination that is slowed and, if it really falls that much over the course of it, I suppose we could imagine that you can dose at once a day instead of twice a day as a slow release formulation. But we would have to think--you know, I have seen only the sparsest pharmacokinetics, but that would be another consideration.

DR. ANDERSON: Dr. Temple.

DR. TEMPLE: I don't think once a day helps you very much because it's the peak you are most worried about almost surely, so I don't think that gets you out of that.

DR. GOLDMAN: Unless you have done--

DR. TEMPLE: Well, there is no accumulation of this dose of drug. It has a short half-life. It only lasts for a long time because it has got a controlled release dosage form.

DR. FOUNTAIN: Right, so the renal elimination, the peak would be dependent on the volume of distribution

rather than the elimination if it eliminates back to zero.

DR. TEMPLE: So, I don't think once a day gets you out of that problem. Do I remember correctly, though, there was really only one person with moderate renal failure that was in there, so that would be why you think perhaps it should be contraindicated for moderate or severe. They excluded severe and they only had one person with moderate.

DR. ANDERSON: I think it also came from their pharmacokinetics that showed that it went--they had data showing that in mild renal insufficiency, the Cmax went up 67 percent, 100 in moderate and more in severe.

I don't want to misstate your argument here, but I will state my own, which is that even the 67 percent bump sort of has reached my level of timidity, and I would even consider personally mild renal insufficiency a relative contraindication to the use of medicine and the way I would employ it.

DR. TEMPLE: There is no such thing as a relative contraindication.

DR. ANDERSON: Well, no, you have to make your own

decision as to what the Agency decides is the right thing to put on a packet but, in terms of my own personal way that I would envision using this, I would personally view that as something that would sway me against it, is the presence of mild renal insufficiency especially given the gap in our knowledge of exactly how critical these levels are and exactly how much we raise the risk when we bump it up.

So, now I will give Dr. Stuve one last chance and then I will sum up our discussion. Dr. Stuve, do you want to weigh in with anything?

DR. STUVE: No, I have nothing to add.

DR. ANDERSON: Well, congratulations on your endurance.

The summary, then, for Question 3(a) is it appears to be the consensus that individuals with known seizure disorders or belief to be, for whatever reason, at high risk of a seizure should not receive this medication, that the issue of renal impairment is an important one with some difference in terms of how severe the renal impairment should be before it represents a contraindication to its

employment.

There was no consensus or there was a consensus that there was no need for pre-screening with EEG prior to use, and there were pertinent comments made related to the ongoing monitoring and the program for risk mitigation.

Dr. Temple.

DR. TEMPLE: I assume part of that means that you think everybody before getting the drug should have a renal function test, at least the zero creatinine in the calculated Cockroft-Gault GFR, right?

DR. ANDERSON: I hear one yes from my left.

DR. TEMPLE: You can't do any of the things you mentioned if you don't do that.

DR. ANDERSON: If you are asking me personally, I am saying yes, but now I am trying to--I am repeating the yes from my left because I am trying to give you whether that is the consensus.

DR. TEMPLE: I am only asking because on a sort of similar related issue, nobody thought you should get an EEG. But I do think--it sounded to me like you are saying

everybody should get a--

DR. ANDERSON: Well, the reason--now I am doing my summary role again--the reason everybody thought you did not need an EEG was because of the poor relationship between an abnormality on the EEG and the ability for that to really change the patient's risk substantially, to improve their risk/benefit ratio.

But I believe the consensus is that the creatinine clearance and its relation to risk of medication side effects is sufficiently well established that there is an advantage to doing that test, but not the other.

Would anyone like to chime in on that, or does that seem close enough? Okay. Dr. Wolfe has a thought.

DR. WOLFE: There are two separate issues, one which Bob has just raised. I think there should be at least a preliminary creatinine and calculated GFR because, otherwise you can't tell for someone, for instance, who has new onset severe renal failure whether they have it or not.

The other issue, though, I think is that just based on the increase in the Cmax, that those who are found

to have moderate in addition to the severe that has already been agreed by the company, they should be excluded from using the drug. That is a huge increase in Cmax just with the moderate severe.

DR. ANDERSON: How do feel you about the milds?

DR. WOLFE: For my own, I might agree with you; from a public health perspective, I don't know. I am ambiguous enough about or ambivalent or negative enough about this drug that I could go with that. But I think that people around the table would probably, if asked to vote, at least vote for the moderate being an exclusion criteria.

So, I would ask if we can just do a quick vote on that because that might help the FDA beyond just the testing level which they raised.

DR. ANDERSON: All right. We will take this roundtable poll and then we will call it a day.

Do you feel that mild and/or moderate and/or severe should preclude the use of this medication?

Dr. Todd.

DR. TEMPLE: Ask about moderate first. Everybody

agreed severe is out.

DR. ANDERSON: Everyone agrees severe is out. I was just trying to get both mild and moderate as a package deal. We will do it one at a time. Moderate renal insufficiency defined as the GFR between, in this case I believe it was between 30 and 50 was the definition of moderate that was used.

DR. TODD: Moderate; don't use mild. Just use a caution and maybe follow the GFR because renal function will change over years, and so these patients would be on this for years.

DR. FOUNTAIN: I agree.

DR. VAN BELLE: Abstain.

DR. GOLDMAN: I agree.

DR. YEH: I agree.

DR. BRASS: I agree.

DR. ANDERSON: I agree.

DR. GREEN: I agree.

MS. SITCOV: Abstain.

DR. WOLFE: Agree.

DR. MORRATO: Abstain.

DR. RUDNICKI: Agree.

DR. ANDERSON: Are there any last issues that for the benefit of the FDA we could bring up before we adjourn?

DR. KATZ: No. I just want to thank everybody. These are tough issues and it has been extraordinarily helpful to us.

DR. WOLFE: And the Chairman did a very good job.

DR. KATZ: I agree with that, too.

[Applause.]

DR. ANDERSON: Thank you very much, everybody. We are adjourned.

[Meeting adjourned at 5:02 p.m.]