pain and then a cardiac arrest and died, and there is a person with a history of angina on multiple medications who developed respiratory depression, psychosis, and ventricular fibrillation, but was resuscitated.

So given the limited number of reports in both Merck's database and the FDA's database, we conclude that there does not appear to be an appreciable risk of life-threatening arrhythmias in patients who take therapeutic doses of cyclobenzaprine 10 milligrams.

Our WAES database contains 29 reports of seizures in patients who had taken cyclobenzaprine. Two reports involved overdoses. Of the remaining 27 reports, 12 would meet the criteria for serious that exists today. Eleven of these 12 reports were confounded. In three of the cases, the patients had a previous known history of seizures. In 10 cases, there was not enough information to assess causality in a reasonable manner. In four cases, cyclobenzaprine may have been associated with a seizure, and in two cases, when we reviewed the case, it doesn't sound like a seizure that's being described at all.

We also reviewed the FDA database looking at seizures and cyclobenzaprine, and we found six reports that did not come from Merck. There were four reports that were serious, including one that was a fatality. The other three reports all had a prior history of seizures. Now,

given the limited number of reports in our database and in the FDA database, the risk of a seizure secondary to therapeutic use of cyclobenzaprine appears to be quite negligible.

Dr. Klein presented data from several sources this morning, from the American Association of Poison Control Centers and the Drug Abuse Warning Network. I'd like to try to put some of the numbers in perspective that we all looked at this morning. This slide summarizes for a 4-year period, 1994 through 1997, what the most commonly reported drugs are to the American Association of Poison Control Centers, and we see cyclobenzaprine during that 3-year period had 15,000 reports, which is an order of magnitude less than is seen with ibuprofen, multi-vitamins, or acetaminophen. So we are not minimizing the fact that there are 15,000 reports, but we'd like to put that in the context of all the other reports that the Poison Control Centers do receive.

The Poison Control Center database collects information about overdoses from all across the country, and their data actually show that cyclobenzaprine has a large margin of safety in overdose. There were three reported deaths with cyclobenzaprine alone. We know that one of those patients reportedly took 800 milligrams, which is 13 milligrams per kilogram, the equivalent of 165

milligram tablets. We do not know the dose ingested in the other two cases. There were 36 deaths in the database in patients who took cyclobenzaprine and multiple other drugs, most commonly benzodiazepines and tricyclic antidepressants. The most common symptoms in overdoses were drowsiness and sinus tachycardia. Serious ventricular arrhythmias or seizures were reported in less than 0.4 percent of the cases of cyclobenzaprine overdose alone.

Looking at the Poison Control database reinforces that cyclobenzaprine is not the same as amitriptyline. If we look at the 101,000 overdose reports in the Poison Control Center database over a 10-year period and compare that with the 11,000 cases of cyclobenzaprine alone, we see that the mortality rate with cyclobenzaprine, three out of that, is much lower than the 1 percent rate with tricyclic antidepressants. And even when cyclobenzaprine is taken as part of a multi-drug overdose, the mortality rate is lower than with the tricyclic antidepressants.

Turning our attention to the Drug Abuse Warning Network data, the last year that we have data available for all drugs is 1993, and cyclobenzaprine appears as Number 42 on their list, with 2,600 mentions in that year. That's slightly less than caffeine in that year, naproxen, OTC sleep aids, and substantially less than the drugs that

everyone recognizes are drugs of abuse.

Information from multiple sources indicates that there is a low risk of abuse with cyclobenzaprine. There are no published reports of recreational use or addiction to cyclobenzaprine. Merck has not received any spontaneous reports of addiction to cyclobenzaprine. The Drug Abuse Warning Network, as Dr. Klein explained, collects information from emergency departments and medical examiners across the country, and the emergency department mentions indicate that less than 2 percent of the time that a patient ended up in an emergency room after taking cyclobenzaprine did the patient state they were taking it for recreational purposes. Most of the time it was an intentional overdose.

Based on the extensive marketed use of the product, over 100 million prescriptions over a 20-year period, we conclude that cyclobenzaprine 10 milligrams TID is generally well tolerated. The most common adverse experiences are related to the central nervous system, and they are generally mild. The number of spontaneously reported serious events differs slightly between our database and the FDA's database, but the pattern within both databases is consistent. Both databases indicate that reports of serious cardiac or neurologic events are rare. There's a low potential for abuse and a large margin of

safety in overdose.

We acknowledge that cyclobenzaprine 5 milligrams can cause drowsiness, and we have developed a label that informs potential consumers about the risk of sedation with the product. In addition to the standard sedation warnings that are included on the back panel, and these are based on the diphenhydramine monograph, we propose to put a flag on the front panel of the box to clearly indicate that the drug may cause drowsiness.

We have also taken a conservative position concerning who should use this product. We propose that patients less than 18 years old and patients 65 or older speak to a physician before using the product. Our new pharmacokinetic data shows that elderly patients taking 5 milligrams TID will have plasma concentrations similar to younger patients taking the current prescription dose, and physicians may wish to advise those patients to decrease the dosing interval or amount taken.

We propose to include warnings advising patients with heart disease, liver disease, thyroid disease, glaucoma or difficulty urinating to consult a doctor before using this product. These precautions are all carried forward from the prescription circular that we have, and they are not unique to this product. They are already on some OTC products such as cough and cold

products and decongestants which contain sympathomimetic or anticholinergic drugs. In addition, we propose on the back panel to include specific symptoms that would indicate that a patient might have a condition other than an uncomplicated back strain and should see a physician for diagnosis and treatment. These red flags are consistent with those developed by the AHCPR guidelines that are an appendix to your package.

We recognize, as Dr. Hemwall stated, that label development is an iterative process. The label included in the NDA and your background package is not the label that was tested in the use study, and it's not the label that was tested in the label comprehension study. The use study tested an early version of the label that did not include a package insert. The label comprehension study tested a label similar to what we have here, as well as an insert. Based on the results of the use study and our label comprehension study, we made modifications to the label, and those are included in the version that you see that was submitted with the NDA.

As Dr. Aikin indicated, the label clearly communicated to consumers that the products should be used for acute neck and back pain with spasm, what the proper dosing instructions are, that the product can cause drowsiness, and that they should consult a physician before

using the product or after starting the medication if they have certain symptoms or conditions.

As Dr. Aikin mentioned, comprehension was excellent, ranging from 80 to 95 percent, for when a patient should ask a doctor before using the product. Consumers also clearly understood that the product may cause drowsiness, with comprehension ranging from 96 to 98 percent. They also understood that they should stop the medication and see a physician if they were not better in 10 days.

We agree that some concepts that were tested have room for improvement. There was some confusion about the difference from analgesics and whether cyclobenzaprine can be taken with pain relievers. Some people did not understand that the product did not work immediately, and some thought that the product could be used to treat leg cramps or arthritis pain. We have data, however, that I will show you that the package insert actually helps to reduce these misunderstandings.

This slide summarizes the percent of consumers who understood that cyclobenzaprine works differently than analgesics. After reading the label alone, 70 percent of the representative sample recognized that this was different than an analgesic. Comprehension improved to 88 percent after they also read the insert. The same pattern

of improvement was seen in the elderly subjects and the subjects who did not complete high school.

This slide summarizes whether people understood that cyclobenzaprine does not necessarily provide immediate relief. After reading the label, 57 percent of the representative sample understood that. Comprehension went up to 75 percent after reading the insert as well. Comprehension also improved in the elderly group, from 46 to 70 percent, and in the less than high school grads, from 52 to 65.

We made several revisions to the label after we saw the results of the use study. The first revision was to delete the word "temporarily" from the uses section of the label. "Temporarily" appears in the indication for OTC analgesics, "temporary relief of mild to moderate pain." The agency asked us to include "temporary" in our uses section for the version that was tested in the label comprehension study, and we believe that that word helped confuse consumers. Because that was so similar to what they're used to with analgesics, we believe that actually helped confuse them and we took it out of the label we submitted.

We increased the font size to make it easier for everyone to read, not just the elderly, and we added to the insert examples of inappropriate use, namely that the

product does not work for treatment of leg cramps or arthritis. We also added an explanation to the insert about why the elderly should ask a doctor before using the product.

We also recognized that both the label and the insert have even more room for improvement. We look forward to hearing suggestions this afternoon, and one of the statements that we know we'd like to include is to clarify in the insert that there's not an absolute contra-indication to driving, as may have been interpreted, but clearly what we're advising people and the spirit of the label with diphenhydramine as well is not to drive until you know how you'll react to the medication, and you should not drive if you become drowsy or dizzy with the medication. But if you're comfortable and have taken the medication before, it's hard to say that it's absolutely wrong to drive once you've had experience with the medication.

The pattern of use study was conducted to examine how patients would self-medicate with cyclobenzaprine. It was not conducted to establish efficacy, and it was not conducted to establish effectiveness. The protocol that we wrote and submitted to the agency was designed to look at how patients would use the product, how many tablets per day and how many days

they would take it. We enrolled 468 patients who believed that they had acute painful muscle spasm of the back or neck. These patients were given 30 tablets, the first version of our label, and a diary card.

The majority of patients complied with directions regarding how many tablets to take per dose and per day. Eighty-seven percent of patients never took more than three tablets in a day, and 89 percent never took more than one tablet as a single dose. Overall, less than 3 percent of the treatment days consisted of more than 15 milligrams, and less than 1 percent of the doses consisted of more than 5 milligrams.

Forty-four percent of the people took the drug as labeled for seven or fewer days, and 48 percent took the medication for eight to ten days. To us, this indicates that some patients actually require more than seven days of medication, and this is consistent with the natural history of the condition and the dosing instructions in the current prescription circular, which, after all, has a similar indication.

Since analgesic labeling allows for use up to 10 days before seeing a physician, we propose, since analgesics can also be used to treat acute back pain, to minimize the potential for confusion among consumers, that we should have the same duration on our product as are on

the nonprescription analgesics. So we will propose in the insert and label you have that 10 days would be the maximum duration of treatment before a patient should see a physician.

We examined analgesic use during the use study, and 35 percent of the patients in the use study did take an analgesic on one or more days during the study. They were used for a number of reasons, be it headaches, arthritis pain, dysmenorrhea. Fifteen percent reported that they used the analgesic to treat the same condition, whether it was neck or back pain with spasm, that they were using the cyclobenzaprine for. If we look at the global ratings of the 15 percent of the patients who used analgesics for their back pain, it's no different than the patients who did not use analgesics during the trial.

Now, assessing whether patients avoided driving was not a primary objective of the study. In fact, the question about driving was added after the study was ongoing, and only approximately half of the patients were able to complete that question. We recognize the question was poorly worded. It did not clearly ask about did you drive if the medicine made you sleepy. We believe that in a future study, we need to clarify how we ask that question, because the label did not say in bold letters "Do Not Drive." The label said "avoid driving," which may be

interpreted differently.

In summary, the data we have presented today shows that cyclobenzaprine 5 milligrams TID is statistically and clinically superior to placebo in patients with acute painful muscle spasm of the back or neck. The median time to substantial relief with cyclobenzaprine is approximately two days less than with placebo. The overall efficacy of 5 milligrams TID appeared similar to that of 10 milligrams TID, the current prescription dose. We established that muscle spasm does indeed resolve more quickly in patients who receive 5 milligrams TID than placebo, and we have shown that patients can recognize when they have painful muscle spasm, and the correlation between patient and physician ratings demonstrates that patients can assess whether their condition is improving.

Cyclobenzaprine 5 milligrams TID was generally well tolerated in the nonprescription studies. The most common adverse experiences were drowsiness and dry mouth, and both were dose related. The subjective level of sedation as measured by the visual analog scale was similar with 5 milligrams to that with the maximum OTC dose of diphenhydramine. Our laboratory studies have shown that 5 milligrams TID does not consistently or substantially impair psychomotor performance and driving-related skills

in young or elderly subjects.

The extensive experience we have with the 10 milligram dose shows that that dose is generally well tolerated. Serious adverse experiences have been infrequently reported, and the available data suggest there is a large margin of safety in overdose and a limited potential for abuse.

Our label comprehension study shows that key directions and key warnings were well understood. The insert actually helps consumers understand the difference from analgesics. The study identified several opportunities for improvement, and we look forward to comments from the agency and suggestions from the advisory committee this afternoon.

Our pattern of use study showed that patients do generally adhere to the proposed dosing instructions. It's worth noting that no patient in our pattern of use study took more than six tablets in a single day. So no patient in the use study exceeded the current prescription dose. Some patients appear that they will need more than seven days of treatment, however, in order to have adequate improvement and resolution of their condition.

As I have presented this morning, we believe that the clinical studies have shown that cyclobenzaprine 5 milligrams TID is safe and effective. It provides a

clinically meaningful benefit to patients with an acute and common problem. The overall risks and benefits are comparable to that of some existing OTC products. We believe we can develop labeling and refine it to allow a consumer to safely and appropriately self-medicate.

I'd like to thank you for your attention this morning and reintroduce Dr. Hemwall, who has a few concluding remarks.

DR. HEMWALL: Thank you, Scott.

I actually have two objectives here right now. One is to provide a wrap-up and put some of this in context, and the other is to give Scott a chance to catch his breath before the questioning starts.

This is an opportunity where I would just like to take a few minutes to place into perspective the important questions that you've been asked today, questions relating to whether or not American consumers will be able to, at their own discretion, buy Flexeril OTC off a store shelf, take it home, follow the directions, and use it safely and effectively.

You heard me speak earlier about the prevalence of the back pain problem in the United States, a problem that affects the day-to-day quality of life for millions of adults each year. In addition to seeking help through the health care system, many consumers currently self-treat

back pain and neck pain with OTC analgesics, rubs, dietary supplements, mechanical manipulations of all kinds. Some of these products even have label claims to be effective against spasm or other terms. In fact, self-treatment of back pain, neck pain, strain, tightness, spasm, whatever words best describe it, has clearly been a part of the consumer mindset for years.

While it is clear that consumers are comfortable with using OTCs to treat this common condition, it is also clear that currently available OTC choices do not always provide adequate relief, and many consumers end up in the doctor's office seeking additional options. Thus, it's no wonder that, as I said before, over 30 million prescriptions are written each year for muscle relaxant drugs, of which roughly one out of three of those are for Flexeril or generic cyclobenzaprine.

For a substantial subset of that population, an OTC Flexeril product would offer real benefit, benefit to informed consumers who are seeking efficient access to an effective product for back and neck pain, access without having to endure the delay, the expense, and the inconvenience of a physician visit, especially for a problem that is often recurring, access to a medication with demonstrated efficacy, providing meaningful relief for many patients up to two days sooner than with placebo.

So OTC Flexeril can provide this real benefit, and you've already heard that the sedative properties are within limits and manageable by OTC labeling. So the question really becomes: How does the benefit relate to any potential risk? Well, consider this. Those of you who are on the Arthritis Drugs Committee are faced constantly with assessing safety of a new chemical entity with clinical experience and perhaps a few thousand patients, and maybe a few hundred of those have been treated for six months or a year, and despite having a clean profile in that NDA, there often remains a lingering concern regarding the potential for rare or unexpected adverse events that might occur in a widespread marketed use outside the setting of controlled clinical trials.

Today, these joint committees have a fairly unique opportunity to look at a molecule with a long history of use in the prescription setting, and we have reviewed for you the extensive safety data of Flexeril 10 milligrams, spanning over 20 years and over 100 million prescriptions. This represents a degree of experience that is uncommon in the evaluation of an Rx to OTC switch. It provides important perspective on the low incidence of the serious adverse effects associated with the use of the 10 milligram prescription dose, a dose twice that proposed for OTC use, and similarly this large experience supports the

low potential for abuse and for serious consequences in an overdose situation.

In addition to demonstrating efficacy and safety appropriate for OTC use, we have developed a solid basis for consumer labeling aimed at efficiently managing consumer expectations of how this product works and directing consumer behavior to maximize the safe use. We appreciate the care and the caution with which decisions must be made while considering a new class of medication for OTC use, and the FDA reviewers have raised important questions which we have addressed in our background book and in Dr. Korn's presentation today.

We're eager to learn from your discussions today. Our team of Merck scientists and outside consultants are ready to assist in your assessment of these challenging issues, and we'll be willing to respond to any and all questions which may arise.

Thank you very much for your attention.

DR. BRASS: Thank you.

At this point, we will begin a session which I expect will carry over to the afternoon of questions for both the sponsor and the FDA. I suspect that there are a number of people on the committees who have large numbers of questions, and so I would ask that initially we each limit ourselves to one or two questions so that we avoid

monopolizing.

The question can be addressed to either sponsor or FDA, both or either, and I would encourage the sponsor or the FDA, if they would wish to comment on a question directed towards the other, to please do so.

Additionally, a reminder to both sponsor and FDA. When responding to a question, please identify yourself for purposes of transcription.

I think I'll take the chair's prerogative and ask the first question, specifically related to the issue of safety. I am concerned that the use of mean data for describing safety monitoring may be misleading, and that, in fact, in a drug that is used in a wide population, one might be concerned about the percentage of people taking the drug who would have significant impairment. We know that 2.5 percent of the patients in the trials had to discontinue medication use because of severe sedation.

You use a responder/nonresponder profile to describe efficacy, and I'd be interested in an impairment/nonimpairment profile in the safety analysis, particularly for the psychomotor type of testing. Can you define a clinically significant degree of impairment, and what percentage of subjects actually exceeded that level?

Additionally, given the relatively small numbers of patients used in those types of testing, are you

confident that there are not 5 percent of the general population who will be severely impaired at the 5 milligram dose?

That was a question.

(Laughter.)

DR. KORN: Dr. Korn from Merck. We'll have a slide coming up to address that.

We did not look at a responder type analysis, but we did look at scatter or variability within the data using these box and whisker displays. Here, for the elderly study which I included in the presentation, we see a box and whisker plot with the median, 25th, and 75th percentiles for the data for vigilance time, reaction time. So it's in seconds. What we see is clearly the median for amitriptyline is higher than for diphenhydramine, for cyclobenzaprine or for placebo. There is some spread to the data, but there are nc bad outliers out there in this group of 32 patients or subjects. They were healthy subjects.

It was reasonably tight data, and again, not skewed far off from that with placebo. Is that the direction you were looking for?

DR. BRASS: I assume this is the best of those scatters? Do you have the others, just to give a sense of particularly the driving skills test, for example?

DR. KORN: Sure. Number 733. Here's the divided attention task overall performance score, which is a composite of tracking and reaction time. Again, we see amitriptyline on the far right, cyclobenzaprine looking a lot like placebo, one outlier with amitriptyline up at the far end. We can do the same thing if you'd like with 735. This is tracking error inside that test, which is the weaving motion. Again, cyclobenzaprine overlapping pretty much with placebo, amitriptyline not that different but with an outlier.

DR. BRASS: Thank you.

Other questions from the panel?

DR. ELASHOFF: It seems to me fairly likely that in practice many patients will be taking an over-the-counter antihistamine when they take Flexeril, and many antihistamines also have strong drowsiness warnings. But I haven't seen any information whatsoever as to what happens if you take both at the same time, and there doesn't appear to be anything on the label suggesting that you ought not to take other things that might be causing drowsiness.

DR. KORN: Scott Korn. You're right. We do not have data in psychomotor trials looking at additive effects, whether it's alcohol, antihistamines, benzodiazepines. We would assume that there would be an additive effect as opposed to a multiplicative effect, and

we're certainly open to suggestions about other drugs that we should include on the back panel that patients should avoid if they were taking cyclobenzaprine. We could certainly add antihistamines to the list of the sedatives and tranquilizers.

DR. ELASHOFF: But we don't in fact know that it's not more than additive, even.

DR. KORN: Right. We would assume that certainly the anticholinergic properties would be additive. We have not looked at psychomotor properties.

DR. BRASS: Dr. Gilliam?

DR. GILLIAM: This is two questions, both I guess toward the sponsor. Have there been any studies looking at the use of Tylenol and/or NSAIDs compared to Tylenol and/or NSAIDs with Flexeril? That's the first question.

DR. KORN: We have not conducted any head-to-head trials that were double-blind and compared use with an analgesic or a nonsteroidal anti-inflammatory drug. There are some published studies, including one done by Dr. Borenstein, that were open-label looking at naproxen sodium and Flexeril versus naproxen sodium alone that appeared to suggest a benefit.

Certainly we know that 85 percent of the prescriptions for cyclobenzaprine are accompanied by a

prescription for either a non-narcotic or narcotic analgesic. So physicians' practice over the past 20 years has been to prescribe both a muscle relaxant and an analgesic in conjunction, but I do not have double-blind data for that.

DR. GILLIAM: In Study 9, there were 46 percent of patients who had muscle spasm previously. Were there any differences in pattern between those who had diagnosed muscle spasm previously compared to those who had not in that study?

DR. KORN: Can you clarify? By "previously," do you mean they used cyclobenzaprine before?

DR. GILLIAM: Yes.

DR. KORN: Okay. We have a slide for that. We see on this slide the proportion of responders on that 5-category global scale. So top three categories for all patients in the use study, for patients who never used cyclobenzaprine before, and for patients who had previously used cyclobenzaprine before. Certainly the mean number of responders appears similar, maybe a little greater variability in the previous Flexeril users. Certainly it's not surprising to us that some of the people on the far right exceeded the dosing directions for what we told them to do, but that may have been because their physician previously told them to take 10 milligrams, so all they

were doing was following the directions their physician had given them before.

DR. GILLIAM: But they had no idea that they were using Flexeril, right? This was a double-blind study, so they didn't really know what they were using.

DR. KORN: This was an open-label, uncontrolled trial. They knew it was Flexeril. The label said it.

DR. BRASS: Dr. Pucino?

DR. PUCINO: For the driving-related skills study in the elderly patients, do you have data going out more than four doses; i.e., if the half-life in elderly patients is somewhere around 33 hours, do you have something like 8 days dosing?

DR. KORN: We do not have psychomotor data drifting out 8 or 10 days. So we don't have psychomotor data at steady state in the elderly. We have sedation data.

DR. BRASS: Dr. Gerber?

DR. GERBER: Many of us subscribe to the view that the ultimate outcome of health care is good function. Pain is clearly one element that may contribute to that, but I'm wondering whether or not you have in this population of patients any data that indicate whether or not they were in fact able to perform usual activities either at home or at work as a result of taking the

Flexeril.

DR. KORN: No. We did not collect outcome measures such as Roland-Morris or cut-down days as part of those trials.

DR. GERBER: It's a very critical issue given that sedation, especially in the elderly, may in fact provide good resting activity at home and markedly reduce daily routines.

DR. BRASS: Dr. Yocum?

DR. YOCUM: I guess I would like to follow up Dr. Gerber's comments, that the premise of releasing this compound OTC is to get the millions of patients who have back pain back to work and functioning, but yet the scores that are being looked at are basically pain relief and global scores without any function. I guess I would pose a question to the FDA, because maybe the company has been misled the whole time. Is this typical for the plan for an OTC muscle relaxant not to look at function, which has been the focus of most rheumatologists for years? I'm unclear as to why function is not included.

Also, I think Dr. Witter alluded to that there were secondary endpoints to be looked at which looked at there was a little bit more on functionality, but I am unable to find any data related to those secondary endpoints. Are they presented at all in any sort of way?

So I guess one is, is this an okay thing for the FDA to not look at function? And two, why aren't we seeing at least the secondary endpoint data?

DR. BRASS: I'll ask Dr. Hyde or Dr. Katz to comment, but I think the point you raise is going to be part of our discussion this afternoon. But if Dr. Hyde or Dr. Katz wants to comment.

DR. HYDE: I don't know that we have a real response to that. I mean, one of the issues was that it was already an approved product and part of this development was to explore the dosing range to see if lower over-the-counter might be appropriate. I don't know if that completely answers your question.

DR. BRASS: Dr. Witter, do you want to comment on the referred-to secondary endpoints?

DR. WITTER: The secondary endpoint that I thought was most useful was what I had presented, which was the physician confirmation of spasm. The other ones, maybe the sponsor might want to discuss them in a bit more detail, but I didn't find them to be of the same kind of use.

I just might comment, Dr. Yocum, that I put up there the World Health Organization proposals and that was part of the discussion that preceded this. I think maybe that's an answer for you.

DR. BRASS: Dr. Harris.

DR. HARRIS: This is to the sponsor. One of my major concerns remains whether or not patients are going to be able to distinguish between back and neck pain alone versus back and neck pain plus spasm. Although there is data showing that the physician and patient concur with respect to their understanding of spasm, I'm still not convinced that patients won't take this as they might an analgesic with back and neck pain alone, that it will end up being in the minds of many patients an analgesic rather than being used for spasm.

I'll ask if you have any data that distinguishes or determines whether or not, or really would convince me that patients won't use this as an analgesic, even without spasm.

DR. KORN: We have not done a study looking specifically at accuracy of self-diagnosis, whether they have spasm and would they be likely to use this for conditions when they don't have spasm. Again, we've done label comprehension work, but the patients were not acutely ill then. They were normal subjects walking through a shopping mall. So we haven't looked at patients who were symptomatic and done label comprehension in those groups where maybe you would get the answer to that question.

DR. BRASS: Dr. Sachs?

DR. SACHS: Since one of the goals of releasing this over-the-counter would be to allow people to treat themselves and therefore get symptom relief faster, I was wondering if you did have some data which showed if you started the drug earlier you did feel better. Also, if you are showing that the drug is relief two days sooner, on the one hand then why would you need to take it longer for symptom relief?

DR. KORN: To answer the second part of your question first, the current prescription circular states that the product can be used for up to two to three weeks, and indeed if we look at our populations after seven days, less than half the patients had complete relief at the end of seven days, which is not surprising given the natural history of the condition. So some of those patients may have given the drug a very high medication helpfulness score. They thought it was helpful. They just hadn't gotten back up to the level of function or pain relief that they really wanted.

So to us, it's not surprising that seven days might not be the ultimate duration of treatment and they may need a little longer.

716, please?

To look at, I believe, the first element of your question, within Protocol 6 and 8, in Protocol 6

patients were allowed to be symptomatic for up to 14 days, but some did enroll after less than seven days or less than three days. In Protocol 8, patients had to be symptomatic for less than seven days, but some did enroll in less than three days. We see that the difference between 5 and placebo, the difference in mean scores for global impression of change at Visit 2 was basically consistent whether they were patients in the all-patients-treated analysis or the patients who had been symptomatic for a shorter period of time, whether it was seven days or three days.

In Protocol 8, the patients who had been symptomatic for shorter actually had a better differentiation from placebo than the patients who had been symptomatic up to seven days.

DR. BRASS: Dr. Abramson?

DR. ABRAMSON: I just had a question relating to the label recommendation that people over 65 consult a physician. I guess it was both with respect to the practicality and the rationale for that. So it's a two-part kind of question. One is, is there a precedent where OTC drugs make that kind of recommendation, that the patient consults a doctor? And what's the likelihood that that's going to be effective?

But perhaps more importantly, there's a notion

that at age 65, all of a sudden the clearance decreases and plasma levels go up. So the question is the basis of the data that shows the trend during which time with age plasma levels increase, and what happens at age 60 and 55 for example?

DR. KORN: We are aware of precedent for a different labeling for geriatric patients and analgesics. If you look at naproxen sodium, there are different dosing directions for patients who are 65 or older versus patients who are less than 65.

DR. ABRAMSON: Requiring them to consult with their doctor?

DR. KORN: No. It's for a different dose. We're going one step past that. We're saying, gee, we don't want you titrating the dose or adjusting the dose, we think you ought to see a physician, because if we're attracting a population that has acute back pain, and I think the AHCPR guidelines are consistent with this, the risk that a 65 or 70-year-old patient with a new onset of acute back pain that's substantial has an underlying condition requiring diagnosis and treatment is quite higher than a 20-year-old who was out shoveling snow. So not just from a kinetic basis but as well as a diagnosis and a risk of misdiagnosis, we believe that elderly patients should be triaged to their physician if they've got acute back pain

with spasm.

You're absolutely right, there's not a threshold effect where the clearance goes up at 65. The clearance would start to go up presumably whenever functional hepatic mass starts to go down, and it is a continuum. Where you draw the cutoff is unclear. But certainly even patients who are 65 and take the product end up with plasma concentrations that they would have gotten if they were younger and currently took the Rx product. So we think that lowering the dose by half gives us a safety margin even if patients disregard the instruction to see their doctor or those patients are 62 and think it's okay and have a higher level.

DR. BRASS: Dr. Sherrer?

DR. SHERRER: Hi. Yvonne Sherrer. I have a question. You gave us information about the rise in prescription usage of Flexeril over the years and its apparent safety, but I know as a rheumatologist, at least in recent years, prescribing patterns for Flexeril has changed. It's often used more in chronic pain as a single nighttime dose for pain modulation and sleep modulation, which, if that reflects a substantial portion of those prescription increases, may reflect a different safety pattern than what you presented in current usage, or at least usage in these studies.

Can you give me an idea of the prescriptions that are given out in the community? How many of them are in fact for acute pain versus chronic pain, a single nighttime usage?

DR. KORN: Slide 804. This slide summarizes data from Medco. In 1997 and 1998, there were 681,000 prescriptions for cyclobenzaprine, and we see that 28 percent of the prescriptions were given as a one-time dose, I assume at night, for probably fibromyalgia. But 54 percent of the prescriptions were written as TID dosing, probably for acute back pain.

DR. BRASS: Yes, Dr. Lovell?

DR. LOVELL: It seems the hypothesis for your psychomotor impairment with your drug is that it's secondary to sedation, and if that's the case, then it makes sense to do it early in the use before it gets into steady state concentration. Could you show us data to compare psychomotor results in patients who reported sedation and didn't report sedation? It seems that an alternative hypothesis is that psychomotor impairment could be due to the fact that this drug is centrally acting on the nervous system and may have impairment independent of its sedating effect, in which case steady state information would be very relevant I think.

DR. KORN: Looking at our psychomotor data in

the two driving-related studies, the median visual analog scale in all treatment groups combined, the median rating before the driving tests were begun was about 47. So we've gone back and looked at the data, the performance data in patients who had a visual analog score of 50 or more at the beginning of the test versus a visual analog score of less than 50.

DR. LOVELL: You mean for sedation?

DR. KORN: For sedation, right. So it was alert/drowsy on the visual analog scale. If they were over 50 on the visual analog scale, there were a higher number of errors in the vigilance test than if they had a visual analog score less than 50. So sedation as reflected on visual analog did seem to predict an increase in errors in the vigilance test, which is a test of basically maintaining wakefulness for 40 minutes. But again, not a steady state.

DR. BRASS: Dr. Anderson, did you have a question?

DR. ANDERSON: Yes. I had a couple of questions, one about the correlation between muscle spasm as assessed by the M.D. and the patient findings. I was wondering what the sample sizes were for those correlations that you presented on Slide 41. Then my second question has to do with the reporting of the driving skills. I was

wondering why you used geometric means in all of those slides.

DR. KORN: In Slide 41, the correlations between physician and patient ratings, the sample sizes were combined from 6 and 8. So there were 200 patients on 10 milligrams, 200 on 2.5.

DR. ANDERSON: So there wasn't missing data.

DR. KORN: No, not at the first visit. We did this at the early time point, at Visit 2. At Visit 3, there was some missing data, but the correlations were just as strong.

DR. ANDERSON: The second question was about geometric means.

DR. KORN: I'm going to let our statistician answer that for you.

MR. TIPPING: Bob Tipping from Merck. The reason that we used geometric means are two reasons. One, it helps with the distributional assumptions of the analysis. It puts it into a normal scale. The second reason is it's a little more intuitive in terms of describing what clinically meaningful differences is. Sometimes in talking about ratios, 10 percent worse or 20 percent worse, the geometric mean ratio analysis done on a log scale transforms to that sort of a definition of what may be clinically meaningful.

DR. BRASS: Dr. Krenzelok?

DR. KORN: I was going to follow up. We do have one slide to address your question about how the correlations looked, as opposed to just giving a correlation coefficient. This shows at Visit 3 the responses on the left-hand side are the physician ratings of spasm: none, mild, moderate, severe. On the right-hand side is the patient global ratings, showing marked improvement at the bottom, worsening at the top. The height of the bars represents the proportion of patients.

If there were a perfect correlation between the physician and the patient, the clustering of 12 blocks would be straight along the diagonal. What we see is that, in general, they are clustered along the center in these three areas. There are very few cases where the physician thought that the patient was worse but the patient thought they were improved, and conversely, where the patient thought they were worse but the physician thought they were improved.

DR. BRASS: Dr. Krenzelok?

DR. KRENZELOK: Thank you. This question is to the sponsor, and it really addresses the issue more of label readability. As I observed your presentation, it would appear that there was, at least from my perspective, in the recruitment of patients to determine label

readability, there may have been some selection bias. In one case you recruited patients, I think in the open-label study, using newspaper ads as one medium for selection, and 56 percent of the people were recruited that way. The other was the mall intercept methodology, again which may interject a fair amount of bias.

I guess my concern is, I wonder if you really have addressed the needs of the people who are illiterate, which are said to be at least 20 percent of the people in this country, and did you do further readability testing on the label to see how the label reads using something as simple as, say, a Gunning Fog Index that you might find on Word or whatever? Thank you.

DR. KORN: We have looked at the Smog test measure of readability, and it's a reasonable level of readability. We went to the mall intercept method looking for patients who had low literacy because we thought it would be easier to find that than through a newspaper certainly, and I think that what we have seen is that we need to skew where we go, what malls we go to, to better enrich either the geriatric setting or the low literacy level. We did not assess literacy directly by some realm or some other measure. We looked at education level as a correlate, and it appears that some people may over-report how many years. They may be embarrassed to state that they

did not finish high school.

So we know that we have to work harder in our next label comp study to find people who have low literacy skills.

DR. BRASS: Dr. Neill?

DR. NEILL: I have one question for sponsor, one question for the FDA.

In looking at the package label, I noticed that apparently the proposed marketing form is for four days of medication, and given the data that I've seen that suggests that the duration of treatment that will benefit a patient is likely to be longer than that, I'm wondering why a package with four days of medication was chosen.

A second issue related to that deals with the somnolence data, which suggests that the maximum somnolence occurs within that first four days.

The second question for the FDA has to do with a change in the labeling indication for the OTC versus prescription product. The labeling for the prescription product includes the phrase "for use as an adjunct with physical therapy and rest," and the OTC labeling does not include that phrase, and I'm curious to know why it doesn't and do we need to consider that as a different indication given that we've had no data for use of Flexeril at this dose as an adjunct to physical therapy and rest.

DR. KORN: The answer actually does talk about non-pharmacologic methods of treatment, be it heat or other methods, and we would hope that that would be in lieu of on the top. We propose to have multiple package sizes. The smallest would be four days. There certainly would be a package size with 30 tablets, which would be a 10-day course of treatment. Many consumers, if they've never tried a product before, would like to not lay out a lot of money and would like to take a smaller investment and make sure they tolerate the product before, if necessary, going back and getting more.

So over time, what we've seen with the H2s and others is they start out small and then purchase larger packages the next time they need the medication because they know they tolerate the drug.

DR. BRASS: Comment from the FDA on the indication question?

DR. KATZ: At this point in time, actually I think the sponsor answered the question regarding the indication. Since what you're seeing now are preliminary labeling as proposed by the sponsor, what you might see as an indication might change later on down the line.

DR. BRASS: Ms. Hamilton?

MS. HAMILTON: I have a few questions for the FDA on the label comprehension range of questions. Some of

this is sort of a refresher course for me, I guess. Basic questions.

Do we know how many patients read inserts?

A second question is, do we know how far down the label they read?

Do we have any data indicating how often consumers actually consult their physician when they're directed to do that on a label, and do consumers typically recognize the technical terminology from other medications they may be taking?

DR. AIKIN: Hi. Kathryn Aikin. The answer to most of your questions is no. We do not know how many consumers actually read the label insert. We do not know exactly what they focus on in the label. Some preliminary indications would be that they tend to focus on the directions first instead of the warnings. We do not have information on how many people actually consult a doctor when instructed to do so. And your final question was?

MS. HAMILTON: Understanding and recognizing the technical name of other medications they might be taking?

DR. AIKIN: They're more likely to understand the technical name if the actual name of the product is next to it and they have taken it previously, which is why there is often the name of the product next to the

technical name.

MS. HAMILTON: Thank you.

DR. BRASS: Dr. Koda-Kimble?

DR. KODA-KIMBLE: I have a basic question to either members of the Arthritis Committee or perhaps Merck's consultants. I'm interested in the pathophysiology of pain related to back and neck pain. I mean, what is garden variety back and neck pain? I don't think people say, "I've got a spasm, I've got strain, I've got back pain, I've got a stiff neck." In the AHCPR guidelines that we received, at that point there were several experts who questioned the importance of spasm in the cause of pain. So could somebody bring me up to date on that? If somebody says, "I've got back or neck pain," what is the cause of the pain?

DR. BORENSTEIN: David Borenstein. I'm supposed to answer this question. I've written a 700-page book on back pain, so I want to make this answer brief. It's a very difficult question to answer, because back pain can mean very different things for different people. I think in the run of the mill circumstance in mechanical low back pain, one is talking about a muscle injury frequently. This will be debated among rheumatologists and orthopedists as to whether the disk is the primary focus of the problem or is it a muscle syndrome.

I do believe certainly in younger individuals, where the drug is supposed to be used primarily, it is a muscle pain syndrome. In that circumstance, I do believe there is muscle injury. As part of the muscle injury, I do believe there is contraction of the muscle as part of that on a reflex basis, which I feel we are able to determine in many individuals on physical examination, as well as some range of motion.

Now, some of these statements can be debated as to how specifically one is able to determine that. But if you ask patients, they have different terms in regards to whether they are able to function or not and whether they feel that they are tight or limited in their motion. If it's a tightness that they feel, I think they equate that with spasm. In my experience, that is where these medications, the muscle relaxants and Flexeril, can be quite helpful.

So I do think individuals do use terms which describe muscle spasm as a component of pain. Now, which one comes first and how much is what depends more on an individual basis. But I do believe that contraction and pain do play a role in those common musculoskeletal problems of the lumbar spine. Hopefully I've answered that to a certain degree, but I can go even further if you want.

DR. KODA-KIMBLE: Is that 90 percent of the

time? I mean, what I'm just saying is if somebody says "I've got back or neck pain," what fraction of the time is that related to spasm? Well, we're using the term "spasm."

DR. BORENSTEIN: The answer to that -- and I'm not trying to dodge the question -- depends. If you have someone like me, it's a smaller percentage because I see only the more difficult patients. I think you see the whole spectrum of individuals. Ninety percent of individuals with back pain have it on a mechanical basis, which means part of this is that it's based upon joints and muscles being affected. Depending upon the age range, you will have more arthritis in the older group, while the younger group will have it more on the basis of muscle injury.

So if you're talking about younger individuals, I think a vast majority of those individuals have it on that basis. The older you get, the less it becomes a problem of muscle and more it becomes one of either joint or disk problems, things of that sort.

DR. KODA-KIMBLE: I have one other question. This relates to the use of the pharmacokinetic data you have on patients with liver disease. In the study, it says you studied people with a Pugh-Child classification of 5 to 11. Could somebody explain to me what that is and whether someone would be able to recognize their liver disease at

that level?

DR. KORN: The patients in the study who have a Pugh-Child score that's large enough to qualify have known cirrhosis, and they certainly can't assess their own laboratory parameters, whether it's a low serum albumin or a high prothrombin. The transaminases are actually not part of the score. So in general, they will not know whether they're a Child-Pugh 2, 3, et cetera. They will know, hopefully from their physician, that they have liver disease, and that's the term we're putting on the box.

DR. BRASS: Dr. Gerber?

DR. GERBER: I am trying to sort out the issue of spasm and pain and how that really does clinically relate to what you are calling efficacy of Flexeril. As I review Slide 40, which is the physician rating of muscle spasm that you report, specifically in the model of the most acute back pain or most acute spasm, there seems to be some interesting information there that doesn't really support my clinical experience of more than 25 years of treating these kinds of problems in that if you have an acute spasm and your medication is effective, it should be working within the first several days.

This data suggests that essentially at Visit 2, there is no significant difference between placebo and cyclobenzaprine 5, and no difference between placebo and

2.5. It takes about eight days average, because that what your Visit 3 is, to show a difference at the 5 milligram level, and that doesn't quite sit with my clinical formulation. Also, looking at the issue of having an acute problem that has an acute relief, I wonder if you'd elaborate a little bit or perhaps give me your interpretation of that.

DR. KORN: We think that 5 milligrams was effective at Visit 2 in Protocol 6. So what we're seeing is that Protocol 8 had less discriminatory ability at the early time point.

DR. GERBER: I am talking about Protocol 8 because that's the shorter duration group that was selected for treatment. They had their acute onset within a week of selection into the study.

DR. KORN: Again, we're not sure why 8 didn't turn out like 6. Even when we look at the subgroup in 6 of patients with more acute pain, we saw better differentiation of 5 milligrams from placebo. So we cannot explain why, but we can say that when you look at the more acute subset of 6, which would also be like the patients you're thinking are appropriate, we do see significant differences.

DR. GERBER: The only other observation I would make about that which I think is worthy of comment, at

least from the clinical perspective, is the natural history of what the physician is calling muscle spasm. By Visit 3, which is Day 8, there's better than a 50 percent reduction in symptoms as determined by the physician, presumably by palpation or some of the other things that Dr. Borenstein was referring to, in the placebo group. So that shows you that you have an appreciable reduction over a one-week period with no intervention, telling you a little bit about the natural history of the symptoms. So one would expect if you're seeing efficacy, to see if relatively early in the course.

DR. KORN: Could I just show one slide here? There is a secondary analysis in Protocol 8 looking at proportion of responders in the all-patients-treated approach with the clinical global impression of change, and these bar graphs show the distribution of the ratings. We see that 5 milligrams had 78 percent responders, versus 66 percent with placebo, and that was a significant P value of 0.007. So in our primary analysis of mean scores, we did not show a significant difference at the early time point, but we certainly did in the secondary analysis of percent responders.

DR. BRASS: At this time, I'm going to break us for lunch. Before everybody disappears, we are going to reconvene promptly at 1:00 with the open public hearing.

Before we depart, Dr. Titus has a few words of wisdom.

DR. TITUS: I have two announcements for the committee members.

I'm sorry. You'd better do it.

DR. BRASS: While I'm pulling out my glasses again and trying to decipher handwriting, I will remind committee members that they are not to discuss issues related to today's subject during lunch.

These announcements look like they say, for the committee members, in the restaurant there's a reserved table in the rear, as always, for participants. We have travel assistance available -- too late for Dr. Abramson. We have travel assistance available at the reception table.

I think that's it. Is that it? Okay.

Thank you all very much. We'll reconvene at 1:00.

(Whereupon, at 12:07 p.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:00 p.m.)

DR. BRASS: Good afternoon. As we begin to reconvene, I just want to go over again briefly what the format for the afternoon's agenda will be. We will begin with the open public hearing, and my understanding is we have one individual who has requested time. We will then continue with our questioning of the FDA and sponsor concerning the presentations from this morning. We will then shift to a more focused discussion of the questions posed to the committees by the FDA, during which there will undoubtedly be opportunities and need for additional questioning of both the FDA and sponsor presenters.

Having stalled long enough, we will now begin with the open public hearing. Dr. Larry Sasich from Public Citizen has requested five minutes of time.

DR. SASICH: Thank you very much for this opportunity to speak before the committee. Before I begin with my comments, I would like to say that due to litigation that Public Citizen has been involved with against the Food and Drug Administration, the FDA's reviews that were distributed to these advisory committees are available to the public now. I believe that this is the first time that FDA review documents have been available at the time of an FDA advisory committee, and I would like to urge all members of the media to take a look at those

documents if they have time before they write their stories, and hopefully at some point in the future these documents will be available prior to the time of advisory committee meetings.

Public Citizen firmly believes that for any drug approval process to be truly safe, it must be as transparent as possible to the public.

Thank you. I'll go on with my comments.

Public Citizen's Health Research Group has not seen evidence presented today that cyclobenzaprine in a 5 milligram dose given three times a day is as effective as existing nonprescription analgesics and anti-inflammatory drugs in relieving the pain of local muscle spasm, and it has a higher risk of serious adverse effects. Perception of pain is critical in your consideration of this drug's switch from prescription to OTC status because it appears that the three primary efficacy endpoints used in the two pivotal protocols, 006 and 008, depends on patients' assessment of pain rather than muscle spasm.

Since we have no evidence that cyclobenzaprine 5 milligram is as effective as currently available nonprescription analgesics, this raises the issue of consumers increasing the dose of cyclobenzaprine to 10 milligrams three times a day from 5. At the 10 milligram dose of the drug, the current cyclobenzaprine labeling

indicates that 40 percent of patients will experience drowsiness. The FDA in its review found the efficacy of cyclobenzaprine, and I quote, "to be clinically modest." Though there may be a statistical difference between cyclobenzaprine 5 milligrams and placebo, the clinical significance of this result remains to be unknown.

A fundamental requirement of any over-the-counter drug is the condition for which the drug is indicated can be accurately and safely self-diagnosed by consumers. In the two pivotal trials just mentioned, an exclusion criteria for participating in these trials included, and I quote, "vertebral body or percussive tenderness." A consumer would have to be remarkably flexible to percuss the entire length of his or her spine alone.

This drug is associated with a number of clinically significant drug interactions, including widely prescribed drugs such as tricyclic antidepressants, and there is a potential for seizure when this drug is used in combination with tramadol, a prescription pain reliever better known as Ultram. There are also a number of medical contraindications to the use of cyclobenzaprine. These include a recent heart attack, heart rhythm disturbances, and congestive heart failure. This drug should be used with caution, if at all, in patients with glaucoma or

predisposition to glaucoma, urinary retention, heart block, or hyperthyroidism.

Cyclobenzaprine has been available in this country since 1977. The drug's long use with the sponsor claiming over 100 million total prescriptions dispensed since it was first introduced, and we have no reason to doubt that, this number would be much more reassuring from a safety standpoint if we had an adverse drug reaction reporting system that could accurately estimate the number of individuals harmed by prescription drugs.

The sponsor made reference to the muscle relaxants methocarbamol, orthenadrene, and chlorzoxazone as being available over-the-counter in Canada, either alone or in combination with analgesics. Chlorzoxazone was relabeled in this country in 1996 with strengthened warnings regarding its liver toxicity. Cyclobenzaprine has been associated with abnormal liver function, hepatitis, jaundice, and cholestasis in less than 1 percent of patients using the drug. This is from the current FDA approved labeling for the product.

The reason that I mention this, I would like to remind everybody that the openness of other drug regulatory authorities, such as the Canadian, is not the same as the FDA. The dangerous antihistamines terfenadine and astemizole were also available without prescription in

Canada, and because of the lack of transparency in the Canadian drug approval process, we do not know what the basis for allowing the use of the muscle relaxants or terfenadine and astemizole in Canada were.

We remain very concerned about the severe drowsiness that the 5 milligram dose of cyclobenzaprine can cause, 2.6 percent in Protocols 006 and 008, the psychomotor impairment that can occur in the absence of perceived drowsiness by patients, its drug interactions, medical contraindications, and cyclobenzaprine's use by the elderly. We are also concerned about the consumer's ability to differentiate mild muscle injury from a serious injury to the spine. The data presented by the FDA about the comprehension by consumers of some important information about cyclobenzaprine is troubling.

In summary, this drug has demonstrated only minimal efficacy to differentiate it, as the FDA so correctly pointed out, from effectiveness, and may not be equivalent to available over-the-counter analgesics and anti-inflammatory drugs, and is clearly less safe than these drugs. In conclusion, we would urge that this committee not recommend that cyclobenzaprine be made available for nonprescription drug use in the United States.

Thank you very much for your attention.

DR. BRASS: Thank you.

I'd like to now continue the questioning of the sponsor and the FDA, and again perhaps I will begin with a few questions concerning the pharmacokinetics of the compound.

First, in clarification, the current material makes reference to a half-life of 18 hours. Yet the previous package insert and a variety of literature suggests a longer half-life for the compound. I'd appreciate clarification of where the 18 hours was derived.

DR. WINCHELL: I'm Greg Winchell from Merck. In answer to your question, the 18-hour half-life that's in our current label is an accumulation half-life based on the accumulation of drug. The previous half-life was a terminal half-life, but the terminal determination was confounded by the presence of interhepatic circulation. So if you look at the terminal elimination phase, you get different slopes depending on when you get interhepatic recirculation.

DR. BRASS: So how was the 18 hours determined?

DR. WINCHELL: By fitting a monoexponential to the accumulation of drug to the trough concentrations on daily dosing. That's why it's an effective half-life.

DR. BRASS: Okay. I think I know the answer to this, but it may help explain some things. Why is a drug

with an 18-hour half-life being dosed TID?

DR. KORN: We adopted the historical precedent, since the 10 milligram prescription dose had been dosed TID for 20 years, we decided not to try to confuse people by shifting the dose recommendation to a less frequent interval. We certainly recognize that you would reach steady state at a reasonable time, but we think that given the fact that there is a response between the amount of drowsiness and the amount of a single dose, we'd rather have smaller doses taken more frequently than larger doses taken more infrequently.

DR. BRASS: Concern was raised about the drug metabolism spectrum and profile. You presented an in vivo profile of metabolites recovered in the urine, and in vitro P450 profiling, and the concern was that the in vitro was using much higher concentrations of the drug. I was wondering if you tried to predict the in vivo metabolite profile as compared to the predicted products from the in vitro data based on the P450 profiling and whether it is both predictive qualitatively and quantitatively to give some confidence to that in vitro data.

DR. WINCHELL: In regard to the in vitro data that was done at high concentration, we do believe that the FDA's concerns with regard to that were well founded. We're actually in the process of conducting more in vitro

studies, of which I have some very preliminary results, at lower concentrations. In terms of the profile, one of the reasons we went to high doses was because in vitro we were only able to get ND methylation, and then we had to run at very high concentrations in order to get a sufficient amount of the D-methyl metabolite to measure. In the studies we're doing at lower doses, we're looking at the disappearance of parent drug. But again, we won't know the metabolic profile of that because it will be too low.

DR. BRASS: Do all three of the P450s identified catalyze the D-methylation reaction, or do differential products from the three P450s in vitro that were active?

DR. WINCHELL: At high concentration, all three were involved. At low concentrations, our very preliminary data, which hasn't been reviewed by the FDA, where we used monoclonal antibodies against individually 3A4, 1A2, and 2D6, none of them individually was able to substantially block the disappearance of cyclobenzaprine at low concentration.

DR. BRASS: Okay. I think we'll hold that because that data is preliminary and the discussion is in the spirit of what is necessary. I think that answer will suffice.

Yes, Dr. Pucino?

DR. PUCINO: Yes, a couple of things along the same line. Do we know anything about the activity of the metabolites?

DR. WINCHELL: The answer to that is no. We don't have (inaudible).

DR. PUCINO: Is there any data using inhibitors of at least the two primary cytochrome P450 systems, the 3A4 and the 1A2? Inhibiting in vivo.

DR. WINCHELL: No. We have no clinical data on inhibitors of those two.

DR. BRASS: Okay. I guess I will continue, then, with some additional questions.

The issue of the predictability of the adverse events has been inferred several times, that a patient who self-diagnoses sedation will be able to avoid engaging in the high-risk behaviors. Do you have data to substantiate that self-assessment in a predictive way that will be helpful in reassuring? Just like you self-diagnose the indication, can you truly self-diagnose the contraindication activity?

DR. KORN: No. We have not looked at the positive predictive value of sedation. What we do know is that in the clinical trials we've looked at impairment at the time of peak sedation, but we haven't looked at differentially those who were or were not.

DR. BRASS: One of the concerns about the toxicity has been drawn from the parallelism between cyclobenzaprine and tricyclic antidepressants. In the area of arrhythmias, is there any data that at the concentrations achieved of cyclobenzaprine in either therapeutic or even in overdose situations, that there's any class 1A type electrophysiologic effects of the compound and/or QRS prolongation in non-fatal overdoses?

DR. KORN: No. Both with 5 milligrams TID and 10 milligrams TID, we have not seen QRS widening, QT prolongation.

DR. BRASS: What about in the overdose situation?

DR. KORN: Again, in the overdose situation -- and Dr. Krenzelok might be able to speak to this as well. In his review of approximately 500 overdoses, life-threatening arrhythmias were just very uncommon in doses of less than 1 gram.

DR. BRASS: I understand. Was QRS prolongation looked for and identified? Because again, I'm looking for parallels, the strengths of the analogy between the tricyclics, and the tricyclic proarrhythmic effects are thought to be related to direct effects which are manifested as Class 1A antiarrhythmic effects and electrocardiographically early as prolonged QRS complex.

DR. KORN: We have not seen QRS widening in a dog study at up to 40 times the human plasma concentration at therapeutic doses. We don't have data on people at that high dose.

DR. BRASS: One of the additional issues that has come up is how this drug will be used in actual use, particularly duration of use, and whether consumers will self-limit their use. Your actual use study was designed to be seven days. In actuality, there was substantial use for 10 days, and in some of the materials it was viewed as there was very little use past 10 days. But I think it's very important to point out two things. One, the final visit was scheduled to be between 8 and 10 days, and therefore use beyond 10 days you wouldn't be able to detect, and they were only given 30 pills. So I think drawing the conclusion that consumers will not use the drug for longer than 10 days cannot be drawn from that study, and that, in fact, a conclusion that can be drawn, they did use it longer than was expected or they were told to use it.

Is there reason to be concerned that, in fact, they will use it longer than 10 days when we tell them to stop at 10 days?

DR. KORN: Well, we have no data to suggest they would be any more likely to do that than they would be

to take ibuprofen or acetaminophen for longer than the 10 days that those products are currently labeled. We also recognize that patients who have reached steady state concentrations, it was certainly by the 7 days or the 10 days that they took the drug. So we have had an opportunity to assess safety at steady state concentrations.

DR. KRENZELOK: I'll just make a comment regarding the QRS prolongation and widening and so on. Back when this drug came out in 1977, we were very concerned that it would have the same profile as, say, the tricyclic antidepressants, and so we were pretty vigilant about making sure these people were admitted according to the tricyclic antidepressant protocol. They were admitted for three days of continuous monitoring and so on, and the safety profile has been very, very good and hasn't even come close to the tricyclics.

So in response to your question, Dr. Korn's answer was absolutely correct. It's a very safe drug. In overdose, we very rarely see any dysrhythmias at all.

DR. BRASS: Dr. Gerber?

DR. GERBER: In pursuing the mechanism of action and its efficacy in muscle spasm, I wonder if the sponsor would comment. In any of your secondary analyses, have you looked at those patients who respond that they

have had significant -- that is, major -- improvement in symptoms, and those same patients potentially reporting increased drowsiness or sedation? I'm looking for concordance between response and sedation.

DR. KORN: We have data that we showed this morning that looks at the percent responders in those who were not sedated versus those who voluntarily reported clinically apparent sedation. Again, the difference in the means in proportion responders for those who did not report sedation was at least as large, in general, as the all patients treated. The sample size gets too small in the placebo group that reported sedation to draw conclusions about that.

DR. BRASS: Dr. Yocum.

DR. YOCUM: I have a couple of questions. The first really relates to concerns about following up on the duration of use of this therapy. We're hoping that patients who have chronicity, which is a concern here, will consult their physician if they have long-term back problems. Do we have any data from the prescription Flexeril use that, in fact, physicians limit use to less than 10 days? Because if the patients are going to go to the physician, and the physicians are already not using it in that way, I don't think it's going to be a limiting factor. That's question number one, which is to the

sponsor.

Question number two relates to the comprehension studies, because I'm not sure whether they're the same studies, one by the FDA, one by the company, or whether they were the same analyzed in a different way. I was very confused about that, because the conclusions of the FDA were a little bit confusing in that it seemed like the first conclusion suggested everybody understood what was going on, but then later on suggested that, in fact, that the elderly consumers may not consult a physician, so that gets rid of that, hopefully, stop point for misuse. That other is that the elderly consumers may use Flexeril for inappropriate conditions, which is also of concern, especially if they're going to use it for chronic situations.

Nowhere in this analysis did I see whether you asked the patient did they understand that if they had back pain for more than two weeks, that they were to consult their physician and whether they clearly understood that. On Slide 89, there's no percentage of whether the patients comprehended that or not. So I'd ask both the FDA, was that comprehended if it was the same questionnaire, and the sponsor too, did they ask that, and do the patients comprehend the issue of chronicity versus acute nature, because I think the labeling concerns me, that while in

fine print it says "acute," there's nothing else in the labeling that talks about acute.

DR. KORN: I'd like to introduce Dr. Mary Moore to address the first part of the question.

DR. MOORE: Well, I'm a rheumatologist and I'll address the first part of the question from that point of view. It was said earlier today that many clinicians, many rheumatologists and chronic pain doctors have begun to use prescription Flexeril chronically. For fibromyalgia and for chronic pain, it's often given as a single dose at bedtime, and other people give it during the day. So there are out there now hundreds of patients, if not thousands, that are taking the prescription dose chronically without any problem. So that would be my comment as a clinician about the chronic use.

DR. LOVELL: The prescription dose is 10 milligrams TID, and I don't think that's commonly used for treatment of fibromyalgia, is it?

DR. MOORE: Very often varying doses are given either at bedtime or during the day. So anywhere from 10 to 30 milligrams at bedtime is given. Other people prefer to give it during the day. All I can say is that it's not uncommon to see 30 milligrams given daily for many months at a time for fibromyalgia and other chronic pain.

DR. YOCUM: So my conclusion would be that it's

unlikely that the physician is going to limit the patient to 10 days or less. So we may well be looking at OTC use for extended use, because there is going to be no limiting factor.

DR. BRASS: I think, again, just from the OTC perspective, just in general, those kinds of warnings are there for two reasons. One is so that if there's another condition present, that the physician has the opportunity to intervene in the chronic use, or if there's a contraindication for chronic use. So I think your assessment is right, but we would still hope that we'd want the patient to still seek attention.

Dr. Aikin, do you want to respond to the questions about the comprehension?

DR. AIKIN: They were indeed the same study, so I don't want to have that be confusing.

In terms of stopping use and asking a doctor, the question "In which of the following situations does the label say that someone should stop using this product and ask a doctor?", 99 percent of the participants answered correctly, if their symptoms do not improve within 10 days. That would imply if they still have pain after 10 days, not would they continue to use after 10 days.

I'm sorry if the conclusions about the general sample and the subsamples -- and I think you're referring

specifically to the people 65 and over -- were not quite the same. I tried to present those concepts that were well understood first, which include dosing, and the concepts that were not well understood, and that is the similarity possibly to analgesics. In that case, participants age 65 and over were more likely to say that they would use it when it was clear they should be contacting a doctor first.

DR. BRASS: Yes, Dr. Abramson.

DR. ABRAMSON: I just had a question about how realistic it is to think that patients can separate muscle tightness and spasm from chronic pain and arthritis. I think as Dr. Borenstein was talking about with low back pain or neck pain, it's hard even for physicians often to understand where that pain is coming from. My question is, how reliable, even among physicians, is interobserver diagnosis of muscle spasm? My own experience is that we can differ quite a bit, even from doctor to doctor, about our perception of that. So is there any data on the reliability among physicians, and then by extension the reliability of patients in diagnosing muscle spasm or tightness versus arthritis-derived neck or back pain, since we're relying on the patient to make that distinction?

DR. KORN: First, there is conflicting data in the literature as to what the interobserver agreement would be on assessment of spasm. In view of that, we had the

same physician examine an individual patient each time they were in the clinic, because certainly we believe within-physician variability should be less than across the physicians. We do not have data on what the accuracy of the diagnosis would be among physicians. We would hope that rheumatologists would be making an accurate diagnosis and know from history before they even resort to the radiograph of the likelihood of osteoarthritis.

DR. BRASS: Yes, Dr. Koda-Kimble.

DR. KODA-KIMBLE: I believe in the actual use study, about 15 percent of patients were using an analgesic or an anti-inflammatory agent of some kind. Perhaps you could give me more detail, but it seems as though, as a surrogate marker at least, the number of people who decreased their use of analgesics did not increase. Do you know what I'm saying? I mean, they didn't decrease their use of analgesics over time.

DR. KORN: That's correct. On Slide 462, we see that the percent of patients using an analgesic on any day during the first seven days of the study was relatively constant, and we would surmise that if they were using an analgesic because the cyclobenzaprine had not been effective and they needed something to tide them over until it kicked in, I would have expected to see more use early on and then trail off. But here it's pretty flat

throughout the study.

DR. BRASS: I have a question for Dr. Lee from the FDA that I'd appreciate clarification on. You expressed concern in your conclusions that there was inadequate data in the pediatric and geriatric populations. Philosophically, how big a concern is that if the label says that those populations should not use the drug without physician consent?

DR. LEE: My concern is that if the label says to ask a doctor and the doctor goes to the PDR without any information in it, basically the doctor has nothing to recommend to the patient. So we still think that a study is necessary so that the doctor has some information.

DR. BRASS: Okay. And then also clarification from Dr. Neuner from the FDA. You made a reference to concern -- I think it was you -- about hallucinations and confusion as being a potential adverse effect. Could you share with us the basis for that concern?

DR. NEUNER: Yes. There was, if you remember from my presentation, there was a slide where I listed the most frequently reported postmarketing events, and on examination of the postmarketing events that were submitted by the sponsor from their own database system, there were I believe 20 cases of psychosis, 12 of which were considered serious by our present definitions, that resulted in the

hospitalization of the patients. This is disturbing considering the fact that this drug has been around for 22 years and that in this day and age the mechanisms of reporting are probably much easier than they were 22 years ago.

DR. BRASS: Have those cases been either specifically examined or the magnitude of that signal compared to other drugs been looked at to say that this is a likely or unlikely possibility associated with the use of the drug?

DR. NEUNER: Due to the large volume of the postmarketing database, as you remember, my review was marked "Draft" because there are still certain elements that need to be reviewed that, unfortunately, due to the time limitations, were not completed at the time that this package needed to be submitted to the advisory committee for their review. So that's under review.

DR. KORN: We have data about the hallucinations, if you'd like to see it.

DR. BRASS: Okay.

DR. KORN: Slide 369. In the WAES database over the past 20 years, we've collected 82 reports of hallucinations, 79 of which occurred in patients who had not taken an overdose. What's interesting to note here is that 58 percent of the time, when we knew the age of the

patient, they were over 65. So this is a signal perhaps that the elderly are at an increased risk of an anticholinergic mental dysfunction. Many of the cases were confounded by the use of other drugs or underlying illness. Many of the cases had visual hallucinations, which is consistent with this. But again, the only signal we see out of this relatively small number is the elderly.

Next slide.

If we look at the FDA database, there are 20 serious reports of hallucinations that did not originate from Merck. There's one death in a patient with other medications as well. There are 13 non-fatal cases of hallucinations where the patients were taking one or more other CNS-active drugs, and 69 percent of the time the patients were over 65. So we view this data, again, as a risk that we can modify and minimize by having the elderly see a doctor before using the product.

DR. BRASS: Yes?

DR. ELASHOFF: The "you should see a doctor before using" does not include pregnancy or nursing, although at the very bottom in smaller print it says that if you're pregnant or nursing the baby, you should talk to a "health professional." It seems to me that that ought to be in the other spot.

DR. BRASS: Let me just point out, for those of

you who are not on the OTC committee, that there is a standard revision going on of the format of the label and the organization of those materials, which this label was prepared prior to. But if the sponsor would like to comment?

DR. KORN: No. We just followed the standard FDA format in the now-final rule for OTC labeling.

DR. DeLAP: I think we just want to be clear that we're separating two different issues here. One is communicating the information in the labeling, and the other is what the consumer actually does with that information if they do get it from the labeling. Those are potentially quite different issues, and I think that we all recognize that people can be very independent and can decide for themselves that what it says on the label doesn't apply to them. We've had the discussion, I think at the Nonprescription Drugs Advisory Committee, about how many people follow the directions on some of the packages I think.

DR. BRASS: Only a thousand times.

DR. DeLAP: And you can probably express that better than I can from memory, but I seem to recall something about the vaginal antifungal products that say to see a doctor if you've never had this before before you start using this product on your own. In fact, somewhere

close to half of the people who buy the product have never had this problem before and are buying it and using it despite the label saying otherwise.

DR. BRASS: My last question for the sponsor has to do with what the basis for the differential -- why individuals seem to respond differently both in terms of efficacy and more particularly in terms of the magnitude of sedation. I was wondering specifically whether any pharmacodynamic modeling had been done to look at whether or not those differences lie in pharmacokinetic differences across the population or pharmacodynamic susceptibility, and how predictable these types of relationships are for future considerations.

DR. KORN: The short answer is no. No modeling has been done.

DR. BRASS: Yes, Dr. Yocum?

DR. YOCUM: I guess again, Dr. Aikin, with the comprehension study, we're seeing a lot of these toxicities that are reported, especially where other narcotic and non-narcotic analgesics are combined with Flexeril or cyclobenzaprine. In the comprehension study, was there any indication -- because in the labeling there are some examples of what patients shouldn't take together with this. Maybe you stated the question. Did they understand that they shouldn't mix these drugs, or not? Was that a

well understood concept?

DR. AIKIN: Well, they talked about whether you could take Flexeril with recommended doses of pain relievers. But as far as other drugs -- and I don't have a good idea of exactly what was in the label comprehension study right off the top of my head. Maybe the sponsor has the answer for that.

DR. YOCUM: I'm just interested because I'm convinced that a lot of elderly with chronic back pain are going to be scarfing up this medicine out there, and they will have visited a pain clinic. We've already looked at some data along this line, and it's 20 or 25 percent of patients with chronic back pain, especially with arthritis, are taking quite a few medications. I guess my concern is the toxicities really seemed to escalate once you begin to mix these drugs together. I don't know.

DR. AIKIN: Alcohol and tranquilizers were certainly mentioned. But by name, I don't think they tested by name.

DR. KORN: Slide 448. There was an element of self-selection assessed in the label comprehension study, and if we look just at the left-hand column, we see that of the people that thought they could use it but we considered that they shouldn't use it, very few of those shouldn't use it because they're taking other drugs, whether it's the

antidepressants, muscle relaxants. Again, the caveat, the limitation to this question was we didn't say "If you're taking muscle relaxants at the same time." So they may have thought they could use this in place of what they were taking now, not necessarily in addition to.

DR. YOCUM: But it looks like there's a difference here in that patients over 65 are more likely to make errors. Is that true?

DR. KORN: Well, this is saying that of those who were over 65 and made an error, obviously all of them were considered to be wrong because they were over 65. So that's where the 100 comes in. For the rest of it, there's really nothing that's really noticeably different than in the younger.

DR. BRASS: Yes?

DR. LOVELL: Can you indicate what percentage of the patients who had demonstrated deficits in driving-related psychomotor tests were not sedated or didn't report sedation as a side effect? Because in the FDA's review, they talk about that sedation is not predictive of that.

DR. KORN: Most of the patients in the studies, no matter what treatment period they were in, reported sedation, probably as a result of boredom, sitting in the clinic waiting for the testing to begin. We did not see a difference, although we have not classified people as

impaired versus non-impaired looking for a difference in whether they were sedated or not by report and whether they were impaired or not by report.

DR. BRASS: At this point, I think we will shift gears a little bit. As I indicated, there will be an opportunity to address specific issues that become relevant during our discussion. But we'll shift to a discussion of the issues that the FDA would like us to discuss, as well as what we would like to discuss, and ask Dr. Katz to charge the committee.

DR. KATZ: Actually, given the nature of the discussion that's been going on for the last hour, and then for the preceding hour before we broke for lunch, I'm not sure at this point it's necessary for me to give a formal charge to the committee, since the committee seems to have already been grappling with some of the issues before them that I would have liked to have drawn to their attention. So, with that, basically I would like to focus the attention on the questions that the FDA has put before the committee to address during the rest of the afternoon's presentations for deliberation.

One additional comment is that Dr. Andreason has joined us, so if there are any questions that anybody has specifically related to his presentation, he's here to be able to answer those now too. Thank you.

DR. BRASS: Okay. You all have a copy of the questions, and I'd like to do them individually. So I will read the first question.

"The data in the original NDA support the use of a Flexeril dose of 10 milligrams TID (in the range of 20 to 40 milligrams total daily dose) as a prescription product. In the current submission for OTC use, do both Study 006 and Study 008 demonstrate a clinically significant effect of Flexeril 5 milligrams TID for relief of painful muscle tightness and spasm of the back or neck due to a recent strain, overuse, or minor injury? In answering this question, please describe the endpoints and analyses that caused you to come to your conclusion." So we want to specifically focus on efficacy and efficacy as modified by clinically significant as posed by the agency.

Is there somebody who would like to get us started? Just like in school, if there are no volunteers, I will call on somebody.

(Laughter.)

DR. BRASS: Dr. Yocum.

DR. YOCUM: I feel that the endpoints that were used, the global measures, have not proven to be very effective or good at showing efficacy in arthritis models, and I'm concerned that the primary endpoints don't give me a great deal of security that this is a clinically

effective result. So based on the endpoints used for analysis, I do not feel that these show clinically effective responses, to make a point shortly.

DR. BRASS: Are there endpoints that you would find superior and satisfying if they were positive?

DR. YOCUM: Yes. I think something is basic, and maybe Dr. Gerber can enhance our knowledge on some better functional endpoints. She commented on function earlier on, but just basic things along the line of a modified health assessment questionnaire or something along that line to show that there was better functioning, because my assumption again is that the release of this compound is to significantly reduce the number of people who are out there suffering so that they can function better. If it's just to relieve pain, I think we should go back and compare analgesics. This doesn't give me that sound of a clinical feeling that it gives great responses.

DR. BRASS: I'll call on Dr. Gerber in a second, but just in relationship to the last caveat you put out, when we review an analgesic, we usually do not ask that it be superior to another analgesic for it to be used, only that it be an effective alternative. So are you saying that standard is inappropriate for this class?

DR. YOCUM: Well, one, I don't think we're dealing with analgesic class, so maybe I was inappropriate

in bringing in analgesics. We have no positive comparator in these studies, so that we have nothing to compare with other than placebo. So we only have placebo-controlled trials in primarily global primary endpoints with no functional. So on that basis, it's rather marginal data as far as I'm concerned. If we're to get into things such as analgesics and comparators and long-term functioning, then I think again we get into a different class. But based on this data which is placebo-controlled and based only on global data, it's rather marginal to go OTC.

DR. BRASS: Dr. Gerber.

DR. GERBER: I would support the relatively easy self-report questionnaires such as the SF-36 or the Modified Health Assessment questionnaire or the Sickness Impact Profile; easy to do, functionally based, very valid, et cetera. I do think that there's one other point, and that is that if this is truly a request, as the sponsors have I thought very succinctly put, for a new class of drugs to come on the market as OTC, then the endpoint, the sort of self-selected or the sine qua non endpoint really relates to such measures as muscle spasm or muscle tenderness or tender points or whatever terms now we are using for more of the soft tissue aspects of back, not neuropathic and not rheumatologic or not orthopedic/arthritic.

In that regard, the endpoints that are cited in Study 009 leaves much to be desired both in terms of the robustness of the differences among the groups, and that is dose-response or placebo compared, and also -- and this is the one that really does concern me -- the time course of responsiveness. So we've got a kinetic problem here. We've also got a robustness of findings, from my perspective.

The third thing is the overwhelming observation that untreated, people get better. I think that really sort of lays the ground for where the work has to be done to convince me, at least, or a potential consumer I would hope, that this would be worth taking any risk taking this medication.

DR. BRASS: Dr. Neill?

DR. NEILL: Yes. I basically want to emphasize the last point Dr. Gerber made, which relates a little bit to your question about whether and why we ought to consider NSAIDs or other analgesics in comparison to this. It's because I believe that AHCPR has found that NSAIDs in general are more effective, and if that suggests an appropriate sequence of treatment, then the question before me would be both, A, for my patient that comes in, should you take any medicine as opposed to just waiting and getting better; if you decide to take a medicine, which

should you take or consider first given your particular circumstance?

That would make me want evidence that suggests that patients are able to step through that sequence just as I would do as a physician if we make what amounts to, in my mind, a second-line agent available over-the-counter given that the data that is already sitting on the table suggests they cannot distinguish between this and an analgesic, and they cannot then logically place this in a sequence that would give them best chance for improvement with the lowest chance for side effects.

So to more directly answer your question earlier I think you directed towards Dr. Yocum, should we consider a new standard for OTC medicines, analgesics or, in this instance, muscle relaxants in not just demonstrating effectiveness against placebo but effectiveness against other agents, I think the answer clearly is yes when there's good evidence to suggest that there is superiority of one over another and when we can infer a time sequence of course of treatment.

And, no, I don't want to do that this afternoon.

DR. BRASS: I didn't ask.

DR. NEILL: Good.

DR. BRASS: Other comments or questions? How

do our consumer representatives feel about the issue of defining clinically significant efficacy?

MS. MALONE: Well, I think people are largely looking for pain relief and for function, better function, and we have nothing to prove that there actually is better function using this.

One other thing. Before it was said about the inserts. I think today people do read them more than they did five years ago, but they're very difficult to read. Even your label is difficult. I'm wearing glasses and I've just had my eyes checked, and I had difficulty reading the small print. My worry is that people over 65, if they bother to read it, will have a difficult time.

Also in line with that, it's not just the label and the package insert. In today's market, there's a lot of media and t.v. marketing done, and the way people are portrayed in the commercials really is attractive for someone to go and use these medicines.

DR. BRASS: And it's probably not an accident.

Kathleen?

MS. HAMILTON: I have a smaller sort of lingering question about how effective this product is in terms of restoring practical function to a consumer as opposed to just relieving pain. So I'm sort of struggling with that.

I also have a sort of nit-picky lay person's question. I noticed throughout this discussion and all the materials that we've been provided that there's a persistent reference to back or neck spasm due to recent strain, overuse, or minor injury, and I haven't seen any of the data that talk about symptomatic relief related directly to muscle spasm or neck or back pain that's specifically related to strain, overuse, or minor injury. Since I know that one of the concerns is the potential for misuse of this product for other situations, I'm concerned that there wasn't any specific relationship between the data and those situations.

DR. BRASS: Does sponsor have any data on an identifiable recent precipitant in the patients in any of the studies?

DR. KORN: No. We know the physicians diagnosed the condition as acute muscle strain, whether it was cervical or lumbar in most cases, but we don't know the precipitating factor.

DR. BRASS: Can any of the rheumatologists or consultants help us understand whether or not there is any reason to believe that the outcome measures used are surrogates for the other outcome variables? Are there any data to suggest that in patients with back pain, that use of these types of instruments are predictive of or not

predictive of response to other instruments? Are there any such data?

DR. MOORE: Dr. Moore. With due respect to the physiatrists, I'm a little concerned about separating pain and function. It seems only common sense to me as a physician that the major reason people would be handicapped by a back or a neck problem would be because of the pain, and therefore if you help the pain, it seems to me that you're going to be -- that I can think of that as a very reasonable surrogate for function. That might not be true in rheumatoid arthritis, for example, but here we have a very localized, very acute situation, and we know that when we look at pain in general, that it is the patient's perception of pain on a visual analog scale which is the best way that you can possibly measure that. No machine can measure that.

So in my mind, I think that that's a very reasonable measure. I might also point out that the people were not only asked about pain, they were asked another question which had to do with medication helpfulness. Now, that's a much broader question. "Did the medication help you?" "Yes."

So I think if you put those two together, you would not be getting much of a different kind of an answer in this acute, localized situation than if you asked

directly a question about function.

DR. YOCUM: I'm sorry, but I didn't see any visual analog scale data. Do you have VAS data? I only see global data. I'd love to see some VAS.

DR. KORN: We only have 5-category global.

DR. YOCUM: I don't think you're presenting the most accurate presentation of pain here, which is a VAS. Globals are not, and we know from other conditions that while tenderness is important, it doesn't correlate well at all with functional measures in many ways, especially here when we're confounded by the factors of drowsiness and sleepiness and not being able to tell whether the two are definitely linked or not.

DR. BRASS: Dr. Gerber?

DR. GERBER: I'm in complete agreement with Dr. Yocum. I'd like to say I trained you, but that's not quite right.

(Laughter.)

DR. GERBER: There is one other issue about the question of visual analog scale. It is reported as a moment in time, which does not necessarily accurately reflect daily routines and activities. So the P values are close, but they are not identical. The reason that one does not rely exclusively on visual analog scale and pain reporting in low back pain is that it's confounded with all

kinds of other motivational and financial issues, and number two, which is very important, that activity can be seen as both the impact of pain on an initial event and/or the ability to sustain activity over time. Both are extremely important for evaluating function, and a pain scale usually does not get at the second one, which is the ability to sustain meaningful activity over time.

DR. BRASS: So if I can begin to develop a consensus here -- and I will allow more comment, but I just want to see if we're on the right track here. In terms of the clinical significance, it is not the magnitude of response on the instruments used. It's the instruments used. Is that what both of you are saying?

Transcriber, they are nodding yes.

Dr. Sachs?

DR. SACHS: I guess I was going to comment on the magnitude of response. Just as being kind of a practical pediatrician who thinks very simplistically, if you look at the numbers reported, what you guys are saying is significant is rating a C. An A is marked improvement, a B is moderate improvement, a C is mild improvement. We are accepting a C as efficacy. Personally, I would rather see an A or a B.

DR. BRASS: Dr. Anderson?

DR. ANDERSON: I was looking at the proposed

WHO core set of outcome criteria for low back pain, and they include both patient global and -- well, there's actually a test there of forward flexion and a QRL index and a disability index, which suggests that, at least in the eyes of the people who developed those criteria, there was some difference between function and pain. So I don't know the history of this and how far along it's gone and what studies there are to support the inclusion of both of these, but it does suggest on the face of it that there are some different dimensions here.

DR. BRASS: Dr. Koda-Kimble?

DR. KODA-KIMBLE: I have a question for the FDA. In previous discussions about Rx to OTC switches, we really haven't discussed efficacy. The assumption was that when a drug was approved for prescription use, that it was efficacious. I do understand that it's been available as 10 milligrams, but I did read in the materials I think that it had been approved as a 5 milligram dose but had not been marketed in that way. Could you clarify why we're discussing this?

DR. KATZ: Actually, the product as approved was approved at 10 milligrams, either two 5 milligram tablets or one 10 milligram tablet three times a day, with a total cumulative dose of 20 to 40 milligrams. So in the past, most of the switches that may have come before you

have been true switches in the sense that the prescription product was moving to the OTC world and there might not be any prescription product left. Here what we're talking about is a lower dose. So therefore because the dose is lower, efficacy needs to be proved.

DR. BRASS: And if I could just expand on that, the other reason for dwelling on it a little bit is when we start talking about risk, to allow an understanding of what benefit we're talking about to offset whatever risk we end up talking about.

DR. KATZ: One additional clarification is that because, again, we're talking about a 5 milligram dose, with a total dose of 5 milligrams TID or 15 milligrams, that it's likely that the prescription dose will remain prescription and that what we'll have is sort of a switch as what we've seen with some of the nonsteroidal types of drugs that have gone over-the-counter where the dose is lower for OTC use as an analgesic and the anti-inflammatory dose is the dose that remains Rx.

DR. BLEWITT: Well, I just wanted to summarize my own feelings and my own interpretation of the data as I see them. For many years I've been looking at muscle relaxants and looking at efficacy criteria and whether these things work at all, and we've always wondered about that, and that's in the practice guidelines.

To me, as I saw this package, these were the first hard data to support that this muscle relaxant actually works. Now, you can look in hindsight at what the efficacy criteria should be, but my concern is that I felt that the sponsor took the approach that this is going to be consumer self-diagnosis, that OTC drugs are generally for symptomatic treatment, and therefore we/they would use symptomatic criteria for efficacy as opposed to quantitative scales or anything like that. So that was their approach.

Because this program was intended to support approval of a nonprescription dose, the primary endpoints involved patient-reported assessments of relief. Then I think the question comes down to what are the requirements for efficacy and what are the criteria for efficacy, which I think I've addressed, and then should there be performance standards, such as functionality, do you need to go beyond efficacy and into functionality.

In my experience, I don't know of any drugs that were really required -- maybe somebody can correct me -- to show functionality. If you approve an analgesic for headache, a new analgesic for headache for switch, do you now have to show that they get back to work quicker because their headache is better? I don't see that as having to be the case. So I don't see why, in the case of muscle

relaxants, we need to have those kinds of standards for efficacy.

So, in a word, in my interpretation, first, it was nice to see hard data, in my view, that these things do work, two well-controlled studies, and secondly that these are consumer-oriented. Thirdly, the diagnosis was confirmed by a physician, and in my own view, I think that from the standpoint of efficacy, that there's little doubt that the sponsor has shown what they set out to do, and I think the committee ought to look at it in that light.

DR. BRASS: Certainly from the perspective of the OTC committee, and my own personal perspective, making patients feel better isn't all bad. What that translates into, how much better, what it means, I agree are legitimate questions. But again, for those of us on the OTC committee, we have seen -- and now just looking only at the efficacy hurdle in this equation -- lots of products that have had either response rates or magnitude of responses on whatever instruments were used that were significantly less than what has been demonstrated for this product in the two pivotal trials in terms of the definition of efficacy.

DR. SHERRER: Hi. I have a comment. I'm not on the OTC committee, so I don't really know what your charge is, and I'm actually new to the Arthritis Committee.

But for me, even if you assume that the efficacy data is good and hard data, I'm with Dr. Sachs, that the improvement is modest, and my concern as a rheumatologist and as a consumer is that is the improvement in relief, given that we have other drugs that also give improvement in relief that are already available, is the improvement seen here compelling enough to warrant putting on the market a drug that we know has mind-altering effects, that while may be low in absolute percentage, when you start talking about huge numbers of consumers using them, then you're talking about large numbers of potentially impaired drivers on the road?

For me, thus far I haven't seen compelling enough data for me to say that it's worth putting that type of drug out there to everyone.

DR. BRASS: Yes. I appreciate your points, but you're skipping ahead three steps.

DR. SHERRER: All right.

DR. BRASS: And I really want to focus on addressing the agency's concern about what is and isn't efficacy, then what is and isn't toxicity, and then what is or isn't a risk-to-benefit ratio in that kind of equation.

DR. BLEWITT: I just had one other comment I had forgotten earlier, and that is that the sponsor had set out to determine, a priori, what would be a clinically

significant outcome, and I think that they did that as well.

DR. BRASS: Yes, do you want to comment?

DR. HEMWALL: Yes. I just wanted to briefly remind the committee in factoring into their deliberations the fact that we did review these protocols when we started out the program with FDA, and there were no discussions at that time about having a functional endpoint. Actually, the studies were done in sequence, so we had the results of the first study before we started out the second study. So often thinking changes and science advances, and the overall criteria may change, but at the time these studies were conducted in agreement with FDA, functional endpoints were not a consideration.

DR. BRASS: If I could just focus on the issue that was raised by several people, certainly anecdotal data suggest that if one is treating chronic inflammatory disease with NSAID X, patient doesn't respond, they may respond to NSAID Y. Is there an individualized response in this type of back pain that suggests that individual patients may respond better to an NSAID versus a muscle relaxant and that there is individualization of responses? Are there any data that would help us understand that in terms of the need or desirability of comparison?

(No response.)

DR. BRASS: I take that as a paucity of data.

Other comments about the efficacy endpoint? Dr. Katz, are there other issues that we haven't hashed that you'd like us to hash out?

DR. GANLEY: This is Charlie Ganley. One of the nuances of the question has to do with looking at mean values of categorical data and how that's analyzed. That's one issue. Also, when you see those mean changes, how do you put some clinically relevant decision on that? That's really what we're trying to address here in whether a categorical analysis would be a better analysis, where you see actually what categories people had fallen into. I think the statistical review that you had seen from the FDA gave you some examples of that in a bar graph. So that's really the two issues of the question we wanted to focus on also.

DR. BRASS: Are you talking about the responder/nonresponder type of predefined response?

DR. GANLEY: No, the actual -- when the global questions actually are giving a whole number and it's treated really as a continuous number and given a mean value rather than looking at a categorical analysis. Okay? And also, when you look at those mean numbers and you see a 0.2 difference or something, how do you really interpret that when you can only make steps or jumps of 1?

DR. BRASS: And just so I'm absolutely clear, are you asking from a statistical standpoint or a clinical interpretation standpoint?

DR. GANLEY: Well, both. I'd be interested in what the statistician would have to say because I brought this issue up to the company about why a categorical analysis wasn't a primary analysis. I find it very hard to look at mean values like that and make some interpretation. You can say possibly that there's a treatment effect, but is that treatment effect clinically significant?

DR. BRASS: I think this goes back to Dr. Sachs' point, and I think in general, on these kinds of 5-point scales, unless you have a wonder drug, antibiotic kills strep, that it's very difficult to get the kind of quintal changes on a mean scale that you're talking about, and some type of categorical characterization is often helpful.

DR. ELASHOFF: Apropos of your question, sponsor cites 33 and 34, which are timed to a lot of or complete relief, show that approximately 50 percent of people feel better by the end of a week. It's a little bit lower than 50 percent for the placebo group and a little bit higher than 50 percent for the drug group. It's sort of consistent, and you can see that it's creeping up there. It was described by the sponsor as one or two days of

relief, but if you look at it a different way, where are you at the end of seven days, slightly fewer than 50 percent of people feel better by the end of seven days if they're on placebo, and slightly more than 50 percent of people feel better by the end of seven days if they're on the 5 milligram dose.

So that's a way of looking at it that doesn't deal with the means at all.

DR. BRASS: I will point out, though -- I think I'm correct, and sponsor can correct me -- that Slides 33 and 34 contradict the prospective definition on Slide 27 of what a responder would be, which included one lower value on the 5-point scale, if I'm interpreting those slides correctly. So those two slides are not the prospective definition of the responder/nonresponder class. Is that correct?

DR. KORN: You're correct, Dr. Brass. The definition is a little different on the "time to" slides than in the prospective definition.

But to address Dr. Ganley's question, we have done a logistic regression analysis, which may be more appropriate for the data, and if you'd like, the statistician can show you the one slide that has that.

MR. TIPPING: This slide represents an analysis for all three primary endpoints for both of the protocols

using what some would consider a more appropriate analysis for ordered categorical data. Again, this is not an analysis assigning a score and proceeding forward analyzing means, but this is an analysis that actually looks at the distribution of patients across each of those five categories. What you see here as a representation of that analysis is the odds ratio, and I think you see some very strong results here across all the endpoints, odds ratios on the order of 1.5 to 2, which would correspond to a 50 percent to a 100 percent chance of a better response, a 1-category better response on the 5 milligram dose of Flexeril than on placebo.

DR. BRASS: Yes, Dr. Lovell?

DR. LOVELL: I was wondering if the statistician could stand back up and explain the bars again? It's hard to read from back here, at least for me.

MR. TIPPING: Okay. The yellow dots represent the point estimate for the odds ratio, and the bars represent the 95 percent confidence interval around that odds ratio. To orient you a little bit more with an odds ratio, an odds ratio of 1 would indicate equivalence between the treatments, or no difference I should say. So odds ratios falling greater than 1 suggest that Flex 5 is performing better than placebo.

DR. BRASS: And that's the odds of a 1-point

improvement or more on a scale?

MR. TIPPING: That's the odds of a random patient having a 1-category better response on Flex 5 than on placebo.

PARTICIPANT: Can we get a comment from the FDA or panel statisticians?

DR. BRASS: Is there a statistician in the house?

DR. ANDERSON: I can comment. They're talking about a proportional odds model, or rather an ordinal response model. So it is one per unit.

MR. TIPPING: That's right, proportional odds model.

DR. ANDERSON: Yes. So those look perfectly valid to me. What sort of other comment would you like?

DR. GANLEY: That's fine.

DR. BRASS: Any other comments about Question 1? Yes.

DR. PUCINO: Does the company have that same data for a 2-categorical jump, which would be a more marked jump?

MR. TIPPING: Well, the odds ratio really represents all those probabilities pooled together. So you can think of it in terms of the odds of a 1-category jump, but it really is representative of an analysis across the

whole 5 points of the scale. I don't know if Dr. Gary Koch would like to add anything to this analysis.

DR. KOCH: Gary Koch. The analysis basically focuses on odds of better versus poorer outcome at each point in the scale. So if you have five categories, it would correspond to the odds of categories 1 to 4 versus zero, the odds of 2 to 4 versus zero or 1, the odds of 3 or 4 versus zero to 2, and the odds of 4 versus zero to 3. Basically, it looks at the extent to which the odds of better versus poorer outcome throughout the scale is higher for one group than the other. So what you're told is that the point estimates are in the vicinity of 1.5 to 2, and this basically means the odds of better versus poorer outcome is approximately 2-to-1 throughout the entire scale of the distribution.

DR. BRASS: Dr. Neill?

DR. NEILL: To clarify that for me, the odds ratio being 1.5 to 2 says nothing about the magnitude of the difference, except that it is greater. Correct? Given that we have no way to measure the difference, I don't know what the difference -- even though it's one unit, and I understand the unit is good to a lot, I don't know what that means clinically, an odds 1 unit.

MR. TIPPING: What an odds ratio of 2 means is that if in the control group at a particular cut point,

like zero to 2 versus 3 to 4, suppose that the odds of that in the control group is 50 percent. An odds ratio of 2 would mean in the test treatment group it would be about 67 percent, because 67 percent over 33 percent is 2, whereas 50 over 50 is 1. So if you're in the middle of the distribution, then an odds ratio of 2 corresponds to about 17 percent.

DR. NEILL: That I understand.

MR. TIPPING: As you move towards the tails of the distribution, it corresponds to a smaller percent.

DR. NEILL: That I understand. I want to make sure that I'm correct in understanding that while the odds inform me about how likely the two groups are different, it says nothing about the magnitude of the difference.

MR. TIPPING: Well, again, it says that the difference, if you're talking about an outcome with 50 percent prevalence, is about 17 percent. If you're talking about an outcome that has 67 percent prevalence, then the difference is about 13 percent. So as you move throughout the scale of the distribution, you have higher or lower base rates.

DR. NEILL: I guess what I'm getting at is that you say the difference is 67 percent or a difference of 50 percent, and what I'm not hearing is 50 percent of what. The what in my mind is the difference between good and a

lot, and I don't think any of us know what that difference is, despite our being able to tell that one group is 50 percent more of it than the other. Does that make sense?

MR. TIPPING: What you're being told by the odds ratio is that the one group has 10 to 15 percent better response than the other group, which is what you saw on the responder analysis.

DR. NEILL: Right.

MR. TIPPING: And the odds ratio simply reaffirms what you saw on the responder analysis using a method for categorized data that incorporates the information in the entire scale. So what you have already seen is reconfirmed by several other methods. There's no add-on to what you've already seen.

DR. NEILL: Great.

Question for the sponsor. I'm curious whether you have a slide that indicates the time to response, including that third good category which is the cut-off between fair and good that you used for responder and nonresponder. So it would look a lot like Slide 33 or 34, but instead the title would be "Time to Response, Time to No Response," or "Time to Good, A Lot, or Complete."

DR. KORN: It's coming up in a second. This is using the definition of the top three of the five as a responder. Again, this is Protocol 6. We have the pink

box being 10 milligrams and the yellow being 5, and the median times are -- I don't know what you want to read off the slide -- a day, a day and a half, approximately.

DR. BRASS: If there are no additional questions or comments, we will go on to Question 2. Question 2 is shorter, so it must be easier.

"Is muscle spasm of the back or neck a consumer self-diagnosable condition? In answering this question, please describe the data relied upon from the application."

Volunteers? Yes, Dr. Lovell?

DR. LOVELL: Well, I'd like to put a challenge to the company. I don't think there is any study done by the sponsor where you looked at the direct question being patients who say they have back spasm and then subsequently be evaluated by a physician to test the accuracy of that self-diagnosis. Do you have any studies to address that particular question?

DR. KORN: No.

DR. BRASS: I think the only data we saw that was like that was the ad for muscle spasm and what percentage of those patients, when examined, actually had muscle spasm, and that was a very high percentage. But other than that, I don't think we've seen any data.

Do any of our experts know of data from the literature or other studies or experiences that would help

us understand this issue?

Yes, Dr. Abramson?

DR. ABRAMSON: I don't know of any data from the literature, unfortunately, but I do think it's a difficult thing to expect patients to make an accurate diagnosis, at least it's a potential problem. Even looking at the spasm rating by physicians of Slide 39, there were certain criteria the physician was supposed to use based on palpation of the muscle, and that's assuming the physicians can do that well, and I have a certain degree of experience in making that assessment and I'm not sure that's easily transferrable to patients, nor is the location of these muscles always easily accessible.

So I think my thought about this is that it would be hard to rely on the patient. Some of the transferral of this from prescription to OTC depends I think in part on the patient making this kind of assessment, and I think one of the hazards may be that a greater proportion of people with back pain or other pain not due to spasm may begin to use this drug and associating it, making that self-assessment. So I think it's a difficult thing for a patient to make objectively.

DR. BRASS: Putting aside the leg cramps and all the other kinds of things people used it for, if we looked at patients in this age group presenting to a

physician with back pain, do we know what percentage of them who met any kind of simple clinical definition -- duration less than, precipitating event -- or any criteria that would allow us to define a high prevalence of spasm population?

DR. ABRAMSON: I think perhaps Dr. Borenstein addressed this before. I think it's very difficult to come up with that number. I think clearly many people with backaches will have some degree of spasm. I don't know what the percentage is, and I think it may vary among physicians and other health professionals when they assess the patient as to what their impression is. It's not an easily objectively documentable physical finding in many people, in many of the patients. I don't know in what percentage people think that's the major or significant component.

DR. BRASS: Yes?

DR. SHERRER: I think this is a really tough issue, and in part it's subjective despite the criteria, and people's muscles can feel differently. Athletic individuals can have very firm muscles and may be misdiagnosed as spasm. In addition, there are people who have spasm and it's asymptomatic. So I think unless you have a control group of individuals who come in, who are symptomatic versus those who are not, and you have the same

physicians diagnose them without knowing whether they're symptomatic and give a rating, you're not going to be able to judge this.

As a physician who examines patients daily, I examine patients in whom I pick up spasm in areas where they don't complain of pain, and there are individuals who complain of pain who don't have spasm, and vice versa.

DR. BRASS: Yes, Dr. Sachs?

DR. SACHS: I think the large question that we're kind of asking here is if you gave this medicine to a consumer who is experiencing pain, would a serious diagnosis be missed or treatment for a serious diagnosis be postponed? I don't know that I've seen information on that. I don't know if any parallels would be drawn with the prescription information, like, for example, if somebody really has a slipped disk and you treat them, with neuropathy, what long-term harm happens.

DR. BRASS: Again, because the OTC group frames this question a lot, there are two sides to it. One is, will you be exposing patients to the risk of a medication unnecessarily because they have a benign condition which stands no chance of responding? And second, are you delaying diagnosis of a condition which a delay of 10 days makes a difference? So there are two sides to the question, and I think there was suggestive data that the

significant other, where delay of diagnosis would be clinically significant, is thought to be very low in this age group, but again, nobody could put a number on it. I think the other concern that I'm hearing from some of the practitioners is that there's a benign disease that stands no chance of responding, and that therefore the patient shouldn't be exposed to the risk. Is that fair or unfair?

Dr. Lovell?

DR. LOVELL: I think it's fair, and I think in the absence of either the sponsor or any of the experts to stand up, we can't answer the second question. I mean, there is no data to answer this question, and I think this is a key question, and it's an answerable question. I mean, it's not an overwhelming type of burden to put on a sponsor. But I think it's a key and critical question, and we have no data to address the question. So I think that it's something that should be studied and answered or the question be addressed and data be generated before we move farther in this particular area.

DR. BRASS: Again, just to be crystal clear for the agency's further deliberations, are you asking for data specifically about the ability of patients to self-diagnose, and if so, is a physician an adequate gold standard? Or are you asking for efficacy data like a 009 type of study of the drug that is placebo-controlled which

would incorporate that self-selection into the efficacy analysis? In other words, there are two different sets of data that would reassure you on this point. If 009 was placebo-controlled, so that patients self-selected, whether correctly or not, and benefitted, that would reassure some people. Other people may not be reassured unless they knew for a fact that the condition itself was properly self-diagnosed. So I'm asking which of the two would be required to satisfy you.

Dr. Lovell, having posed the question, which of the two data sets would be necessary?

DR. LOVELL: I think that actually both questions very succinctly and nicely differentiated the two questions, and I think they're both very important questions and both should be at least addressed and answered before we move ahead.

DR. BRASS: Yes, Dr. Korn?

DR. KORN: We can point you to data to address the second element of that question. Certainly the Agency for Health Care Policy guidelines panel and other groups that have tried to create algorithms for the treatment of acute back pain have all concluded that in a representative population, the risk of a very serious underlying disease requiring definitive emergency management that cannot wait 10 days is exceedingly low in the absence of recognized red