and the other question. Since there are factors that can influence someone's subjective feelings of sleepiness, do you have any objective measures that support the indication of daytime sleepiness? Specifically, the one trial that I am aware of that had an MSLT and did daytime sleepiness as a primary outcome measure, in fact, appears to be not supportive of the indication.

DR. HOUGHTON: Yes, in the Scrima trial he used the MSLT measure and that was not statistically significant, as shown. The objective data that we propose supports very strongly the effect of adequate dosing of GHB was the SXB-20 trial that Dr. Black discussed. That is not only a profound improvement in the MWT at the 9 g dose but a defined dose response across all doses. That is very positive data.

DR. KAWAS: In ten patients, it appears.

DR. HOUGHTON: Twenty-one.

DR. MANI: May I also add that that was an open-label, non-randomized study?

DR. HOUGHTON: Sure, but using an objective measure.

DR. RISTANOVIC: I am I am Ruzica Ristanovic, medical director of Sleep Disorders

Center, in Evanston, Illinois. I would like to comment on add-on Xyrem in the presence of other stimulants. Other studies attempt to try to document the effectiveness of other stimulants in narcolepsy-related sleepiness documents, including the most rigorous trial of modafinil in double-blind, placebo-controlled studies. They document that these drugs improve sleepiness but very seldom outside of the range of pathological sleepiness as measured by Multiple Sleep Latency Test and Maintenance Wakefulness Test. So, the patients remain sleepy. That is the message. Add-on treatments are approved for other indications in other neurological diseases, such as epilepsy. So, I assume that this application for that particular indication is not for monotherapy but as an add-on to concurrent use of stimulants. I would like to bring this to your attention. So, patients do remain sleepy on stimulants and they need additional treatments.

DR. KAWAS: Dr. Temple?

DR. TEMPLE: Dr. Houghton also seemed to be distinguishing between monotherapy and add-on therapy. That is not the problem. The problem is whether there is adequate support for use as an

addition for whatever else the patient is on, and whether there are well-controlled studies that support that. So, add-on would be perfectly fine. That is usually true in a lot of conditions, not just neurological ones, where you continue to give standard therapy and try to improve it.

I just want to make one observation about the evidence. We do expect to see replicated or reproduced findings. Some of the issues here are whether the fact that the endpoints are secondary and need some correction means that there isn't adequate support. A lot of these things are matters of judgment that the committee can weigh in on. Not everything is, you know, a yes/no. Some of the things are moderately subtle and that is why this is being brought to you for judgment. There is one study that is obviously stronger than the rest but the others can be considered, and you sort of have to think about how many real endpoints there really are; how much of a correction is needed. Those are difficult discussions but worth considering.

DR. KAWAS: Dr. Katz?

DR. KATZ: I agree, but I think we would still have to have the application meet the

standard of independent replication, in other words two trials. You can decide that one of the other trials actually does meet the usual standard, again, taking into consideration the multiplicity and that sort of thing. All I am saying is that I don't think we can say we have one study that looks good. If you believe that GHB looks good and the others sort of contribute to a feeling that it probably is okay, I mean, we really need two independent sources that you believe demonstrate the effectiveness.

The only other point I wanted to add is to something, Claudia, you said which has to do with Dr. Houghton's view that they are not going for a claim of daytime sleepiness; they just want, I guess, to have language in the labeling that says that it improves that symptom. Most of the drugs we approve are for symptomatic claims, so there is no question that the inclusion of this language in the indication is a claim as we always understand that term.

DR. KAWAS: Dr. Guilleminault, followed by Dr. Wolinsky, please.

DR. GUILLEMINAULT: If you look at all the published data on modafinil, on amphetamine, on

methylphenidate, none of these drugs ever normalized all the objective tests on alertness and daytime sleepiness. None of them, including the modafinil data which were approved by the FDA. The MSLT and MWT for all these drugs are pitiful. The only data which shows significance was the Epworth Sleepiness Scale, which is a subjective scale, in all these trials. So, we cannot expect to have any positive result with subjective tests in any of these drugs. We will always have to rely on subjective tests even if the subjective test is not great. Everybody in the field agrees that the Epworth Sleepiness Scale is the most used scale despite the fact that it has a lot of downfall, and we have to remember that when we look at what has been approved and what is being used.

DR. KAWAS: Thank you, Dr. Guilleminault. I think that many people would agree with those comments, but my question to you would be not whether or not the Epworth Scale subjective measurements are good but do we have two randomized, controlled trials that show an improvement in subjective sleepiness.

DR. GUILLEMINAULT: That was my initial question because my understanding is, when the

statistician from the FDA responded, she said that when she did a nonparametric analysis she found out that she had a p value of 0.03. So, my understanding is that she had a significant finding even when she did the reanalysis. That was my understanding of her response.

DR. KAWAS: Would you like to comment, Dr. Yan?

DR. YAN: I am sorry, the previous number is not right. I checked. The number for the nonparametric analysis, the p value was 0.0109.

DR. WOLINSKY: I have a couple of questions first for some information before I ask the real question. For the informational questions perhaps Dr. Mignot could help with. So, the first question I have is if you could enlighten us or re-enlighten us about how many patients that have narcolepsy have had cataplexy as a component symptom. What proportion?

DR. MIGNOT: In most case series it is about 70 percent.

DR. WOLINSKY: The second question is that at least for most of these studies which were done and presented to us since cataplexy was being measured, as is appropriate, the number of

cataplectic attacks was relatively high. I think in these studies it was around 20 cataplectic attacks per week. So, how many of the 70, 75 percent of patients with narcolepsy who have cataplexy have cataplectic attacks at that level?

DR. MIGNOT: I would guess 20 percent.

DR. WOLINSKY: Thank you very much.

DR. MIGNOT: Yes, roughly.

DR. WOLINSKY: And then they would fall down below that level for the remainder of the 55 percent of narcoleptics with cataplectic attacks.

DR. MIGNOT: If you analyze the spread of the number of cataplexy episodes per week, but you have to balance that also with the efficacy of current treatments. A lot of people that currently have cataplexy that is relatively mild just don't want to take the antidepressants because they have so many side effects, especially sexual side effects, dry mouth, all these problems --

DR. WOLINSKY: This is not the question though. So, now the question to Orphan which has really, truly become an orphan drug question, is since all of the studies that have been done have enriched for cataplexy, do we have any data that would suggest that if cataplexy is adequately

controlled or if there is no cataplexy so we don't have to worry about the control of cataplexy there would be any effect of the drug on daytime sleepiness in non-cataplectic narcoleptics?

DR. REARDAN: I think Jed Black wants to make a comment on that.

DR. BLACK: Just a comment on the prevalence of cataplexy in the 70-75 percent of folks with narcolepsy that had cataplexy, the frequency of events -- this is something that Dr. Mignot is not aware of, the cataplexy was subdivided into major events and minor events. About 20 percent or so would have the major events to that level, but when we look at the minor events a far greater percentage of that 70 percent, which may be up to 80, 90 percent of that 70 percent, will have that number of minor effects. Those are not complete attacks where they fall down. In fact, with most narcoleptic patients, they distinguish between the two and they will often only report to the physician the major events. But in the diaries that Orphan had set up all the events are characterized.

DR. WOLINSKY: So, the second question --

DR. BLACK: We have no idea. That is an

excellent question that I think needs to be determined, but in the studies that have been completed that question cannot be answered.

DR. REARDAN: Jed, the only study I can think of maybe is SXB-20 where cataplexy was not an entry criterion and I don't know what the cataplexy incidence in that trial was. Bill is shaking his head -- we didn't record it and we didn't quantitate it.

DR. BLACK: We can't comment on that.

DR. REARDAN: It is true that in most of our studies patients were selected because at entry criteria they had to have a baseline cataplexy.

DR. KAWAS: Dr. Penix?

DR. PENIX: Before we address the two separate indications issue -- and I guess, Dr. Black, I could direct this question to you -- in the GHB-2 study you did look at all cataplexy events, I guess, and then total and partial cataplexy. In the background material, in the separation of the two it appeared that there was no significant difference in any of the three doses of GHB on total or complete cataplexy but your effect was primarily in partial cataplexy. Is that correct?

[No verbal response]

So, my question in that regard is what is the clinical significance of partial cataplexy, and you mentioned that patients frequently do not want treatment for partial cataplexy. So, is this a big problem? I presume that the patients that would perceive a problem would be the ones with the complete cataplexy but there we see no significant difference. So, is there a problem there with that?

DR. BLACK: I think this is a good point, and the difficulty comes in trying to separate the two because it is not sort of a box of partial and a box of complete; it is a gradation, you know, ranging from small partials to large partials and the completes. So, I think this analysis is difficult to perform. Clinically the degree of improvement with traditional anticataplectic medications that we use is similar. So, the reduction in partial -- if that is all that is being seen here and I am not convinced that clinically that is the case -- while the statistical analysis didn't demonstrate a significant difference in the complete cataplexy attacks, clinically there is an improvement in all

the different categories, and it is very substantial in traditional anticataplectic medications as well as with GHB.

DR. PENIX: Could Dr. Mignot comment on the clinical significance of partial cataplexy? Is it a big problem?

DR. MIGNOT: Yes, it is a big problem. In fact, the problem is especially the social aspect of cataplexy, when you have to realize that you are just in the middle of a crowd and are meeting some friends, and you can never tell when it is going to happen. It may happen in very odd circumstances. So, often even the doctors don't know what it is and they just look at it and they wonder why this person is kind of losing slight control and has to sit down. There is also almost a social aspect with fear of cataplexy that can occur at any time, any moment and, yes, it is a very significant problem.

Again, it is a balancing act because the drugs that we use are somewhat effective but they have all these side effects and you just have to choose between two evils. I am pretty sure that, for example, GHB, based on my relatively limited experience, has less side effects than

anticataplectic classical tricyclic antidepressants, and that a lot of patients would prefer to take GHB even for partial cataplexy.

DR. PENIX: The case that you showed of the nine-year child I assume is complete cataplexy --

DR. MIGNOT: Yes.

DR. PENIX: -- but you are also saying that patients with partial cataplexy have a significant impairment of their life.

DR. MIGNOT: Absolutely. But, as Dr. Black mentioned, it is not an "all or none." I mean, most patients, the ones that are complete, have a lot of partial cataplexy. You never know how bad it is going to be. Most of them are small, little attacks, and sometimes they may even be perceived only by the patient. Sometimes the face may melt; the head drops. Sometimes they just have to sit down; sometimes they don't have to sit down. I showed a young kid because it is more dramatic, but you would see the same thing in some of the patients with partial cataplexy occasionally.

DR. BLACK: I am realizing that a definition may be useful here. In general when we were describing patients who documented the partial

versus complete, we told them to think about complete as an episode where they fall to the ground with complete paralysis or where, if they weren't sitting, they would have fallen to the ground with complete paralysis. Otherwise, anything else is partial -- so, slurred speech, head drops, dropping things are the partials, and those become very important for quality of life and daytime performance. Driving, those kinds of things can become a very significant event for partials.

DR. MIGNOT: Yes, one thing I should also emphasize is that in a very large number of series that, for example, have analyzed several hundred patients with narcolepsy and cataplexy, as a mean the large majority of patients have several attacks per day, several attacks per week. Between several attacks per day and several attacks per week, that is generally partial or complete attacks and it is not something that appears just once, you know, every ten years. It is really something that occurs regularly and sometimes totally unexpectedly.

DR. KAWAS: Dr. Falkowski?

DR. FALKOWSKI: That leads me to a

question just for clarification. For the purposes of these clinical trials, were the cataplectic events something that was just perceived by the patient and recorded in a diary, or were they verified by some third party?

DR. REARDAN: These were taken from patient diaries. So, it is patient recorded episodes.

DR. HAGAMAN: I am Dr. Hagaman and I just wanted to address the partial versus the complete cataplectic events. I think that you have to take it on an individual basis. We have patients that come in that are teenagers that have tests in front of them and they have a partial cataplectic event and they drop their pencil; people that cut hair that have scissors in their hands and they drop their scissors. So, even though they have not had a complete event, this has been a very debilitating event in their lives. So, it is a continuum and I think you just have to really look at each person as an individual and what they are doing.

DR. KAWAS: Dr. Dyer?

DR. DYER: How variable in the same patients are the number of cataplectic attacks per week? What is the variance in that?

DR. MIGNOT: We have looked at that quite a bit.

Actually, I did some diaries in a large number of patients with cataplexy. It is really totally unpredictable and that is one of the most scary parts about cataplexy when you have narcolepsy. Of course, if something emotional is going to happen, say a patient is going to go to a wedding, often they will kind of fear that event much more because they think it is very likely that they are going to have cataplexy in front of everyone and, indeed, they may actually have a lot more cataplexy because it is an emotional event.

Still, I have followed, for example, patients and sometimes they may have like 80 for one week and then the following week they may have only three or four. I mean, it can really vary quite a bit. And, one of the main reasons is really that emotion is something that is very variable. In fact, someone mentioned how easy it is to observe cataplexy. It is very difficult to get it on tape because typically the patient come to your office; he really wants to show you what it is but, you know, he is tense and it just will not occur but as soon as he leaves the office and

something happens -- boom, he is going to collapse. So, it is very difficult to predict and it is quite variable.

DR. ROMAN: For Dr. Mignot also, you mentioned that cataplexy probably is the result of what you called dissociated REM. However, if I recall correctly, the polysomnographic analysis has shown that Xyrem actually decreases the amount of REM sleep and increases delta sleep. Would you like to speculate on what could be the mechanism of action to improve the cataleptic component?

DR. MIGNOT: That is a very, very difficult question. One of the difficult questions, of course, is the mode of action of GHB. I have looked into it myself for quite a while because I was trained as a pharmacologist, and it is not clear. There are two camps. Some people think it acts on GHB receptors, specific receptors; others think that it acts through the GABA-B receptors. We know that it has some strong effect on dopamine transmission. If you inject GHB in animals the rate of activity of dopaminergic cells shuts down and dopamine can increase in the brain proportionally to the dose. We have done quite a bit of studies that have shown that the

dopaminergic system is very important to regulate both wakefulness and also cataplexy and the regulation of emotion. I believe it is by changing the balance of the dopaminergic system, that improves cataplexy the following day maybe by increasing dopamine in the brain during the night, but this is highly speculative and a lot more research needs to be done.

The fact that it does not increase REM -- first, it is quite variable because some studies have shown that it does increase REM and this contrasts dramatically with what all hypnotics do. If you take MVN or all the other benzodiazepine-like hypnotics, what they do is actually, rather, reduce slow wave sleep and reduce REM sleep. Xyrem doesn't do that. It actually promotes slow wave sleep and, if anything, would promote REM sleep or doesn't change it. That is still, you know, much more in the right direction of promoting normal sleep, including REM sleep.

The last comment I want to mention is that it is not sufficient -- if you know a lot about narcolepsy, it is not sufficient to just explain narcolepsy as a disorder of REM sleep. Indeed, they have all this transition to REM sleep but they

also have impaired wakefulness per se. For example, if you do MSLTs they don't always go into REM. They will often just fall asleep into normal sleep. So, it is not only REM sleep that is disregulated in narcolepsy, it is also wakefulness and by improving slow wave sleep you presumably also can improve the wake aspect of narcolepsy. My answer may be a little complicated but I would be happy to discuss it in more detail.

DR. KAWAS: Dr. Van Belle?

DR. BLACK: Just another comment on that, the Broughton study showed an increase in REM at a lower dose. The first dose of the SXB-20 that I participated in showed at 4.5 g the first night an increase in REM, which was then followed by a dose-related decrease in REM over time, which is very different from REM suppressant agents where there is a robust, or in fact the largest effect that can often be seen on the first night of administration.

So, we don't know exactly why it is that over time the REM with higher doses is reduced, and why with the first dose, and with the lower doses, as has been demonstrated here with Roger Broughton's work, why the REM is increased. There

has been established sort of a competitive reaction between slow wave sleep and REM sleep. It appears that there may be factors that regulate slow wave sleep that also are important in regulating the appearance, or lack thereof, of REM sleep. It may be that gama hydroxybutyrate is sort of normalizing slow wave activity which then results in a more normal control or regulation of the REM or REM-related events.

DR. KAWAS: Can I ask for my clarification, what dose the company is proposing?

DR. REARDAN: Bill, can you take that question?

DR. HOUGHTON: Yes, the dosage regimen that we are proposing is that patients be started at 4.5 g and then titrated between the range of 3-9 g to clinical efficacy. Although in the strictest mathematical sense the only statistical efficacy in the GHB-2 study was clearly defined at 9 g, that may well represent that the study was too short because in the open-label study that followed, as I showed, the maximum nadir occurred at 8 weeks, and when those patients were followed over the course of 12 months they maintained efficacy across the dose range. Certainly, there is an advantage in

terms of the important side effects to dose titration. In all of the treatment IND protocols and the safety studies the data was generated at between 3-9 g. Now, 80 percent of the patients were maintained between 6 g and 9 g, but there was certainly facility for down-titration from the 4.5 or maintenance there as well.

DR. KAWAS: Thank you. Dr. Van Belle?

DR. VAN BELLE: It seems to me that there is reasonable agreement with respect to efficacy for cataplexy at least between the FDA and the sponsor. So, I would like to get back to the secondary endpoints. I would like to ask a question to the sponsor's statistician, Dr. Trout, as to whether he thinks that multiple comparisons is a problem. Secondly, if multiple comparisons are a problem, how he would adjust.

DR. REARDAN: Do you want to put this in relation to a specific trial or all the trials in general?

DR. VAN BELLE: Well, I bring it up in connection with the analysis of Dr. Mani where he clearly comes to conclusions that differ from yours with respect to the efficacy of some of these secondary endpoints.

DR. TROUT: You know, it is hard to answer that question. I think the way I would answer that is as follows: The GHB-2 analysis, the results that we found and also that were expressed earlier were very strong. So, even with the fact that there is some multiplicity, we also have, remember, some other outcome measures which were related to this particular general area in terms of daytime sleep attacks. So, there were at least two measures that suggested improvement with respect to that particular outcome.

The other second study that has been discussed is the Lammers study, and that study is obviously much smaller. It is obviously a weaker study, and there is some issue with regard to whether the appropriate method of analysis was there. So, I think that is a harder one to address.

Now, there are two kinds of multiplicity going on here, which you are well aware of. One is the multiplicity with regard to the multiple dosing levels and that was accounted for in our analyses. The question that was brought up by Dr. Mani with regard to the multiplicity of secondary endpoints, and I am not a betting man but I think there is

certainly evidence to suggest that daytime sleepiness is being affected possibly. But I don't go to Las Vegas nor Atlantic City.

DR. KAWAS: Actually, while we have Dr. Trout up, I would ask him with regard to excessive sleepiness on the Epworth Scale in the GHB-2 study, while there certainly was a difference in the two groups, there were also major baseline differences in sleepiness for the responders and the non-responders. In fact, those that appeared to respond had a baseline that was better than the improvement in the other group. There was a significant difference. Are you concerned about these and how these might affect the results?

DR. TROUT: There is always concern about baseline differences, and that was attempted to be accounted for in two mechanisms, one, we looked at change from baseline and we also did a covariate adjustment to try to account for that.

DR. KAWAS: Dr. Katz?

DR. KATZ: I would like to ask Dr. Trout a question also. Dr. Yan mentioned that we didn't believe that the data were normally distributed, and when you transformed the data it didn't really help very much. I don't want to get bogged down in

a hyper-arcane discussion about normally distributed data, but when we did that we got a p value for that comparison -- I guess it was the Epworth, of about 0.01 --

DR. MANI: I am sorry, it wasn't the Epworth. You are talking about the Lammers study where you are talking about the frequency --

DR. KATZ: I thought we were talking about GHB-2.

DR. MANI: Oh, sorry, fine.

DR. KATZ: So, if we are right, it takes the p value which was 0.0001 or something like that to 0.01, and then when you get to the multiple comparisons issue it makes it less weak. I agree if you take a p value of 0.001 or 0.0001, no matter what you do to it as far as a multiple comparison, it is still going to be significant. But if it is 0.01 it is a little different story. So, I am just wondering, again without getting into excruciating details, what about this question of the data being normally distributed and not necessarily being improved very much by transforming it? Is there common agreement about that or not?

DR. TROUT: My recollection, and it has been sometime since I have seen the results of the

analysis, is that it suggested that we didn't see a particular problem with the normal distribution as, for example, was the case with cataplexy which was clear. I am not sure if Dr. Yan did a nonparametric covariance analysis or not. I haven't seen those analyses. And, I think the point was made earlier that that would be, I think, an appropriate thing to do in order to account for some potential baseline differences. If she did, then whether it is a reflection of a decreased sensitivity of a nonparametric analysis or whether it is a normal distribution -- I can't answer that without seeing the data. Maybe it was just a standard, nonparametric analysis which might help account for the difference.

[Comment away from microphone; inaudible]

DR. TROUT: No, I know that but Dr. Yan did a nonparametric analysis because she was concerned about the normality, and did look at the log transformation and it didn't have any impact on that, which doesn't surprise me at all.

DR. KAWAS: I would like to ask the sponsor, I mean, there clearly was a dose relationship in terms of the adverse events. Were any other factors looked at that may be related to

the adverse event profile, things like age, even previous psychiatric history, other medications? Whether or not they drank alcohol? Anything?

DR. HOUGHTON: No, we didn't go as far as an alcohol history. Certainly for the major psychiatric, a preexisting history of major psychiatric disease emerged. Major psychiatric disease was actually a protocol exclusionary criterion, but in those that, for instance attempted suicide, post-study it was discovered that they had a previous psychiatric history and in actual fact in one of the patients a previous suicide attempt had been made. There was major depressive disease reported in those, but for those who developed psychosis there was definite recorded preexisting psychiatric history.

In terms of age, we haven't done a breakdown of the database, and in most instances there was not a dose relationship. There were just instances that were mentioned in the presentation. Confusion and sleepwalking suggested a dose relationship. In the GHB-2 protocol which was obviously blinded, there was the association with nausea, vomiting, confusion and enuresis that was definite, but that didn't extend across the whole

study database. So, the relationship with dose is not well defined.

DR. KAWAS: But how about relationship with anything else? For example, were the patients who had confusion more likely to be the elder patients? You might be able to tell I am in aging.

DR. HOUGHTON: I can identify well. Do we have a breakdown of confusion by age? A range would be still useful.

[Slide]

Here is a slide that shows that the distribution of age was between 25 and 73 years, with 67 percent over 50 years of age, but the range is still wide. There is the distribution across doses. Four events at 3 g, 10 at 4.5, 12 at 6 g, 8 events at 7.5, and 13 events at 9 g.

DR. KAWAS: Thank you. Do we have any other questions from the committee? If not, we will move on. Dr. Katz?

DR. KATZ: A quick question, if I heard you correctly, there were 14 events reported as convulsions, but when you went back and looked at that, 13 of them were actually cataplexy. So, presumably cataplexy was a verbatim term. How is it that cataplexy got coded as convulsions?

DR. REARDAN: The COSTART dictionary puts cataplexy in as a convulsion. It is a definition. Convulsion has ten different terminologies, verbatim events, and they all code up to convulsion.

DR. WOLINSKY: Along those lines, how come there were only that few number of convulsions when we were studying cataplexy in the trial? I mean, I don't know that it is easy to explain this in both sides of one's mouth.

DR. HOUGHTON: No, and we are not trying to. If there was a cataplexy event that occurred of a severity to be seen as unusual for that patient, and the patient volunteered it as an event, then it was recorded as an adverse event. Or, there may have been injury related to the cataplexy events. We do have representation in the database. I can recall absolutely a fractured ankle in the washout study. So, there were traumatic events associated with a major cataplexy event that would have been of sufficient impression on the patient to report as a separate event.

DR. WOLINSKY: But then the event would not have been withdrawal from the primary measure of efficacy even though it was also registered as

an adverse event?

DR. HOUGHTON: I am sorry?

DR. WOLINSKY: Was it still counted as an event in the measure of efficacy if it was also shifted to be counted as an adverse event?

DR. REARDAN: Yes, the patient diaries recorded cataplexy. If they record cataplexy as an event itself, that was part of the efficacy outcome. It wasn't necessarily an adverse event. If they had an adverse event -- fall and break an ankle, cataplexy is coded as part of that adverse event. It is the cause of the adverse event and so it shows up in the database.

DR. KAWAS: Dr. Simpson?

DR. SIMPSON: I have two questions. One really was just a clarification of this business about the sleepiness. I think we have all agreed that there has to be some adjustment for multiple comparisons on the sleepiness index, and the GHB-2 study, even if you make an adjustment, there are certainly some of the indices about sleepiness which seem to be significant. But coming back to the Lammers study, have we established whether or not, once we have made an adjustment, we have any significance there or not? Because that is the

pivotal trial, isn't it, because we need two?

DR. REARDAN: Remember that the Lammers study was a very small trial, 24 patients. Daytime sleepiness was a secondary endpoint in that study, and I forget the p value. Maybe Dr. Yan or Dr. Katz could comment. I don't think any formal study of multiple analysis was done, except maybe by Dr. Yan --

DR. YAN: No.

DR. REARDAN: -- and I think she needs to comment on that.

DR. YAN: For Lammers study there was no prespecified analysis, except the Wilcoxon assigned rank test. It was across the study and we considered it not very appropriate, and for a secondary analysis none of the statistical analyses were specified. The problem with this Lammers study is that if you use different statistical analyses which are considered appropriate, you get a very different result. Some could be less than 0.05 and some ranged to something like 0.2. So, the results are not consistent and we don't have a reliable method to see which one we could consider.

DR. REARDAN: We don't disagree with that. I mean, the problem with Lammers is that it was a

one-sentence statement about how he was going to analyze it, and it was an inappropriate statistical analysis for a crossover study. So, that creates issues about not having a prospective statistical plan appropriate for the study. But even in that initial Wilcoxon analysis the daytime sleepiness was statistically significant. It was not corrected for multiple analyses.

DR. KAWAS: Dr. Simpson?

DR. SIMPSON: I just have another question that I wondered if you could clarify. In a lot of these studies you talk about an intent-to-treat analysis, but when I read it I wasn't clear whether or not that meant the patients that were randomized were actually included always in the analysis or not.

DR. REARDAN: Yes, the intent-to-treat would include every patient who received drug. Is that correct?

DR. TROUT: Yes, every patient who received at least one dose.

DR. SIMPSON: So, how did you then deal with the patients who dropped out?

DR. TROUT: In the GHB-2 analysis we selected an endpoint. So, in order for the patient

to be included in that analysis there had to be at least one post-baseline measure of cataplexy or sleepiness, or whichever outcome you want. So, it was an endpoint analysis that was done in order to accommodate that.

DR. KAWAS: It looks like we are completely behind schedule and we will have a very late lunch, I will warn everyone. The FDA's invited speakers on risk management issues is the next component of this discussion. The first speaker is going to be Dr. Carol Falkowski, of the Hazelden Foundation, in Minnesota, who will be speaking on the epidemiology of GHB abuse issues.

FDA Invited Speakers on Risk Management Issues

Epidemiology of GHB Abuse Issues

DR. FALKOWSKI: Hello. Good morning, almost afternoon.

[Slide]

This is the title of my talk, GHB Abuse in the United States. I am Director of Research Communications at the Hazelden Foundation. I have been a member of the National Institute on Drug Abuse's Community Epidemiology Work Group since 1986. I am author of a book, called, "Dangerous Drugs: An Easy-to-Use Reference for Parents and

Professionals." What is missing from this overhead is that I served on the Drug Abuse Advisory Committee for the FDA from 1995 through 1999.

[Slide]

In the very short time that I have, I am going to try and just hit the big points about what we know about the abuse of GHB in the United States, starting off with measuring drug abuse. There are a number of things that are thought to bear when we talk about measuring something as complex and multi-dimensional as drug abuse. This includes population surveys. It includes hospital emergency room episodes; medical examiner data; addiction treatment data; law enforcement data, as well as ethnographic studies that look at specific populations of users that are more anthropological and ethnographic in nature.

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I also want to make the point that all data systems have limitations, and this is particularly true in the case of new drugs of abuse. For example, if we are talking about GHB and trying to measure the number of patients who have presented to addiction treatment centers across the country with GHB as their primary drug

of abuse, it is now the case that it is often grouped in a category of drugs called sedative hypnotics. It is not its own line item. So, in preparation for a meeting like this it is very hard to get an accurate count of the extent to which GHB itself is the presenting drug of abuse.

Similarly, surveys that are conducted -- we have not added GHB to the National Household Survey or the Monitoring the Future Survey, although to the Monitoring the Future Survey that looks at drug use among 8th, 10th and 12th graders ecstasy, another club drug, has been added.

Also, in terms of law enforcement indicators, there is no field test for GHB so it is hard to also get that indication of it as well.

In addition, new methods of abuse are hard to track. I recall, in 1986, when we started at the national level wanting to track crack cocaine, we knew about how to track cocaine but, all of a sudden, we were looking at it by a different route of administration. So, it was a challenge to all of us to start switching our data systems just to measure crack instead of cocaine, to make that distinction.

Existing data systems are slow to respond,

and there is a system-wide learning curve when a new drug of abuse appears on the scene. That means it is a learning curve in terms of emergency room personnel, treatment providers, law enforcement, as well as prevention agencies, and that is why we rely on a lot of the scientific literature put out, particularly in emergency medicine, to inform the field about emerging drugs of abuse and how people present with those problems.

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My background in this has been as part of the Community Epidemiology Work Group. This is a group of drug abuse researchers from twenty cities in the country that has been convened by the National Institute on Drug Abuse since 1976. This model of drug abuse epidemiology has also been adapted in different parts of the world. There is a similar group in Europe, in Canada, Mexico and Asian cities.

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The Community Epidemiology Work Group is an early warning epidemiological surveillance network that detects new drugs of abuse, patterns of use and populations at risk.

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It involves researchers looking at the same data from different geographic areas and in this case, as I mentioned, there are people like me in twenty cities in the country who write quantitative reports on drug abuse twice annually, and we are convened by the National Institute on Drug Abuse twice a year.

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Having done this and written over twenty reports on drug abuse trends in my city and met with my colleagues, it has given me a sort of broad-based perspective on how emerging drugs are measured and how we get a handle on them. But everyone looks at medical examiner data. We look at the data from the Drug Abuse Warning Network, which is data from a representative sample of nine federal short-stay hospitals with 24-hour emergency rooms, and that is conducted in 21 cities, as well as some other areas of the country.

We also look at treatment data, law enforcement data and price, purity, trafficking and the sale of drugs, as well as supplemental research data and information from multiple sources.

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I want to start my introduction to GHB by

telling you about the abuse of a group of drugs that are called club drugs. That is really the first time in a long time we have had a name like club drugs applied to drugs because they are used in a particular setting. That is why they came to be called club drugs. It is a mixed category of drugs. It includes stimulant drugs as well as depressant drugs that are used in nightclub settings. GHB is also known in these settings as liquid X, gamma, G, easy lay, Georgia Home Boy or great hormones at bedtime. MDMA or 3,4 methylene dioxide methamphetamine is ecstasy, e or x. Ketamine is known as special K. It is a veterinary anesthetic, a dissociative drug similar in effects to PCP. Flunitrazepam, Rohypnol is a long-acting benzodiazepine, which was dubbed the original date rape drug which is a drug not approved for medical use in this country; methamphetamine and LSD.

If there is one point to make about club drugs as a term, one thing that has emerged is the fact that clearly these drugs are not limited to club settings and I will be talking to that in a moment. It is not just clubs where they are used.

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To give you a little slice of the

progression of GHB and how it came on the CEWG radar screen, it was first mentioned in 1990 through a poison information center from my colleague in Miami. Then, from 1990 to 1994 it appeared in the Miami and the New York city reports. In 1996 it appeared in 6 other cities, and by the year 2000 most cities in this 21-city work group were reporting GHB. It reports 23 deaths in the 20 CEWG cities, and I refer you to a handout that I prepared that sort of gives the chronology of how my colleagues describe the growing abuse of GHB in their cities.

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Now, in terms of user typologies, they tend to be young adolescents through adulthood. There is really no age group but when we look at population surveys in this country of who are drug abusers, by and large the biggest bulk of drug abusers are people who are under the age of 35.

The motive for use is multiple. It includes not only intoxication, but also people seeking intoxication effects in the absence of alcohol. I have had people describe it to me as it gives them the effects of alcohol without having to waste that time drinking alcohol. This is by young

people who haven't developed the taste.

It is also used by weight lifters and body builders for its alleged anabolic effects. It is also marketed in nutritional supplements to promote better sex, better sleep and some people take it to counter the effects of other club drugs. One of the characteristics of drug abuse in nightclubs that has come up over the past year is the fact that people seem to have the impression that if you take just a little bit of this and a little bit of that nothing can really hurt you in a club setting. So, you might take a little bit of ecstasy to get you going, with a little bit of cocaine to keep you there, and maybe a little bit of heroin to take the edge off. This sort of mixing and matching is also part of the user typology.

The settings it is used in are nightclubs, raves, parties, but also in homes, in health clubs, gyms and other settings. The sources of it come from health food stores, mail order kits, the Internet or at these clubs where it is being used by the capful. Sometimes at these clubs, because ecstasy dehydrates you, people have a lot of water bottles and it is not unusual to have a water bottle that may have GHB mixed in it, and for ten

bucks someone can get a swig of it. This makes it very imprecise dosing, as you can imagine.

[Slide]

In terms of deaths, in terms of the consequences of use -- there is a huge bullet missing from this slide, which I will get to. So, if everybody wants to find their slides and write a bullet in it, I would appreciate it. Deaths -- there have been 71 documented deaths, according to the Drug Enforcement Administration, through November of last year. Again, the problem is that because it is a new drug of abuse people don't know. You know, you have to know what you are looking for to be able to find something and this has clearly been the case in trying to document GHB deaths. It is a huge issue and I hope we get enlightened on that this afternoon.

Also, there have been adverse medical reactions, not only people who come into emergency rooms, but the countless people, which is quite hard to quantify, who have episodes but never get emergency room treatment for it. But there have been medical reactions, adverse ones.

Dependence -- there has been a reported increase in people presenting to addiction

treatment centers with GHB as their primary substance of abuse, and an increase in the reported addiction to GHB by those who may not make it to treatment programs.

I work at the Hazelden Foundation. We are based in Center City, Minnesota, with campuses in Chicago, New York City and West Palm Beach. There were 5 patients in 1999 who had a history of GHB abuse, and that had grown to 39 in the year 2000 and we are just one treatment center.

Finally, the missing bullet on here is drug rape. One thing we have seen in this country since the early 1990's is the use of drugs, this predatory use of drugs where you administer drugs to people without their knowledge for the purpose of disabling them to commit crime on them. The first drug that came to this sort of notoriety was Rohypnol, but now we are in a situation where GHB is often used in drug-induced rape. In fact, several years ago when President Clinton signed the federal date-rape law, the Samantha Reid and Hilary Farris Date Rape Act, that was in response to two cases of drug rape that were not related to Rohypnol but to GHB. So, that bullet should be up there, drug rape.

Also, another bullet would include the trafficking, sale and manufacture, the law enforcement consequences.

[Slide]

Let's look at hospital emergency room episodes of GHB. This looks at them from 1994 through 1999. You can see the increase in hospital emergency department mentions of GHB. Mentions is sort of unusual term for people who aren't familiar with the Drug Abuse Warning Network, and it quite literally means, in a retrospective review of patient records, that they find a mention of GHB. Sometimes it is the sole drug that precipitated the medical emergency and sometimes it is used in combination with other drugs. For every drug abuse episode in the Drug Abuse Warning Network there can be the mention of 4 drugs and alcohol, but when alcohol is used in combination with other drugs; it is not an alcohol tracking system.

[Slide]

So, this is what it looks like through 1999. This looks at it by half year increments. You can see this takes us into the year 2000 and we have the first half of the year 2000.

I want to go back to just my opening

remarks about club drug abuse. I think in the general population when we think of club drugs, you know, what we hear about, what everybody is talking about, what seems to be in U.S. News and World Report, in Newsweek and Time Magazine is ecstasy.

[Slide]

This is from exactly one year ago. This is Time Magazine from June 5, 2000. It talks about ecstasy. For many folks, club drugs -- you think ecstasy.

[Slide]

This was, I believe, from Time magazine as well. You see the water bottle there. If you didn't see Time magazine, you may have seen The New York Times Sunday magazine insert. This is from January of this year, talking again about ecstasy. This is from January 2001.

So, since it is in the same category of drug, I think it is relevant to look at how GHB emergency room episodes compare with those of ecstasy.

[Slide]

Ecstasy, or MDMA, is in the pink and GHB is in blue. You can see in the first half of the year 2000 that GHB hospital emergency episodes have

surpassed those of ecstasy.

[Slide]

Efforts to control GHB -- a number of states have done things to try to control GHB abuse in their states. This is sort of a listing of the scheduling of it in various different states. It was added, as you know from the materials the committee received, to the Federal Control Substance Act.

[Slide]

Finally in conclusion, GHB is a significant, growing drug of abuse. We have seen rapid growth in the adverse medical consequences related to GHB since 1999 and, in fact, hospital emergency mentions of GHB now surpass those of ecstasy or MDMA. We have seen rapid growth in adverse medical reactions despite not only federal scheduling but the scheduling in numerous states. We have multiple user typologies. This is not a substance that is sought after simply by people at parties and raves. These products that contain GHB as well as its precursor drugs, GBL and 1,4-BD, are sought after by people who believe the claims on these nutritional supplements and take them for promoting muscle growth, for sleep; and take them

for better sex, as well, and as I said, use it in sort of predatory way. Dependence is clearly possible.

So in closing, here we have a drug with an established widespread abuse record. With GHB we needn't talk about abuse potential. With GHB we have abuse reality. We have a decade of GHB abuse in this country; a decade of deaths and hospital emergency room episodes and dependence. We have escalating abuse of GHB in spite of recent efforts to control it and, yes, people acquire this drug and its precursors in many ways. But make no mistake, the effects being sought are the GHB effects. The chemical agent in the body that is producing these effects is GHB, and this undisputable fact is entirely relevant to our discussions today.

I have to take issue with the statement from the sponsor that says Xyrem is not the problem. If Xyrem equals GHB, then I believe it is a problem. This drug, if approved, will exist outside the confines of this room. Patients will use it outside the confines of clinical trials. In America, in 2001 we have a serious, significant and growing problem with GHB abuse in this country, and

it just so happens that this coincides with Orphan Medical seeking approval for this drug.

This drug already has avid followers, and there is no reason to assume that another source of GHB would not be sought after by these folks, and I think we need to bear that in mind throughout our discussions. Thank you.

DR. KAWAS: Dr. Falkowski, can I ask you one question? With regards to the emergency department data for GHB, I recognize the difficulties of all of this kind of data but, for example, MDMA is not infrequently the only drug and when they go to the emergency room that is clearly because of the MDMA. Can you give us any kind of quantification or semi-quantification? You mentioned that sometimes GHB is the only drug.

DR. FALKOWSKI: The question was how often is GHB used in combination, and let me find that.

DR. KAWAS: For the emergency room data.

DR. FALKOWSKI: Yes, that is what I am looking for. I have it right here. It is 70 percent of the time. Like many other drugs, GHB episodes involve drugs other than GHB as well.

I would also like to add that I believe these hospital emergency room episodes

underestimate GHB because drugs that are used in a predatory way, that are administered to people without their knowledge are not DAWN reportable. So, if someone comes to the emergency room and says I believe somebody gave me something and it is making me sick, that is not a DAWN reportable thing. That is being addressed by the Substance Abuse and Mental Health Services Administration. But what that means is that people who are drugged with any sort of drug are not picked up by this particular reporting system.

DR. KAWAS: And, what are the most common drugs or classes of drugs that go along with GHB when people take them in combination? What are the favorites?

DR. FALKOWSKI: It is probably ecstasy, MDMA, and to a lesser extent ketamine and also alcohol.

DR. SANNERUD: I have some data on the DAWN statistics too. When drugs are used in combination, 50 percent alcohol, 11 percent stimulants, 8 percent marijuana, poly drugs, hallucinogens and sedatives and all these are at least at 3 and 2 percent each.

DR. KAWAS: Dr. Dyer, I believe you are

our next speaker.

DR. KATZ: Claudia, if I could just ask a question, and I don't know who best to direct it, but you said 70 percent of the time the reports are of GHB in association with something else. So, presumably 30 percent of the time it is the sole drug. I have a sort of methadologic question. How reliable would you say that information is, just in general? What is sort of the nature of the information that is recorded and from whom that allows us to conclude that, in fact, GHB is the only drug that was taken? Who reports that, and how reliable are those reports, just as a general rule? Number one.

Number two, how many of the deaths and very serious adverse events were associated with GHB use alone?

DR. FALKOWSKI: I believe you could address the reliability of DAWN. You are a DAWN reporter. Again, regarding the deaths, you know, the Drug Abuse Warning Network also collects data from medical examiners, but the people in the 20-city work group of mine rely more often on getting data directly from the medical examiners, first because it is more timely and also because it

casts a better net. It captures situations that are not only due to drug-related toxicity but also ones where the use of drugs were considered by the medical examiner to be significant contributing factors to the death. So, that is what I can say about deaths.

Also, I have a table, if you are interested, that I could make available that shows exactly DAWN emergency room data for 1999 and what were the co-ingestants.

DR. KAWAS: Our next speaker is Dr. Jo Ellen Dyer, from the California Poison Control System at UCSF, speaking on adverse medical effects with GHB.

Adverse Medical Effects with GHB

DR. DYER: Thank you and good afternoon.

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In 1990 I identified and made the first reports on GHB abuse from over-the-counter sales of GHB. Over the next 11 years I have been following GHB. I have an interest in it and I have been reporting on the progress, the adverse effects and the trends in use.

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This is a description of the California

Poison Control System data of GHB reports to our center. We logged these reports over 10 years. The first years are when the San Francisco center stood alone so it is a population base of 7 or 8 million. We became a system in '97 so we have 4 years of data for the entire state.

We are a medical toxicology consult service, so we are not a required or mandatory reporting center. So, this reflects just the tip of the iceberg of use and abuse and adverse effects that are out there.

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In our experience GHB produces a profound coma. This has been known for over 40 years, starting out in surgical anesthetic studies where it was evaluated as an anesthetic and now through numerous occurrences of coma in users through this widespread public use, where accidental overdoses are occurring because of the narrow and variable therapeutic index for this drug.

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Looking at 5 studies, anesthetic studies that cover over 700 patients -- there are many other studies; I just picked a small set of them -- you see the effects of GHB in a controlled

situation. GHB causes unconsciousness and a profound coma. This is what is intended with an anesthetic. The respiratory effects that are seen are Cheyne-stokes respiration. There were aspirations. There was a case of unexplained pulmonary edema. In many of these cases the patients are intubated and the airway is attended to. If their airway was left to chance in these situations, it would be compromised. They lose their airway protective reflexes. They have no gag. So, with the high incidence of vomiting, about 30 percent in these studies, combined with the loss of gag, it is not difficult to see how aspiration is going to occur.

There are cardiovascular effects, like bradycardia, and then there are isolated incidences where blood pressure rose up to 30-60 mmHg for unexplained reasons really. There is myoclonus that we see. There is an emergence delirium, confusion. There are also secretions like salivation, vomiting, incontinence and diaphoresis.

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If I look at 16 reports that cover 175 cases of adverse events where GHB was in public use, you see these same physiologic responses to

GHB. You have profound coma. They develop a mild respiratory acidosis; bradycardia; myoclonus; confusion; emergence delirium; and then the secretions. This raises doubts for safety of use among a generalized public population.

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If we look at a closer group where we did a study in our emergency department, and this is the San Francisco County emergency room that sees over 200 patients a day -- we looked at GHB overdoses that we had over 3 years. This is just a retrospective descriptive study where we were trying to get a handle on what is going on. We found that of those cases, about 33 percent had no co-ingestion. This was documented by either toxicology or patient report. Those patients came in, a quarter of them, with Glasgow Coma Score of 3. So, they were profoundly comatose and 33 percent of them had coma scores between 4-8. The coma lasted 15 minutes to 6 hours.

Again, a third of the patients had these same symptoms, bradycardia, respiratory acidosis, hypothermia, vomiting. We saw hypotension in about 11 percent. Those cases were primarily cases where alcohol was co-ingested. Then, on emergence these

patients are difficult to manage. They can have an emergence delirium which includes combative, agitated behavior.

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Because of that evidence and wanting to focus in closer and get some GHB levels to find out if that is truly what we were looking at, we did a prospective study over 6 months, looking at 15 cases of GHB overdose, and 73 percent of those came in with a Glasgow Coma Score of 3. Our intent was to document the presence of GHB, to detect the co-ingestants and what they were or if there were none, and then to verify that our ability to predict an overdose is truly GHB by the toxidrome that we are using, whether or not that was effective.

So, all of these 15 cases did have GHB that was measurable. They were young, ages 20-39; 73 percent were male. The study inclusion criteria were patients presenting with Glasgow Coma Scores less than 8 and 73 percent of these patients had a Glasgow Coma Score less than 3.

In 5 of the cases there were no other drugs or alcohol detected. The GCS was 3 in 80 percent of those cases. So, profound coma from

accidental overdose; no other obvious cause.

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It is clear to us that there is really substantial evidence that GHB causes coma. Coma is life-threatening, and these deaths are occurring from accident or injury and from respiratory compromise. We are seeing that through aspiration; through apnea; through positional asphyxia -- these are profoundly comatose people, they can't even move to open their airway -- and through pulmonary edema.

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So, I have reviewed 20 GHB related fatalities where I had autopsy reports. I just sent letters to medical examiners asking for their reports. In these cases, the ages ranged from 15 to 46 years. Three-quarters of them were male; 20 percent of them had no concurrent ingestions. If we look at those that had co-ingestants, the 80 percent. We will see that many of these substances are legal commonly ingested things. Tylenol was one of them; caffeine; alcohol. The levels of alcohol went up to 0.17 percent. The legal limit for driving ranges from 0.08 to 0.1. So, most of these cases were in the lower range, right around

the legal limit of driving, saying that they had maybe one or two drinks and none of these would reach an alcohol level that would cause coma.

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The societal costs that were seen from GHB abuse, there are many driving under the influence arrests that have occurred with GHB. There were a whole lot that were not recognized until GHB testing became available and now they are being recognized. I don't go out really and collect this data but there are two vehicular manslaughter, I guess they would call it, cases where a person driving under the influence of GHB has hit and killed another individual. One of those was in '96 and one was in 2000.

Another societal cost is the assaults where the victim is under the influence of GHB given to them or slipped to them by the assailant. It is common enough that they have a term for it. It is called being "scooped" by GHB. The assailant then attacks the victim while they are unconscious or amnestic to the effects of the drug, making prosecution and even reporting of these very, very difficult.

These are 4 cases. There are others. But

in these GHB was clearly documented as the cause. The first was a woman who was drugged and assaulted by her boss as they went out with a group of colleagues after work. She had GHB in her urine. There were 10 victims of some DJs in Los Angeles that were slipping GHB into drinks and then assaulting them. There was a 24-year old that was eventually prosecuted more for trafficking drugs after a woman had reported an assault to them and, in kind of the bargaining, he admitted, yes, he had drugged her twice with GHB and she has no memory of the first event at all. Nothing. The last is two 15-year old females who were unconscious at a party. One was hospitalized and one of these girls died.

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We also see addiction as another burden from GHB abuse. We are currently seeing one to two cases a month at our poison center, and this is eight cases that I collected. The age range is young, 22-38, again three-quarters male. The pattern just continues through all these of the demographics of who is using. Of these, 63 percent started taking GHB for body building. They had what they thought was kind of a legitimate use of

this dietary supplement. In this group, 88 percent of them were employed or students. These were functional members of society that have had trouble now because of this drug. These are not people that really had drug-seeking behavior. The onset of symptoms we see within 1-6 hours. It progresses over a couple of days. The duration is 5-15 days.

Now, these are often unrecognized by healthcare professionals when they present for treatment. GHB abuse addiction is not really very well known out there. These are severe neuropsychiatric symptoms with autonomic instability that we see. I have had physicians who have treated many, many cases of severe alcohol withdrawal that have called me up and said, my gosh, I am impressed; I am so impressed by this withdrawal symptom. The patients become agitated, combative, delirious. They are hallucinating. They require sedation, a milligram a minute of IV Ativan has been used over a few hours to gain control. They require four-point leather restraints and intensive care. One of the patients in this series died while being hospitalized for GHB withdrawal.

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Substantial and compelling evidence from case reports of accidental poisoning and from toxicology supported adverse events really shows us that these effects are due to GHB. It is not some contaminant or something else that is causing these. And, there is an insufficient or no safety margin between the effective level of the therapeutic dose of these drugs that these people are taking and the dose that causes these effects. As you can see from the sponsor's study, the adverse effects that they are reporting are very similar. The confusion, the nausea, the vomiting are very similar to the things that we are seeing.

One physician, Dr. Gallamberti from Italy, who is doing therapeutic use of GHB withdrawal states talks about a 15 percent problematic GHB use among his population. This can be dose escalation. This can be GHB overdoses up to 10 times a year, or GHB dependence.

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This slide just looks at the kinetics to illustrate that there is really a very narrow therapeutic index with this drug and there is a lot of variability. The pharmacokinetics of GHB are capacity-limited absorption, capacity-limited

elimination. The coefficient of variation of some of these parameters is 50 percent. There is a lot of variation and we don't really know what the consequence in different populations and different people of these really variable kinetics is going to be, or why they are so variable. You are used to using phenytoin. It has capacity-limited elimination. We know that when you are bumping the dose of a patient on phenytoin you have to be really careful because they can exponentially increase their level. Well, the same thing happens with GHB and we don't know where that is yet. There is not enough experience. And, with phenytoin the absorption is pretty good. We know the bioavailability of IV phenytoin and oral phenytoin. Here, I don't think it is so constant. It really changes with food and there is a capacity-limited absorption that is going to vary between patients. So, this is a really difficult drug to control, particularly orally on an outpatient basis.

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So, what is the current level of GHB abuse that is out there? We really don't know. If we wanted to project from one survey that was done,

Dr. Miotto, a UCLA physician that works addiction medicine did a 45-minute structured interview with 42 GHB users. Among that group, 69 percent had admitted that they had lost consciousness, had periods of consciousness laps from minutes to hours. There was variability in the amnesia dependent upon how often people used. Twenty-eight percent admitted having an overdose; 9 percent had been to the emergency department for an overdose.

Now, there is an interesting misconception here where they don't consider the loss of consciousness to be an overdose, and people overdose and when they are in a profound coma are not taken to the emergency department. So, there are really some problems there, and this gives us an example of the kind of under-reporting that is out there.

If we try and extrapolate from the amount of drug that we are seeing marketed illicitly, this is just one arrest in Marin County, a small county north of San Francisco, where they had 207 L of butanediol. The average street dose varies around 2 g. If you look at that, that is 103,500 doses in one capture at one house, and there are many, many of these. There are lists of different amounts

that have been busted all over.

Then there is the problem that Carol has already talked about, surveying and policing the issues of this type of new drug abuse. There is no systematic method in place for data collection on this.

There is rapid metabolism of the drug. It clears from the blood in within about 6 hours; it clears from the urine within about 12 hours. We can't test these people and find it. When we are trying to get evidence in a drug assault case, it is gone. It is really difficult to detect. And, should we increase our level of detection to the very, very minute nanogram kind of range, then we are going to start running into the biological background so we aren't even going to be able to do that if we increase our ability to detect. There are also very poor assays currently out there. None of the hospitals have an assay for this, and none of the law enforcement has a field kit for it. So, it has to be taken into a lab and specifically run through a complicated GC mass spec procedure to get a level out, which is expensive.

The current documentation clearly grossly underestimates the amount of use that is out there.

And, it is very clear that there is a little, if any, safety margin with GHB use in the therapeutic doses that are proposed. GHB is a very potent new drug of abuse. It has been around 10 years. We thought it was going to come and go as a fad, it hasn't and it is not going to. The use is still increasing.

There is a very high acute toxicity in accidental overdose -- coma, bradycardia, myoclonus, vomiting, aspiration -- we are seeing a lot of it, and it has very high abuse and addiction potential. So, I think that we have to be very careful and it is very difficult to try and minimize these potential risks, the risks of having it get out into the drug abusing population but also among patients that we are going to be giving this drug to take at home. At the poison center, every night at bedtime, 9 to 11 o'clock I am called by people that say, oh, I'm sorry, I accidentally took a double dose of my medication. What should I do? In this case, they are all going to go to the emergency room. There is really not a margin of safety with this drug. Thanks.

DR. KAWAS: Thank you, Dr. Dyer. The next presentation is from the sponsor, presentation on

risk management and abuse liability, Dr. Bob Balster, from the Medical College of Virginia.

DR. REARDAN: Yes, I would like to now introduce Dr. Balster who will present his views with respect to abuse liability of Xyrem and GHB. Dr. Balster is a previous chair of the FDA Drug Abuse Advisory Committee and a widely published abuse pharmacologist from the Medical College of Virginia. He is editor and chief of a leading addiction journal, Drug and Alcohol Dependence, and a past president of the College on Problems of Drug Abuse.

Sponsor Presentation on Risk Management and Abuse Liability

DR. BALSTER: Thank you very much, Dayton. Good morning or good afternoon, I guess it is now.

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Well, as you have just heard, the development of Xyrem as a medication has taken place in a context of a national epidemic of the abuse of its constituent GHB, and also the abuse of a number of GHB-related drugs that I will tell you about.

As Dr. Houghton told you, Orphan is very well aware of this problem and has consulted many

drug abuse experts to try to understand the problem better. My own analysis of this situation is that Xyrem has certainly not contributed to the problem that exists today with the abuse of this class of compounds. I guess where I may disagree a bit is that I am pretty convinced that Xyrem is not going to be a player in this over the long term.

I think in order to understand and make an appropriate public health response to this situation, you need to know a little bit about what some of the causes are of this GHB abuse problem.

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So, I hope to make two points in this presentation. The first point is that I believe that the recent abuse of GHB-like substances probably reflects a ready availability more than their inherent pharmacological propensity for abuse.

I think I will make this point by first off reviewing for you the incredible availability of these compounds, and then also review very quickly scientific studies that have been done on the abuse liability of GHB as it is compared to other drugs of abuse you might be familiar with. Secondly, I believe that Xyrem, if approved for

medical use, will not contribute to the public health problem of the abuse of these GHB-like substances in any significant way.

[Slide]

Before we continue, it is very important to know the cast of characters here. I think next to the federal government, the next worst developer of abbreviations is a drug abuse research community, with MDMA, and PCP, and GHB, and BD -- it must be hard to kind of keep track of the players but, of course, the drug we are talking about here is GHB, gamma hydroxybutyrate. But there are a bunch of other drugs that are basically part of this national drug abuse problem.

You have heard a little bit about them, but these precursors, gamma butyrolactone or GBL, 1,4 butanediol or 1,4-BD are precursor compounds that, if obtained, can be easily and readily converted into GHB. They also can be consumed directly because they are metabolized by the body into GHB. So, they themselves are drugs of abuse like GHB. Then there are others that are also available.

Now, of all these chemicals only GHB is actually a scheduled drug. It is Schedule I under

the Controlled Substances Act for the abusable versions, GHB; Schedule III for an approved medical product. So, only GHB is scheduled. Now, GBL is what is called listed so its availability is diminished. These others are still freely available without any drug abuse controls.

[Slide]

You have heard a lot about GHB abuse but I am pretty convinced that what we are seeing here is something that has resulted from an amazing situation of the availability of these compounds. To remind you, GHB was available legally and legitimately through health food stores up through 1990 when you could buy it anywhere, and the abuse problem with this drug began during that period of time.

Then through that time and afterwards GHB could be obtained through the Internet. There was an amazing number of sites set up to sell GHB. Then, as GHB became less easy to get because Internet sources dried up, the Internet sources were selling the precursors, etc., etc. I will show you some data a little bit more, but these precursors are not going to disappear any time soon from public availability. Now that the

availability of GHB has been restricted by the federal scheduling actions and actions by the FDA, people can now purchase the precursors and make their own GHB. Essentially anyone can do that. It is a very simple thing and the recipes are right there on the web. As I said before, they themselves are widely abused. So, we have a class of chemicals here that are really basically part of what has been referred to as a GHB abuse problem, but it is really an abuse of a class of drugs, and you saw some evidence on that.

[Slide]

At this point I want to review the scientific literature on the laboratory studies of the abuse potential of GHB. You may wonder why I would want to do that, I mean, why would I want to review literature on abuse potential when the reality of GHB abuse is clear to us from epidemiological data that Dr. Falkowski mentioned and clinical data. The reason to do this is to try to understand what the basis for this is, and to know whether or not this wide abuse is due to some features of this incredible availability, or whether the drug has sort of the inherent pharmacological desirability that you would

associate with a really dangerous drug like cocaine or heroin where, no matter how many billions of dollar we throw at the problem, we are getting nowhere with it, or does GHB represent a drug which is less desirable or has less propensity for use.

[Slide]

Just to remind you, there is a well-established science of abuse liability evaluation, and it is used in evaluating new compounds that are under development. It is useful in making decisions about drug abuse control, and data such as these are used widely by the FDA for making regulatory decisions. All of these data are reviewed in your packages, but just to quickly tell you, first off, GHB is a unique drug. It is not just another depressant drug like barbiturates or even benzodiazepines that have its own receptor and its own characteristics.

In studies which are called drug discrimination studies, which allow you in a way to compare unknown drugs to known drugs of abuse, again, GHB lacks equivalence to these classical depressants like barbiturates or any other classes of drugs to which it has been directly compared.

In self-administration studies -- these

are laboratory studies where you can actually measure what we call the reinforcing effects of the euphorigenic potential of these drugs -- actually in this particular class of studies GHB has very weak reinforcing effects. It is difficult to obtain them in laboratory studies and there have been a number of those. We did one of these ourselves in our laboratory and we essentially found no evidence of GHB self-administration under conditions where we reliably get self-administration of cocaine, heroin, barbiturates, etc., etc.

The case of physical dependence is a little bit more complicated. You heard from Dr. Dyer about the fact that abusers can develop dependence and show withdrawal signs, and there is no question about that. These people are taking maybe 10 or more times the therapeutic dose. We are talking about 70, 80, 100 grams a day, and they take them every 3 hours or so because they have to maintain the blood level. Yes, in those cases you get dependence, but in patients receiving Xyrem, where they are getting it in lower doses and they are taking it only in the evening, as you have heard from the reports, there have not been

significant problems of dependence. So, yes, it can occur in abusers but it isn't really an issue in patients. Importantly, animal studies, for example, where you try to show the dependence of GHB and compare it, for example, to barbiturates, it is not easy to develop a model for GHB dependence in animal studies because it has less inherent dependence producing properties than these other drugs.

[Slide]

So, my conclusion when I reviewed the literature on the scientific studies of GHB, when I was asked to do that, I basically thought it looked a lot like what I would say is a Schedule IV drug. Schedule IV drugs, you remember, are benzodiazepines and chloral hydrate and drugs of this type, and that is sort where it fit. It isn't like cocaine. It isn't like heroin. In fact, that analysis of looking at the data has been made by others with very much the same recommendation as mine, that is, it sort of fits pharmacologically with Schedule IV.

For example, the WHO expert committee which met not too long ago to make a recommendation to the UN Commission, the WHO expert committee

recommended Schedule IV and, in fact, the UN Commission ultimately placed GHB in Schedule IV. Schedule IV, under the Psychotropic Convention is very analogous really to our Schedule IV that you are familiar with under the Controlled Substances Act.

[Slide]

We are not here to talk about GHB abuse which we know is a significant problem. We are here to talk about Xyrem and what its role may be in the drug abuse problem in the United States. There are two issues we are really worried about here. Number one, we are worried about the possibility that patients legitimately prescribed Xyrem will abuse it in some way, or misuse it or escalate and then, secondly, we are worried about whether or not it might be diverted into sort of illicit channels and become part of a problem in that way.

[Slide]

Turning first to the issue of patients, first off, I think most of you know, and it is important to always know this, that the development of abuse among patients receiving therapeutic doses of abuse drugs is a much smaller problem than some

people realize. It is actually fairly unlikely to occur in a general sense. Of course, in the trials with Xyrem there weren't problems of abuse; there wasn't evidence that people were escalating their dose or complaining and asking for more, and that sort of thing.

It is important also to recognize that narcolepsy patients are patients that are receiving controlled substances all the time. The stimulant class of drugs, all those drugs that Dr. Mignot spoke about are all scheduled compounds. In fact, many of them are Schedule II where they can't even get them half the time because the production controls on Schedule II reduce their availability.

Then the issue about their dependence, if you understand, for example, that with benzodiazepines, when you discontinue benzodiazepine administration you will often see a withdrawal syndrome, well, that is because benzodiazepines have this incredibly long duration of action with active metabolites that accumulate so that the body continually maintains levels of benzodiazepines. So, when you quit using them there is a withdrawal syndrome. With GHB, as you saw from Dr. Houghton's presentation, the duration

of action is just a couple of hours. It would take many, many, many multiple daily uses, way more than the patients are going to get, to maintain the kind of levels of GHB that would be expected to produce dependence. So, yes, in abuse cases where people are just going all day and all night but not with patients.

[Slide]

Turning now to illicit diversion of Xyrem, first off, that hasn't happened yet. So, we are not aware of any diversion of any Xyrem through any of the products. This is, of course, only in clinical development but I think it is important to know. Most importantly, the company has been very much worried about this issue and has developed a distribution system that you are going to hear about, called the Success Program, which I personally believe is going to substantially prevent any opportunities for diversion. Lastly, Xyrem, whether you approve it or not -- it is going to make very little difference in the overall availability of this whole class of chemicals in the national scene.

[Slide]

To illustrate that, this slide shows you

the product amounts anticipated, annual production amounts for this class of chemicals I mentioned to you. So, if Xyrem is approved the anticipated first year production amounts of gamma hydroxybutyrate are about 82,000 kg. GBL, gamma butyrolactone, the precursor that can be made into GHB easily and consumed itself, is 83 million kg, a thousand times more. 1,4-BD which is not a controlled substance and has no drug abuse control under it whatsoever right now, is widely available through all sources in large amounts, and is made in the neighborhood of 377 million kg. For those of you who don't do the metric system, that is 400,000 tons of 1,4-BD. And, all of these drugs are basically substituting for one another. So, whether you take Xyrem in or out of that graph, it is not going to make a difference.

[Slide]

In conclusion, I believe that the epidemic of abuse of GHB-like drugs has resulted really primarily from its extraordinary availability. In fact, when GHB was controlled -- it is hard now to get GHB. It is hard even for me to get GHB as a research scientist. So, the problem has now switched to these precursors that are available.

Secondly, the scientific studies of GHB show that you are not talking here about cocaine or heroin. It is a weak depressant of maybe the benzodiazepine, chloral hydrate type. Thirdly, I believe that Xyrem abuse is very unlikely among patients for the reasons I said. Lastly, the contribution of Xyrem to the public health problem, which is the matter of concern, is essentially not significant. So, you know, have your way with the drug in terms of efficacy and safety but I don't think you need to be worried that this drug is going to be a major factor in the drug abuse problem with this class of drugs. Thank you.

DR. KAWAS: Yes, a quick question, Dr. Leiderman.

DR. LEIDERMAN: Yes, I would like to ask Dr. Balster two questions. I would like you to comment on the species of animal that you are addressing when you talk about self-administration in drug discrimination studies. Two, I would like you to comment on the data that those models show with other classes of drugs.

DR. BALSTER: All the studies are reviewed on that slide on abuse potential with laboratory animal studies, using fairly well developed

methodologies. The self-administration studies that Dr. Leiderman referred to were studies that were done in monkeys in sort of a standardized method that is done through a program directed by the College on Drug Dependence. Those are the models, and I can show you data if you give me the time to do it. Maybe later, if the committee is interested, I can show you data. But these are models in which basically it is extremely easy to get animals to actually literally self-inject most of the drugs of abuse -- cocaine, amphetamines, opiates of all types, barbiturates, depressants, benzodiazepines -- benzodiazepines are a little harder but in the model that was used that I showed the negative results from, benzodiazepines were the positive control. So, basically the only area where that model has been not very successful and underestimates abuse potential is with hallucinogenic drugs and marijuana type drugs.

DR. LEIDERMAN: Yes, many of the Schedule I drugs.

DR. REARDAN: We just have about another ten minutes. If we can prevail on the committee, we have one last speaker, and that will be Patti Engel, who is going to describe for you the risk management system that the company

has developed to help control diversion. Patti?

Risk Management

MS. ENGEL: Good afternoon. My name is Patti Engel, and I am here today to talk to you about the risk management program for Xyrem, which we call the Xyrem Success Program.

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This program will ensure the responsible distribution of Xyrem, namely, to meet two goals. First, to ensure that patients who desperately need the medicine can get it. Secondly, to keep this out of the hands of those people who might abuse it.

[Slide]

To develop this program we consulted broadly with a number of people interested in the issues not only germane to patients but also that of drug abuse. As you can see, we spoke with drug diversion investigators, field law enforcement, forensics experts, toxicologists, pharmaceutical distribution experts, drug abuse trend experts.

[Slide]

Through those discussions we followed FDA's proposed risk management guideline, which is risk management through risk confrontation, in

essence egging the partners and the shareholders to not only identify the issues but also assess the risks, identify the options and select a strategy. The program that I am going to be sharing with you today is certainly a draft program that the company has designed after discussions with these numerous stakeholders.

[Slide]

This slide I show to you really to point out the standard route of distribution of a pharmaceutical product in our country today. This includes not only commonly used medications like products for blood pressure control or products for arthritis, but also products under Schedule II, including such agents as amphetamines. Typically, a product is manufactured and goes to a number of national, regional and local wholesalers, eventually getting to 63,000 retail drugstores around the country. One can only imagine the number of loading docks, transport vehicles and hands that touch a pharmaceutical product in this traditional distribution system.

[Slide]

As we contemplated the distribution of Xyrem and how to do this responsibly to meet the

prior stated goals, we determined that a closed distribution system would best fit everyone's needs for this product. The product is manufactured at one single manufacturing facility. It is sent to one single national specialty pharmacy. Eventually it goes by courier to patients with narcolepsy.

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The benefits of this program are that not only is the product distributed from a central location, but all the controls and all the records are in one place.

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So, how will this work? Because a number of doctors prescribe medicines for narcolepsy, we will focus our promotional effects on those physicians. They include such specialists as neurologists, pulmonologists, psychiatrists, internal medicine physicians and several primary specialties who practice sleep medicine.

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Our small sales force will call on these physicians, communicating the clinical benefits of Xyrem in narcolepsy. At those calls, the sales representatives will also review with each physician something that we call the physician

Success Program. I will go into the details of this program in a more in depth fashion in just a moment. But it is important to know that each physician will sign that they have reviewed this program with the sales representative and understand the program. I should also note that at no time will we embark upon physician sampling.

[Slide]

I promised to come back to the components of the physician Success Program. I know that many of you received copies of this but I would like to highlight some of the main points. First, because we know individuals all learn differently -- some by hearing, some by reading, other methods -- we have made this a multi-faceted program which includes videos, brochures, pamphlets that describe four main areas.

The first is to highlight to physicians that the distribution process for Xyrem is different, that their patients won't be able to get this at the corner drugstore. The second important issue that this binder points out to physicians is the dosing and administration of Xyrem. The next important issue is that of home storage and secure handling. The fourth is an important module that

we call "doctor be wary" which is an educational module that educates doctors about the ways that drugs are commonly diverted in this country so they can be aware of patients who are attempting to illegitimately get a prescription from them for this product. Each of the kits will also contain a number of unique prescribing forms for Xyrem which will be necessary in order for the prescription to be filled. This is, in essence, a special prescription form. As well, contact information will be provided should the doctor have any questions at all about the program.

[Slide]

Once the physician decides to prescribe Xyrem the physician faxes this special prescription to the specialty pharmacy. Now, I am going to come back to how this prescription is verified. So, I will ask you to hold on that point for just one moment. But, based on that prescription and based on the patient's geographic location, the pharmacy assigns that patient to a dedicated pharmacy team. So, each time that the patient deals with the system they are talking with the same pharmacist and the same reimbursement specialist.

[Slide]

I mentioned that as the prescription comes to the specialty pharmacy there will be a number of checks to determine if the physician is, in fact, eligible to prescribe Xyrem. We will be utilizing DEA's NTIS or National Technical Information Services database to ensure that each physician has an active valid medical license, and also to ensure that that physician has current prescribing privileges which allow him or her to prescribe Schedule III medications in this country. As a backup check, the specialty pharmacy will also be checking with the appropriate state medical board to determine that there are no pending actions on the behalf of the state for that given physician.

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As a secondary step, the specialty pharmacy will also do a check on the patient in essence. What they will do is when that prescription comes in they will call the prescribing physician's office to determine that, in fact, that patient is real and a prescription has, in fact, been written for that patient.

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Once insurance reimbursement is obtained, the specialty pharmacy contacts the patient, first,

to determine the patient or the patient designee's location and availability for shipment, and also to describe to them the contents of the shipment. I will come back to the details of this in just a moment, but it is important that you know that each patient, when they get their first prescription of Xyrem will receive a multi-faceted educational program called the Xyrem patient Success Program, and I will come back to the details of that in just a moment.

In that same shipment they will also receive their Xyrem, and that will look something like this, with child resistant closure not only on the primary container but also on the dosing cups which are provided by the company.

[Slide]

The shipment that goes to the patient is sent by a special system that has a special, unique tracking system called the Rapid Trac System. this system will allow detailed real-time tracking of that package which is delivered only by the authorized signature. If the patient or their designee is not available for receipt of the package at the time agreed upon with the specialty pharmacy, the package will be returned to the

specialty pharmacy after one delivery reattempt. So, a package will not sit on a delivery truck or in a hub for weeks at a time or anything like that. If the package is lost the system will allow an investigation to begin regarding the shipment's whereabouts at that point of loss.

[Slide]

I spoke a moment ago about the patient Success Program. Again, this is a multi-faceted program which includes video, brochures and pamphlets which deal with a number of important issues for patients. First addressed, of course, is the distribution process since it is so important that the patients understand that the only way they will get Xyrem is through the special pharmacy and not at their corner drugstore.

There is information about Xyrem's dosing and administration because we feel that that is an important message to be delivered in an understandable and a very consistent manner.

There is information on home storage and secure handling, and we also are very clear with patients about the criminal and civil penalties that the public law assigns to any illicit use of Xyrem. So, if I were, as a valid narcolepsy

patient, to take my Xyrem prescription and use it to conduct a rape or in an assault situation, or if I were to sell it to someone for illicit use I would be penalized, I would be subject to C-I penalties. The patient Success Program also includes contact information for the specialty pharmacy should the patient have any questions at all, and also reimbursement information.

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After the Rapid Trac System shows that the package has been received by the patient, the specialty pharmacist will call the patient within 24 hours not only to confirm receipt of that package but also to again reiterate certain important points with the patient. Those include the penalties for illicit use of Xyrem; Xyrem's dosing and administration; home storage and secure handling. The pharmacist will also take the opportunity to discuss with the patient the child-resistant features on the primary container as well as the child-resistant features on the dosing cups that are provided.

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The central data repository designed for Xyrem really allows for identification of a number

of unusual types of behavior, including any duplicate prescriptions, any attempts of over-prescribing, or any attempts at over-use by patients. The benefit here is that that information is available prior to filling the prescription so appropriate pharmacist intervention can occur.

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As you can see, the Xyrem Success Program is a comprehensive program which is designed to responsibly distribute this important medication in order that patients who need it have it available, and it is inaccessible for those who might abuse it. Thank you.

DR. REARDAN: Dr. Kawas, that completes our presentation and we will turn this back over to you.

DR. KAWAS: Thank you very much. I want to thank all of you for all of your nice presentations but, rest assured, you will have more questions in the afternoon. We are running quite late so we are going to cut lunch a little short and we will plan on reconvening at 1:30, at which time the public hearing component of this meeting will happen.

[Whereupon, at 12:50 p.m., the proceedings were recessed for lunch, to resume at 1:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. KAWAS: We will reconvene the meeting of the Peripheral and Central Nervous System Advisory Committee discussing Xyrem. We are now in the open public hearing portion of this meeting, and we have quite a few people that we will be hearing from and additional people who want to add to the list. I would like to ask all of the speakers to please do their best -- not their best, you must stay to five minutes. You will have a one-minute warning sign with your timer. If you go over, please don't take it personally but you might hear my voice ending your part for the meeting. This is in order to allow us to hear from everybody who wants to speak, as well as to get onto the deliberations of this committee. The first speaker in the public forum is Sharon Fitzgerald of Littleton, Colorado.

Open Public Hearing

MS. FITZGERALD: Good afternoon. I am Sharon Fitzgerald from Littleton, Colorado, and I am a narcoleptic. I am a volunteer member for the Orphan Medical Patient Council and the Narcolepsy Network is paying for my travel and my hotel to allow me the privilege of speaking with you today.

Five minutes isn't long enough. I have provided a longer version for you to read. Please, please read it. It explains my experiences with the five major symptoms of narcolepsy and how Xyrem gave back my American dream, the ability to pursue happiness without stumbling on the way when it gets tough, and without literally falling on my face when the goal of happiness is reached.

I have had daytime sleepiness since 1969. It threatened my ability to be a good mother and protect my children, and it trapped me in a series of entry level jobs. Not knowing it had a name, I tried to hide my problem from employers and I hid in restrooms for many years for 15-minute naps at unpredictable times lots of the time.

My symptoms dramatically increased and worsened in 1977 when I was in law school. I was raising school age kids on my own, being widowed at the age of 32. In daytime, against my will, I took naps in my classes, going instantly from consciousness to dream state sleep, the switch being so quick that I actually wrote words from my dreams in my class notes about things like my mother and helicopters, and wondered where they came from when I read them. These were usually

followed by a mark where I dropped my pen as I stopped writing, and that would startle me into wakefulness and I would stay awake for a while and take more notes.

Going to sleep nearly every night, my mind created vivid illusions of my very worst fears, often a murderous rapist breaking into my house from behind wherever I was sitting or lying. My knowledge of where I was, was accurate. I could not scream. I was paralyzed and I couldn't turn around to defend myself. These are called, as you know, hypnagogic hallucinations. I didn't know that at the time.

At the same time, the symptoms of nighttime wakefulness became more severe. I experienced long hours of anxiously lying awake, punctuated by times of intense dreaming so real and so vivid that in the daytime I couldn't remember whether events I remembered were real or dreamed. You may understand that I feared for my sanity, and this is when I sought medical help.

I was my doctor's first experience with narcolepsy. It took a very long time for him to find a diagnosis. When he did, it was because of my mild cataplexy and he found the diagnosis an

announced that was the good news because the bad news was there was no treatment. I self-medicated for years with Sudafed and coffee.

With determination -- if you knew me you would know about it -- and special accommodations from the university I actually finally managed to graduate from law school, but I turned down the dream job that was offered, clerking for a district court judge, because I feared I would fall asleep in front of the courtroom. He told me our first case would be about two nuns who had been brutally murdered and I feared I might experience cataplexy.

By this time my cataplexy had increased to the point that all my facial muscles would relax and my speech would become momentarily slurred. It passed so quickly that I couldn't hide it. I was a sole practitioner. I couldn't bill enough hours to earn a living. I took Ritalin; I took antidepressants unsuccessfully. I found a job with the State of Colorado. It didn't require my legal expertise but I got lucky, I found out about the trials. I had rebound cataplexy, like what they showed you in the pictures, and it was horrendous for several weeks, waiting to be on Xyrem and my secret was brought out at work. But they didn't

fire me because I told them I was going on Xyrem.

Its effects were immediate and dramatic. I have experienced no side effects. I get good restful sleep. I awaken refreshed. I stay reliably awake at work with fewer stimulants and I don't fall down. My supervisors noticed my increased wakefulness and rewarded it with committee chairmanships and memberships and, in 1999, a promotion. In 2000, January 1, I became an administrative law judge for the Division of Workers Compensation in the Colorado Department of Labor and Employment. It is responsible; it is emotional. I can do it. My colleagues know I have narcolepsy and they know that with Xyrem it doesn't interfere with my job performance. For years I was unable to safely carry my children or grandchildren. I carried my newborn to his first examination and that is just the beginning of my story.

DR. KAWAS: Thank you, Ms. Fitzgerald. Next is Richard Gelula, the executive director of the National Sleep Foundation.

MR. GELULA: Thank you. The National Sleep Foundation is an eleven-year old organization that was developed by the American Academy of Sleep

Medicine to educate the public about sleep and sleep disorders, and our leadership has always been drawn from the top tier of sleep experts, sleep scientists and sleep physicians. We are independent. We raise our money in a variety of ways including government grants, corporate grants, and many memberships, individual contributions that have played a major part, particularly from people and families affected by sleep disorders. Our funding from Orphan Medical for the last two years has been a total of 160,000 out of a two-year total of about 5 million. Our budget is about 2.5 million a year. And, their support has gone to broad activities -- sponsorship for National Sleep Awareness Week where they join in with other sponsors, and there is no name or brand specific recognition or benefit for them. So, I wanted to point that out.

The Foundation is qualified to address this and our interest is due to the fact that we have invested about a million dollars in narcolepsy research, including center grants for the genetic research done at Stanford. We presently have one of our postgraduate fellowships at UCLA studying the neurophysiology of cataplexy. We also have

established the National Narcolepsy Registry which has registered to serum DNA registry with about 700 patients and family members registered. That is managed at Montefiore Hospital in the Bronx, and it has been a resource for seven scientific investigations.

To summarize the position of the National Sleep Foundation on sodium oxybate, the National Sleep Foundation calls upon this panel to fully consider the safety and efficacy of sodium oxybate for the treatment of narcolepsy and cataplexy, and to do so in a comprehensive context that fully recognizes the extreme psychological, emotional, economic, social and health toll that this affliction exacts from people who suffer from it.

NSF does not presume to second-guess the evidence that has been submitted about the safety and efficacy of this drug, but it goes on record to say that such considerations should only pertain to affected patients and not other societal considerations. It is safe and effective for people with narcolepsy, like the speaker before me. Sodium oxybate should be made readily available to them. Any concern for illicit use should be addressed strongly through other channels, such as

law enforcement and professional licensing. The fact that narcolepsy is an orphan disease, for which only one medication is currently indicated, would be weighed as a factor in favor of approval of sodium oxybate because it is likely that availability of an approved drug will foster faster diagnosis and more appropriate treatment, and will also -- and we think this is very important -- stabilize patients who usually first experience the dreadful effects of narcolepsy and cataplexy during their developmental years, before the completion of their educations and initiations of a career.

I would like to summarize a few key background points. Narcolepsy and all of its primary characteristics, including cataplexy, are truly life-altering afflictions, a term that best connotes the life-diminishing and debilitating aspects of this disabling disease. Untreated, narcolepsy not only causes vivid nightmares and undermines the safe and secure feeling that most people get when they go to sleep, but it makes daily existence, both objectively and subjectively, frightening and strange, even alienating to the self and others. It makes the well-controlled process that routinely governs the existence for

almost all other humans, the alternating cycle of sleep and alertness, into something entirely different, an uncontrollable process where the maintenance of conscious attention becomes random and cannot be sustained or relied upon. Both the phenomenon of overwhelming sleep attacks and the muscular weakness and collapse that occur with cataplectic attacks undermine the sense of predictability and confidence required to fully develop and function in our contemporary world.

But a true understanding of narcolepsy goes beyond physiology. The cumulative effects of the distinctive daytime and nighttime characteristics of this disease are truly traumatic. They not only disrupt; they undermine and frighten and change the core experience of the individual, exacting a toll that ranges from difficulty coping and functioning to total disability.

I think some key characteristics that should be taken into consideration are that narcolepsy is not well understood or accepted. People who suffer from this suffer alone. They don't have generally the benefit of support groups, even though there is a fine support organization

out there, but the people are just spread out. There isn't enough concentration. Most people with narcolepsy do not have a relative with the disease such that it is even strange to them. People suffer a double blow because it is thought their sleepiness is volitional and a sign of laziness.

Thus, I think it should come as no surprise that people with narcolepsy suffer from a high rate of depression. It has been estimated from 30-70 percent in various studies. The good news is that in one study health quality of life was improved through effective administration and medical treatment, and I think that would pertain as well to sodium oxybate.

In sum, the National Sleep Foundation believes that narcolepsy exacts an unusual and cruel toll. We really call upon this panel to continue to do the professional job that brought you here today and fully consider the personal, psychological, emotional and human aspects of this disease and the great need for an effective medication. Thank you.

DR. KAWAS: Thank you, Mr. Gelula. The next speaker is Ms. Abbey Meyers, who is president of the National Organization for Rare Disorders,

Inc.

MS. MEYERS: The National Organization for Rare Disorders, which is known as NORD, came together initially because voluntary agencies for many rare diseases worked together to pass the Orphan Drug Act. So, we are the orphan drug folks who work to monitor the development of these drugs.

I have several conflicts of interest with this drug because for 20 years I begged practically every company I ever met to pick up this drug and to adopt it. It is a 20-year saga. And, I wrote something for you that you will be able to read about the history of development of the drug.

Also, about a year ago I bought some stock in this company. If I wanted to make money I would have put it in Merck, but the idea with the drugs that they are developing is I feel I have to make my own personal investment in the survival of the company.

For this drug FDA, rightfully, has asked for a risk management program, and there are several really good models to look at, most notably, I would like you to remember when you are discussing the risk management what happened with Clozaril because when Clozaril first got on the

market with the drug for schizophrenia, they had a very stringent distribution program, and they were sued by 30 states, attorneys general, because the laws in those states said that you could not restrict the distribution. In the settlement of that case, the federal court assigned us, NORD, with the task of distributing the drug to the people in this class action settlement.

So, I am very sensitive to what happens. FDA approved Clozaril's distribution program but then the law said that they couldn't do it. So, people really want the freedom to be able to get the drug when they want it, when their doctor prescribes it.

The other program you should look at is thalidomide because it is an extraordinarily important drug, again very orphan. Nobody wanted to go near it because of the liability problem. But they have a wonderful distribution program and I think it should be a good model for the field when there are drugs with specific dangers involved.

I also want to give you several cautions. Don't make the distribution too restrictive. For example, don't allow just certain specialists to

prescribe it because people with narcolepsy have a great deal of travel problems. Many of them don't have driver's licenses in many states. They may hold on to their driver's license but actually if it was ever reported to the state that they had narcolepsy they would lose it. It is just like epilepsy. So, you have to be sensitive to that.

There are many current problems with Ritalin and Dexedrine and the amphetamines that they are using because the government limits the amount of manufacture every year. So, at the end of the year they run out of drug and there are times when they just aren't able to fill their prescriptions and they can't order it by mail order because it is a controlled substance. So, these people have suffered so tremendously because of these distribution problems. With those drugs, pharmacies don't stock a sufficient amount and they will only dispense one month at a time.

Don't require a distribution program that is going to cause legal problems. So, ask yourself that, whether the program that has been designed by Orphan Medical could be loosened up a bit.

The other thing goes back to what you were talking about this morning, labeling. You know,

does this drug help with daytime sleepiness, etc.? I want to caution you that if you label this drug just for cataplexy with no effect on daytime sleepiness, there are a lot of insurance companies that are not going to reimburse for it. So, labeling on a drug is extraordinarily important to patients because of the managed care insurance system. So, try to be as liberal as you can on that, thinking about whether insurance companies are going to say no, except to just people with a particular type of narcolepsy.

Also, recognize that it is a unique disorder that is just as crippling as epilepsy, and that these people are already paying a very heavy price because of the problems they have with their current drugs.

Illegal use has to be handled, which I know that you are going to do, but you must pay attention to the valid use of this drug. Thank you.

DR. KAWAS: Thank you, Ms. Meyers. You are the first one who hasn't used all of your time and that is greatly appreciated. The next one is Robert L. Cloud, from the Narcolepsy Network.

MR. CLOUD: Good afternoon, and I wish to