DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

Wednesday, June 6, 2001

8:15 a.m.

Holiday Inn
Bethesda, Maryland

PARTICIPANTS

Claudia H. Kawas, M.D., Consultant and Acting Chairman
Sandra Titus, Ph.D., Executive Secretary

MEMBERS:

Ella P. Lacey, Ph.D., Consumer Representative,
LaRoy P. Penix, M.D.
Richard D. Penn, M.D.
Gerald Van Belle, Ph.D.

CONSULTANTS:

Gustavo C. Roman, M.D.
Jerry S. Wolinsky M.D.

XYREM CONSULTANTS:

VOTING:

Pippa Simpson, Ph.D.
Carol Falkowski, Ph.D.

NON-VOTING:

Christine A. Sannerud, Ph.D.
Jerry Frankenheim, Ph.D.
Jo-Ellen Dyer, Ph.D.

ON PONE-LINK - NON-VOTING:

Ronald Chervin, M.D.
Christian Guilleminault, M.D.

FDA:

Robert Temple, M.D.
Russell Katz, M.D.
Ranjit Mani, M.D.
John Feeney, M.D.
Deborah B. Leiderman, M.D.

C O N T E N T S

PROCEEDINGS

Call to Order and Introductions

DR. KAWAS: Good morning, everyone, and welcome to the Wednesday, June 6, 2001 meeting of the Peripheral and Central Nervous System Advisory Committee. My name is Claudia Kawas, and I think we can begin with introductions, please, perhaps over by Dr. Temple's side.

DR. TEMPLE: Bob Temple, I am the Office Director.

DR. KATZ: Russ Katz, Division of Neuropharmacological Drug Products, FDA.

DR. FEENEY: John Feeney, neurology team leader, FDA.

DR. MANI: Ranjit Mani, medical reviewer, Neuropharm., FDA.

DR. LEIDERMAN: Deborah Leiderman, Director, Controlled Substance Staff, FDA.

DR. SIMPSON: Pippa Simpson, University of Arkansas Medical Sciences, biostatistician.

DR. FALKOWSKI: Carol Falkowski, drug abuse researcher, Hazelden Foundation.

DR. ROMAN: Gustavo Roman, Professor of Neurology at the University of Texas, San Antonio.

DR. WOLINSKY: Jerry Wolinsky, Professor

of Neurology, University of Texas, Houston.

DR. TITUS: Sandy Titus, FDA, the administrator of the Peripheral and Central Nervous System Committee.

DR. PENN: Richard Penn, neurosurgeon at the University of Chicago.

DR. LACEY: Ella Lacey, professor emerita, Illinois University, Carbondale, Illinois.

DR. VAN BELLE: Gerald Van Belle, Department of Biostatistics, from the University of Washington.

DR. PENIX: LaRoy Penix, Associate Professor of Neurology at Moorehouse School of Medicine.

DR. SANNERUD: Christina Sannerud, Drug and Chemical Evaluation Section, Drug Enforcement Administration.

DR. DYER: I am Jo Dyer, with the University of California, San Francisco and the San Francisco Poison Control System, California.

DR. FRANKENHEIM: Jerry Frankenheim, pharmacologist, National Institute on Drug Abuse.

DR. KAWAS: Today we have met to discuss the consideration of Xyrem, proposed to reduce the incidence of cataplexy and to improve the symptom

of daytime sleepiness for persons with narcolepsy. The main focus of the deliberations will also be on risk management issues.

If we could ask Dr. Titus to begin with the conflict of interest statement?

Conflict of Interest Statement

DR. TITUS: Before I begin the conflict of interest statement, I just want to announce that we have two people on line with us, Dr. Chervin and Dr. Guilleminault. They are both in a room listening to us and will participate with us on the mikes.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The special government employees participating in today's meeting have been screened for interests in Orphan Medical's Xyrem and for interests in the products and sponsors deemed by the agency to be competing. Based on the agency's review of each participant's response to the conflict of interest screening, it has been determined that there is no potential for a

conflict of interest with regard to this meeting.

With respect to FDA's invited guests, there are reported affiliations which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Ronald Chervin would like to disclose for the record that he has a contract with Cephalon to study Provigil, but not for use in narcolepsy. He is the principal investigator, however, no funds from Cephalon, present or past, have contributed to his personal salary and none have been made available for his non-research related use. Further, in previous years Dr. Chervin was a co-investigator with Cephalon in a narcolepsy clinical trial.

Christian Guilleminault has been the administrator of the Sleep Disorder Clinic in Palo Alto, California, where the study of Xyrem was performed by a team of researchers.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon. Thank you.

DR. KAWAS: Thank you very much, Dr. Titus. We will begin with Dr. Russell Katz, of the FDA, who will give us the FDA overview of the issues. I want to point out to the committee members that they have much of the materials that they will be seeing during this meeting in front of them.

FDA Overview

DR. KATZ: Thanks, Claudia. First, I would like to welcome the committee back. You were here just a few months ago so I appreciate your coming back so soon.

We have a number of invited guests who are augmenting the committee today, and many of them are experts in the evaluation of issues related to drug abuse, and I would just like to welcome them, in particular Drs. Simpson, Sannerud and Frankenheim.

We have two other experts who will actually be speakers later this morning. Dr. Dyer

will speak on her experience with GHB use and misuse in cases she has seen, and Dr. Falkowski will talk about the epidemiology of GHB abuse in the United States.

Finally, as Dr. Titus mentioned, we have two acknowledged experts in sleep disorders who are attending the annual sleep meetings in Chicago, but who have agreed to sit in a hotel room for however long this takes and participate by phone. So, Drs. Guilleminault and Chervin, wherever you are, thank you. Thanks for being here.

As you know and as you have heard, today we will ask you to discuss NDA 21-196, which was submitted by Orphan Medical for the use of Xyrem, gamma hydroxybutyrate or better known as GHB, for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy.

GHB is a simple molecule and it is ubiquitous in mammalian tissues, its function though is not really well known. Its relevant regulatory history goes back to about 1990, and prior to that date it was freely available in health food stores. But in 1990 the agency began to receive reports of widespread recreational use in a number of different types of folks, for a

number of different types of reasons, or GHB and began to get numerous reports of serious adverse events associated with its misuse.

It was not entirely clear that all of these events were necessarily related to GHB. It was difficult to interpret some of these reports because there were concomitant medications that were unreported and it wasn't entirely clear whether or how much GHB was in a particular preparation that someone had taken. Those sorts of issues made it difficult to completely interpret the reports, but many of the reports were of events that were known to be consistent with GHB's effect as a potent CNS depressant, including things like respiratory depression, coma and other decreased levels of consciousness. So, it was reasonable to believe that GHB was at least in part responsible for some of these reports.

As a result of these reports, the agency withdrew GHB from health food shelves and made it illegal to use. However, illicit use continued and continues to this day, not only with GHB but with two related drugs which are precursors, GBL and 1,4-butanediol, and there have been similar reports of serious adverse events associated with the use

of those products.

So, against this background of use, the investigation of GHB as a treatment for cataplexy began. Based on the results of a single trial performed by the sponsor and their commitment to perform additional trials, the sponsor was granted a treatment IND in December of 1998. For those of you unfamiliar with a treatment IND, it is basically a mechanism to permit use of an investigational drug outside the context of a controlled trial for a serious disease for which there aren't other available treatments. It is usually granted relatively late in the development of a drug so that by the time you grant it you have some reasonable idea, based on controlled data, that the drug is probably effective and reasonably well tolerated.

Just another relevant piece of history, in 2000 Congress passed a law which placed GHB in Schedule I and also placed it into Schedule III for any approved uses that may be granted.

The NDA that we are discussing today was submitted in September of 2000 by the company, and it contains the results of four controlled trials which the sponsor believes establish substantial

evidence of effectiveness for cataplexy and excessive daytime sleepiness in patients with narcolepsy. It also contains, obviously, safety experience.

I just want to talk about the safety experience for just a little bit. As you know from the briefing documents, much of the safety data in the application was not generated by the company but by an individual investigator under his own individual investigator IND. This is Dr. Scharf, and he is an acknowledged expert in the use of GHB and he has been treating patients under his IND for about 16 years. His data comprise almost 30 percent of the patient safety database in the NDA. If one looks at patient time, his experience constitutes about 70 percent of the total patient exposure.

As part of a routine investigation of the NDA to look at source documents, the agency investigators found that they were unable to locate some critical source documents of Dr. Scharf's IND, and it was difficult to confirm the sponsor's submission of Dr. Scharf's data. However, subsequent to that, Dr. Scharf has made extensive efforts to provide the additional source documents

and agency investigators have reinspected that data. I believe the conclusion of that investigation is that we find that the records, for the most part, do support the sponsor's descriptions of Dr. Scharf's data. And, we believe we can make certain statements about that data at this point.

We were particularly interested in the 80 or so patients that Dr. Scharf treated that did not move on into the company's treatment IND. He treated a total of 143, or thereabouts, patients, 60 of whom went into the sponsor's treatment IND. So, we had a good idea of what was happening to those patients but there were about 80 that didn't and who were basically discontinued from treatment under Dr. Scharf's own IND.

So, except for a handful of patients, we believe we know why those 80 patients discontinued and their status. I believe we can say reasonably comfortably say that nothing catastrophic that we don't know about happened to those patients but, unfortunately, we have relatively little well-documented data regarding other less serious adverse events in that cohort of 80. Other than patient diaries, we have essentially no

documentation about exactly what dose those patients took and for how long.

I have gone into this at some depth because the safety experience in the NDA is relatively small as compared to a typical NDA, and that is by agreement. This is an orphan product. Based on the sponsor's estimated prevalence of cataplexy of about 25,000, it received orphan designation and one wouldn't necessarily expect that a safety database of a typical size, which is somewhere in at least 10000 to 2000 patients in the typical NDA, would be submitted in an orphan application. So, we agreed with the sponsor that about 500 patients treated for appropriate durations, at appropriate doses would be acceptable.

But, given the relatively small database and some of these residual questions about a reasonable proportion of it, that is to say Dr. Scharf's data, that may take on some additional meaning and we would like you to think about that as the day goes on.

In addition to the safety and the effectiveness data which is required in an NDA of course, the sponsor has proposed a detailed risk

management program, and that has three goals: to inform patients and physicians about the risks of GHB; to minimize the risks to those patients; and also to minimize the likelihood that subjects for whom the drug has not been prescribed will be exposed to it. This latter point not only refers to diversion and its use illicitly by folks who shouldn't be taking it, but also to the accidental use of GHB in the home, perhaps by small children, and you will hear how GHB is administered and what form it is prepared in, and we think that is a potential risk. So, we would like you to think about that as the day goes on too.

As far as the risk management program, you will hear about it in great detail from the company but, in brief, it consists of a couple of sort of major components. One is that the product will be made available through a central pharmacy and will be shipped directly to the patient at home. Physicians and patients will also receive detailed materials about the risks and the appropriate use of the drug after the first prescription is filled. Actually, they will receive those materials initially and all subsequent refills of prescriptions will be contingent upon patients and

physicians documenting that they have read these materials, and they understand the risks and how to take the drug appropriately.

All patients and physicians will be entered into a registry, and there will be close surveillance instituted to ensure that untoward events are minimized, for example, to ensure that patients don't go from doctor to doctor trying to get refills of prescriptions that are inappropriate.

So, with these data and against the background of misuse of GHB out in the population at large, we bring you today's application and we will ask you to formally vote on three questions. One is whether or not you think that substantial evidence of effectiveness has been submitted for the indications that the sponsor has proposed, that is to say, cataplexy and excessive daytime sleepiness in patients with narcolepsy. If you find that they haven't, we would be very interested to know whether or not you feel that substantial evidence has been submitted for either of those two indications.

While you listen to the effectiveness data, we would like you to pay particular attention

to the question of dose and for which dose you think evidence of effectiveness has been submitted. If you find there is substantial evidence of effectiveness for a particular indication, we need to ask you whether or not GHB can be considered safe in use given appropriate labeling. Now, we are not going to discuss necessarily the specifics of proposed labeling but, nonetheless, we ask you to think of it in that context.

Again, in assessing the safety of the product, we ask you to concentrate on at least the question of what dose you have found to be effective and whether or not there is sufficient safety experience at that dose for the drug to be approved.

Finally, we want to take a formal vote on the question of whether or not you think it is required or should be required that the drug be approved only with the risk management program of some type, not necessarily the one specifically proposed by the company. Obviously, the company has proposed a risk management program but we need to know whether or not you think it is mandatory that it be approved with such a program in place. If you do, we have a number of questions that we

would like you to discuss -- not necessarily take a formal vote on but discuss with regard to a risk management program and some of the provisions that the sponsor has proposed.

There are some aspects of the program that they have proposed that we would like you to pay particular attention to and discuss. For example, there is some considerable sympathy in the agency for including a provision in the risk management program that would restrict the use of the drug to patients with whatever indication you believe has been supported, that is to say, to restrict as much as possible off-label prescribing. That is one possibility.

There is also some enthusiasm internally for physicians and patients to document that they have reviewed the relevant materials before the first prescription is filled. So, we would like you to think about that as well as we talk about the risk management program.

So, as you can see from the agenda, the company is going to present the safety and effectiveness data, after which Dr. Mani, from the Division, will come up and present briefly some of our views about the data you will have just heard.

Specifically, I believe we have some different views about the evidence submitted for establishing a claim for excessive daytime sleepiness in narcolepsy, and there may be other additional safety issues that we would like to bring up at that time, in particular the question of an event that has been called sleep walking.

I think with that as background, I will turn it back to Dr. Kawas. Thank you.

DR. KAWAS: Thank you, Dr. Katz. Orphan Medical presentation is to follow. Dr. David Reardan, Orphan Medical?

Orphan Medical Presentation

DR. REARDAN: Hi. Good morning. Good morning, ladies and gentlemen, members of the committee and FDA.

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My name is David Reardan, and I represent Orphan Medical as head of regulatory affairs. Orphan Medical is a small, 60-person firm, dedicated to the development of orphan drugs. We have obtained marketing approval for six orphan products from FDA since we were founded, in 1994.

The firm became involved with Xyrem when approached by FDA that same year, and Xyrem was

designated an orphan drug in 1994. Today we will share with you the data that has been collected with respect to the efficacy and safety since our IND was submitted, in 1996.

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Dr. Mignot, director of the Narcolepsy Institute at Stanford University, will present a picture of a narcoleptic patient and the serious medical need such patients have for new therapeutic treatments.

Dr. Houghton is the chief medical officer and chief operating officer at Orphan Medical, and he will present next on the efficacy that has been collected. Dr. Houghton was chair of anesthesia and critical care in Australia.

Dr. Black, director of the Stanford Sleep Clinic and an investigator for several trials, will share with you the EEG pharmacology of Xyrem. Dr. Houghton will then present the safety data and finish up with a benefit/risk assessment.

Following presentations by two FDA invited speakers with respect to GHB abuse, Dr. Balster, director of the Institute for Drug and Alcohol Studies at the Medical College of Virginia, will share with you his views on abuse liability.

Since there is public abuse of GHB and its analogs, the company has developed a risk management program for Xyrem that will be presented by Patti Engel, our vice president of marketing and sales.

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In addition to those presenting today, the following experts are available in the audience to answer questions from the committee or FDA: Dr. Emsellem, Dr. Hagaman and Dr. Ristanovic are all directors of their respective sleep institutes, and have been investigators in our clinical trials. Dr. Okerholm is a consultant in the area of pharmacokinetics and drug metabolism; Dr. Reno in the area of toxicology; and Dr. Richard Trout, who is a professor emeritus in statistics from Rutgers, is here if there are any statistical questions.

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This is the chemical structure of sodium oxybate, more commonly known as gamma hydroxybutyrate, or GHB. Notice that it is a simple 4-carbon hydroxy fatty acid and, as such, quite easy to synthesize. In fact, kits have been illegally promoted on the Internet for its manufacture. If an amino group were to replace

this alcohol functional group at position 4, you would have GABA, gamma aminobutyric acid, another CNS active chemical. Oxybate is a natural compound in the human body.

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Gamma hydroxybutyrate was first discovered in the 1960's by Dr. Labore, in France, and was investigated as an analog for GABA. It was found to have hypnotic properties and was first approved in France, and later a few other countries of Europe, as an adjunct in anesthesia. It was used in labor and delivery for quite a few years. The injectable form is still available today in parts of Europe.

In the 1970's initial work was begun in Canada to test its properties in narcolepsy. Following initial promise for use in patients with narcolepsy two controlled trials were conducted by independent investigators, one in the U.S. and one in The Netherlands. In 1994, due to the promising investigator trials, FDA Office of Orphan Products approached Orphan Medical to consider the compound for development.

Since there was no patent protection and the market was very small, no other firms were

willing to consider the development of GHB for narcolepsy at the time. Orphan Medical agreed to sponsor this medication. Our new drug application was submitted in October of 2000 and was designated by FDA for priority review.

The clinical development has been fairly straightforward and all controlled trials conducted to date have shown sodium oxybate to be effective and safe for the treatment of narcolepsy. This project has been made more difficult because of the abuse situation.

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Let me explain why Xyrem is not going to be a factor in the abuse of GHB and its precursors. Orphan Medical was aware abuse existed at the time the company agreed to sponsor development of Xyrem. At this same time, Internet was burgeoning. Due to its ease of synthesis and ready availability of precursor chemicals, GHB was initially an easy target for promoters of illegal drugs.

But GHB is not the only problem. GBL and 1,4-butanediol are precursor chemicals that can be easily converted to GHB and are, in fact, converted to GHB in the human body. These precursors are widely available as bulk chemicals and are being

illegally used in the United States, and the abuse problem is growing.

Federal legislation, enacted in 2000, helped to control the availability of GHB and GBL but not 1,4-butanediol and other precursor chemicals that can be used for the same purpose. In many states, even with GHB schedules, GBL and 1,4-butanediol are not controlled.

We believe that approval of Xyrem for use by patients with narcolepsy will not add to the general abuse problem of GHB and its numerous precursors.

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The proposed indication for which we are asking FDA for marketing approval is to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.

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Narcolepsy fits the definition of orphan disease in the United States, with less than 200,000 patients. There are estimated to be about 135,000 patients, of which 55 percent are diagnosed, with about 24,000 seeking treatment for cataplexy.

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I would now like to introduce you to Dr. Emmanuel Mignot, from Stanford. Dr. Mignot has been widely published in this area and is considered one of the premiere international experts on narcolepsy. He has not participated in any of our clinical trials.

Medical Need

DR. MIGNOT: It is my privilege to talk to you today about narcolepsy. I have been working on narcolepsy for about 15 years, both at the level of basic research as well as clinical care. I am a medical doctor and I see patients with narcolepsy.

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I am going to try to summarize in a few minutes really a lot of data about narcolepsy and how it impacts people.

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First, I would like to start briefly by reviewing the symptoms of narcolepsy. Narcolepsy is usually associated with 5 different symptoms. The most disabling and the most problematic in patients with narcolepsy is sleepiness. Patients with narcolepsy are sleepy all the time; tired; they have sleep attacks; they cannot stay awake for a long period of time, and it is usually why they

come to see the doctor. They just cannot live a normal life. Especially in work conditions, as you probably know, it is very difficult -- you have to be awake all day long and it is a major problem in narcolepsy.

Now, it is not enough to diagnose narcolepsy. Narcolepsy is not just sleepiness and there are a lot of other medical conditions that are associated with sleepiness. Patients with narcolepsy also have a series of symptoms that correspond to the fact that they go very quickly into rapid eye movement sleep. As probably many of you know, rapid eye movement sleep is a stage of sleep that only occurs 1.5 or 2 hours after you fall asleep where you are actively dreaming but your body is completely paralyzed and you have these rapid eye movements.

Patients with narcolepsy go into REM sleep extremely quickly, sometimes in a few minutes, and that leads to a series of symptoms where patients sometimes are half way through REM sleep, being still awake. Consequently, they may experience odd symptoms that we call the dissociated REM sleep event, abnormal REM sleep event. Those are cataplexy, hypnagogic hallucinations and sleep

paralysis.

An example is cataplexy. When a patient gets emotionally excited, typically when they are happy, they meet a good friend, sometimes when they are angry but most often when they are joking, in a nice environment and happy about something, they may feel suddenly weak; they become paralyzed; sometimes they fall down to the ground, completely paralyzed and they cannot move. In very rare cases they may even go into REM sleep. We believe somehow being emotionally excited stimulates the paralysis of rapid eye movement sleep that every one of us experiences during sleep, except that in patients with narcolepsy it may occur in the middle of the day in response to emotion.

Also, when they fall asleep they sometimes have hallucinations because they go so quickly into REM that sometimes they dream while they are still awake. I remember a patient, for example, who every night would fall asleep and he would see someone coming and strangling him. Or, they may hear people talking; or see people walking in the room. It can be very frightening and it can be a very terrible experience for patients with narcolepsy.

Another symptom of abnormal REM sleep that patients with narcolepsy have as well is called sleep paralysis. When they wake up from a nap or when they fall asleep, sometimes they again go so quickly into REM and disassociated REM sleep events that sometimes they may be paralyzed from REM but still be awake. Basically, they would wake up from sleep and they cannot move, not even their little finger. It can be very scary. It lasts a few minutes and then finally they can move. Some patients with narcolepsy have multiple episodes of sleep paralysis when they nap during the day, and so forth, and that is another very bothersome symptom.

Finally, patients with narcolepsy, contrary to what people way, don't sleep too much; their main problem is that they just cannot stay awake. They fall asleep very quickly in many circumstances, but they are unable to stay asleep for a long period of time. In fact, patients with narcolepsy don't sleep 20 hours a day. What happens is that at night they don't sleep well. Often that is another symptom that is very bothesome. They fall asleep very quickly at night but after one hour they cannot sleep again. They

are just awake and cannot sleep.

Then, all these symptoms are quite severe and, of course, affect the lives of patients. And, since GHB is recommended in cataplexy, which is muscle atonia triggered by emotion, I will just show you a quick video of a patient with cataplexy.

This is a boy, a 9-year old. Narcolepsy usually starts during adolescence and here the clinicians are trying to make him laugh to just try to elicit the symptom, and you see he is falling down and he is completely paralyzed and he is losing his muscle tone. Some of these patients have that many time per day and it can be extremely socially disabling. You can imagine being at a party or being with some friends and having this happen to you. In this kid it was particularly severe.

Most cases of narcolepsy start during adolescence but occasionally it starts as early as 5 years of age. It peaks around 15 years of age. It is often extremely problematic because I am sure you realize when you have this type of thing happening to you and sleepiness at school, especially when you are 15 years old, when you are an adolescent, it really wrecks your life apart,

especially when it is not properly diagnosed.

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There have been a number of studies, and I won't have time to review them, that have shown that the quality of life of patients with narcolepsy is extremely impaired, as much as depression, epilepsy or other reference conditions in almost all the scales that you look at. Clearly, it is a very socially disabling disorder.

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It is also, of course, a disorder that impacts just your daily life. For example, driving -- patients with narcolepsy have a very increased rate of accidents and sometimes many of them refuse to drive just because of falling asleep or having cataplexy while driving.

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We have objective tests for diagnosing narcolepsy. In fact, it is not just a psychological disorder. You can actually use a test like the Multiple Sleep Latency Test, where you ask patients to come to the sleep lab. You check that they sleep normally and the following day you ask them to nap every two hours and you measure how fast they fall asleep. You see,

normally people won't fall asleep or nap in the middle of the day, or they would fall asleep with a 15-minute latency in the dark. A patient with narcolepsy, as soon as you switch off the light, they are sleeping. In a few minute latency, they are asleep. So, we have objective ways to show that these people have a problem.

[Slide]

Also, in this nap you see that they go very quickly into REM sleep. Normal people won't have REM sleep before one hour after falling asleep, but patients with narcolepsy will go straight into REM. You can actually demonstrate -- we call that sleep onset REM period -- that patients with narcolepsy have all this sleep abnormality and REM abnormality using sleep testing.

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Current treatment for narcolepsy is completely symptomatic. We don't treat the cause of the disease; we only treat the symptoms. Typically, the treatment now uses two drugs, two lines of drug. A patient with cataplexy will be treated usually with two drugs. One is a stimulant which would be a classical amphetamine-like

stimulant or this more recent drug that was just approved that is called modafinil, Provigil, which works on sleepiness. It will keep a patient awake but will never normalize him; it only improves him. And, they all have a lot of side effects. You know, the stimulants can even produce psychosis in some rare cases but, of course, they raise blood pressure. They produce psychological changes. They have a lot of other side effects.

We all know now that they all increase dopamine in the brain. We have done a series of studies which have shown that. Even modafinil, the most recent drug -- we know now that it works by increasing dopamine in the brain. And, they don't have anything different from each other so some of them are definitely safer than others.

For the antidepressants, for the treatment of cataplexy -- this works well on sleepiness but it doesn't work on cataplexy or nightmares, or hallucination or sleep paralysis. For this you use antidepressants. Why? Because antidepressants depress REM sleep and they also suppress cataplexy and all the other abnormal dreaming that patients with narcolepsy have. The problem is they also have a lot of side effects. Actually, the new

SSRI, they don't work as well as the old tricyclines. Often you even have to use the old tricycline antidepressants because norepinephrine uptake inhibition seems to be the mode of action of these drugs, more than serotonin. They don't really work that well and, of course, they have a lot of side effects and a lot of different problems.

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Finally, I want to stress again that we need new treatments for narcolepsy just because all the treatments we have now just don't make people normal. They just help them to be better. You can best illustrate that using the MSLT/MWT, which is a slightly different test where, instead of measuring how fast people fall asleep in the dark, you ask people to try to stay away in the dark and you see that normal people can stay awake. They don't fall asleep in 20 minutes, whereas patients with narcolepsy fall asleep very dramatically after a few minutes in the dark.

Even if you treat them with modafinil which is a very good treatment for narcolepsy, which was recently approved, you improve them but they never become normal. Then, it is clear that

what we have is not enough. We just need better, and this would be the same for amphetamines. Even high dose amphetamines don't normalize these patients. That has been shown by multiple studies.

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We have worked for more than 15 years trying to find the cause of narcolepsy, and recently we have isolated the gene for narcolepsy in a canine model where the disease is genetically determined, and we found that it was a receptor for a norpeptide that is called hypocretin. We found that in humans with narcolepsy it is not like dogs with narcolepsy; it is not the receptor but a peptide called hypocretin which is expressed in about 10,000 cells in the brain, here in the hypothalamus, which is missing in patients with narcolepsy.

This is brain tissue of a patient with narcolepsy. You see here is the normal; everything is gone. If you measure in the cerebrospinal fluid, this is a normal level in a normal person, or in patients with MS or other neurological symptoms, and you see in all patients with narcolepsy that this hypocretin molecule is gone. We know now that the cause of narcolepsy is not

dopamine or norepinephrine, which is the current treatment for narcolepsy, which are stimulants and antidepressants acting through these neurotransmitters, and probably replacing this hypocretin would be an ideal treatment for narcolepsy. But this finding was only made one year ago and it is going to take probably 10 years or many years before we actually have a treatment based on this new discovery.

[Slide]

To summarize the medical need, I think I have convinced you that narcolepsy is a serious and disabling condition that needs treatment, and these patients are in desperate need of better treatment. As you will see from the presentation afterwards, GHB is one of the effective treatments which helps a lot of people. So, current treatments like amphetamines and antidepressants don't work well in terms of efficacy. They have a lot of side effects. They all work the same way but they don't act on the cause of the disease and, clearly, we know that GHB, even though it probably doesn't act on hypocretin, acts differently from other drugs. And, it is one more drug that would be available to help a lot of patients with narcolepsy.

Finally, even though there have been numerous, very recent developments that are very exciting in the hypocretin area, unfortunately, you all know it takes a long time until drugs are available and it is going to take probably many years until this available.

This is a very quick summary of what we know about narcolepsy to date. Thank you.

DR. REARDAN: Thank you, Dr. Mignot. Dr. Houghton will now present the data which has been assembled in support of the efficacy of Xyrem. Dr. Houghton is a qualified anesthesiologist, with 18 years of clinical experience in critical care medicine and numerous years experience in pharmaceutical drug development. Bill?

Efficacy

DR. HOUGHTON: Good morning.

[Slide]

I am sorry to start with such a complex diagram but this just outlines the pattern of studies that we will be talking about this morning. On the left-hand side here are the 4 controlled studies on which the assessment of efficacy will be based, but what is unusual about this program is that patients, in an uncommon way, move to

extension protocols. So, as Dr. Katz pointed out, even though the total database may be small, the total duration of exposure of patients is quite promising.

The first study that I will talk about is entitled OMC-GHB-3, and the patients, at the completion of this short-term treatment study did progress to a long-term, open label study and then had the opportunity to move into one of the treatment IND protocols, with some of them still participating in that study.

A second contributor to that protocol was the patients who completed the first 6-month safety treatment IND protocol, and the significance of all of that is that it was from this protocol that the patients are represented in the long-term pivotal blinded efficacy study that supports the long-term efficacy of Xyrem.

[Slide]

The first and pivotal study is a randomized, double-blind, placebo-controlled, parallel group, multi-center trial comparing the effects of three doses, 3 g, 6 g and 9 g of orally administered Xyrem with placebo for the treatment of narcolepsy. As I mentioned, this was a study

conducted in 136 patients in 16 centers.

[Slide]

The primary efficacy parameter was the change in the number of total cataplexy attacks in the last two weeks of the treatment period compared to the two weeks of the baseline period.

Secondary efficacy parameters that were considered included complete and partial cataplexy attacks; daytime sleepiness; inadvertent sleep attacks during the day; hypnagogic hallucinations; sleep paralysis; and a clinical global impression of change.

[Slide]

Patients naive to sodium oxybate therapy were chosen with a bona fide diagnosis of narcolepsy for at least 6 months. They were required to have a record of a polysomnograph or Multiple Sleep Latency Test within the last 5 years to exclude other causes of daytime sleepiness, and particularly sleep apnea.

They were required to have a history of daytime sleepiness and cataplexy for at least 6 months, and recurrent daytime naps that occurred almost daily in the preceding 3 months.

[Slide]

The overall study design was divided into 5 stages. Firstly, there was a screening period in which the patients were required to qualify for entry criteria and then withdrawn from their existing anti-cataplectic medications over a 4-week period to avoid rebound phenomena which were considered a safety consideration. At the end of this withdrawal period they entered a washout period, which was determined by at least 5 times the half-life of their preceding drug to remove any effects of those drugs. However, if patients weren't on any cataplectic medications, they were still required to remain 5 days in that washout period to familiarize themselves with the use of diaries.

They then proceeded to a baseline period of 2 to 3 weeks, using daily diary recording to establish the severity of their disease and to confirm that they had reached a stable stage in their disease. They then entered a 4-week blinded, randomized treatment period, with a visit at 2 weeks, a telephone call the day after commencing treatment, and then safety telephone calls 3 times a week during the treatment period, at the end of which they were abruptly withdrawn from drug and

followed up 3 to 5 days later to assess any rebound phenomena and any adverse experiences that may have ensued.

[Slide]

As is shown here, the patient groups were very evenly balanced at baseline. They represented a fairly severe group of narcoleptics, with an average incidence of cataplexy of around 34 per week at baseline.

There was a dose-response relationship across the doses based on median change in the total number of cataplexy attacks that, when compared to placebo, approached significance at the 9 g dose, with a p value of 0.0529, and achieved highly significant change at the 9 g dose.

[Slide]

This dose relationship is clearly shown in the plot of median change from baseline in the number of cataplexy attacks per week, and the spread of the data is demonstrated as the quartile lines around these median values.

[Slide]

A more clinically relevant presentation of the data is the percentage change in the number of cataplexy attacks from baseline. This was

calculated as the distribution of percentage change values for each individual patient and is again presented as the medians. This representation clearly shows that the major change in cataplexy occurs in the first 2 weeks, but with ongoing change in the subsequent 2 weeks, as represented in 2 of the dose groups.

[Slide]

Secondary efficacy variables included assessment of excessive daytime sleepiness using the validated Epworth Sleepiness Scale which rates the patient's feeling of daytime somnolence by scoring on a scale of 0-3 the probability of falling asleep in the circumstances of 8 common life scenarios. This results in a potential maximum score of 24.

[Slide]

This slide demonstrates a clear dose-related reduction in the Epworth Sleepiness Scale, reaching a significant level of 0.0001 in the 9 g group compared to placebo. This change was incremental beyond the effects of stable dosing of stimulants because stimulant medications were maintained constant throughout the study. In all Xyrem-treated groups some patients improved beyond

the defined narcolepsy range, with some patients in the 6 g and 9 g groups actually improving into the normal range as rated by the Epworth Sleepiness Scale.

The second component of daytime sleepiness, the number of inadvertent naps during the day, was also significantly reduced compared to placebo in the 6 g group and 9 g dosing.

[Slide]

The severity of the disease at baseline was rated by the principal investigator according to the following validated scale. Then, at the end of the treatment period a blinded global impression of change according to the rating shown here was made, rating from very much improved through no change to very much worse.

[Slide]

Assignment of these modal values indicated a primary distribution of the placebo patients mainly to no change or minimally improved, but there is an obvious predominance of assignment in the 9 g dose to very much improved and much improved.

[Slide]

Because of the complexity of presenting

these assigned categories, a post hoc simplification was applied to group the patients that showed clear clinical improvement into a responder group, and all others were called non-responders. This again displays the dose-response trend in the categorical data, with a clear statistical difference between the 9 g group and the placebo group.

[Slide]

Other secondary measures that achieved significant change included the number of awakenings at night, subjective sleep quality, morning alertness, the ability to concentrate. Hypnagogic hallucinations and sleep paralysis, which had a much lower incidence at baseline, showed a non-significant trend towards improvement.

[Slide]

The next study that I would like to present is the study that was suggested by the FDA to provide evidence of long-term efficacy of Xyrem based on the return of cataplexy following the cessation of long-term treatment with the active drug.

[Slide]

Patients entered this blinded, randomized

study from the long-term open-label study I showed you initially having completed the GHB-2 protocol and proceeded into the GHB-3 protocol for periods up to 2 years, or from the initial treatment IND protocol. This provided assessment of potential adverse consequences of the abrupt withdrawal of long-term therapeutic doses of Xyrem as well.

Patients having taken the drug for 6 months to 3.5 years were screened, and after blinded randomization entered a single blind baseline period in which daily diaries were used to record the severity of their cataplexy. They then entered a double-blind phase of 2 weeks wherein they were randomized in a 50 percent ratio to either continued, unchanged dose of Xyrem in a blinded fashion or to placebo. Randomization was performed in a centralized manner to ensure equal representation of dosing in the comparative groups.

[Slide]

The primary efficacy variable was the change in the number of cataplexy attacks in the double-blind period compared to baseline. There was a median change of zero in the Xyrem group but, as seen, there was a marked increase in the incidence of cataplexy in those randomized to

placebo. This was highly significant.

[Slide]

When the median change from baseline by week was calculated, you can see that there was a step-wise increase in cataplexy which supported the long-term efficacy of the drug in a statistically significant manner, but they represent a gradual return of cataplexy rather than an acute rebound phenomenon.

[Slide]

I will now present very briefly some supportive data from 2 early controlled, crossover design studies that have been published, and for which Orphan Medical purchased the databases and included in the NDA submission.

[Slide]

The first was a study conducted by Dr. Lawrence Scrima, then of the University of Arkansas, in 20 patients, 10 males and 10 females, using a dose of 50 mg/kg, much lower than some of those in the previous studies and equivalent to about 3.5 g per day in a 70 kg man.

Following the withdrawal of anticataplectic medications, he recorded a baseline period during which the patients were required to

have a minimum of 10 cataplexy attacks, then were randomized into an initial treatment period of 29 days, followed by a washout period of 6 days, and then crossed over to the alternate treatment, again followed by a washout of 6 days. Stimulants were continued throughout this study and all patients were actually transferred to methylphenidate as their stimulant.

[Slide]

The primary efficacy measures are identified, with the average number of cataplexy attacks compared to baseline and objective sleepiness index as determined by the Multiple Sleep Latency Test. This was to represent a measure of daytime sleepiness.

Because of logistic issues in the study conduct and methodologic issues in design and definition, this is presented as supporting data only to represent cataplexy response at a lower dose. As can be seen, this patient group again represented a reasonably severe narcoleptic population. They had a baseline measure of 20 cataplexy attacks per week. There was an initial fairly significant placebo response, as was shown in the previous studies, but by week 3 and week 4

statistically significant differentiation between placebo and active treatment was shown, and there was a statistically significant overall response in the study. There was no significant change in the sleepiness index as the measure of daytime sleepiness, however, in this study.

[Slide]

The second study that I will present very briefly was conducted by Dr. Lammers, in The Netherlands. It is, again, a randomized, blinded, crossover design study in 24 narcoleptics. The other significant difference in this study was that concomitant medications for both cataplexy and excessive daytime sleepiness were continued throughout the study.

Following a 1-week baseline to establish disease severity, the patients were randomized to a 4-week treatment period at a dose of 60 mg/kg in divided nightly doses, followed by a washout period of about 3 weeks, and then a baseline period of 1 week again preceding a second treatment period of 4 weeks.

[Slide]

As is obvious here, the severity of cataplexy during the baseline period was much lower

in this study, potentially the consequence of continued anticataplectic medication in some patients. But, again, there is a significant response. According to the statistical plan which was very scant that was represented in the published study, and agreed to by the FDA, there was an incorrect or unsatisfactory statistical management of this study. The change in cataplexy was not statistically significant. When the results of this study were submitted by Orphan, they were reanalyzed with an ANCOVA analysis as had been applied in the GHB-2 study, and this change was significant according to the ANCOVA analysis.

[Slide]

Other measures that showed significant improvement included hypnagogic hallucinations and daytime sleep attacks again.

[Slide]

Although not eligible for determination of efficacy since it is an open-label study, I would like to briefly mention three aspects of the follow-on study to the pivotal GHB-2 study. And, 117 patients chose to participate entering the study at the 6 g per day dose and then slowly titrating to clinical efficacy between the doses of

3 g and 9 g. This study, therefore, represents the proposed clinical use of the drug and, although primarily a safety study, represents some important dynamic information.

[Slide]

This slide shows the response in cataplexy over the 12-month period. What is surprising is that the maximum nadir occurred at about 8 weeks, and then the sustained efficacy was maintained across the 12 months in all dose groups.

[Slide]

A similar pattern was seen in the Epworth Sleepiness Scale, which shows the same time frame with maximum response at about 8 weeks, and then maintained efficacy over the course of 12 months in this open-label study. What is also interesting to note is that most of the patients in most dose groups were maintained beyond the defined narcolepsy range.

[Slide]

When the distribution of doses to which the patients were titrated is shown, it is seen that 6 g per day is the most common dose, followed by the 9 g dose group.

[Slide]

This represents the pattern of dosing seen in other open-label studies where doses were titrated to clinical response. What is important to note is that there is not a change in dosing between the 6-month and the 12-month dosing groups, suggesting no tolerance development to maintain the dynamic effects shown.

[Slide]

This slide represents the cohort of patients that entered the SXB-21 protocol via the GHB-2 and then GHB-3 protocol. Represented here is the incidence of cataplexy for each individual patient at the baseline in GHB-2. They were then maintained in the study I have just shown you over the course of up to 2 years, and this is the incidence of cataplexy of each of the individual patients in the single-blinded baseline in the SXB-21 protocol. When the paradigm of random assignment to placebo is shown, then there is certainly a demonstration of efficacy between those who were randomized to the placebo group in SXB-21 versus those that maintained their Xyrem treatment, which certainly helps to support the efficacy statement in the GHB-3 protocol.

[Slide]

Finally and to summarize, we have presented data to show efficacy of sodium oxybate to reduce cataplexy in 4-week treatment periods in a dose related manner that is highly statistically significant at the 9 g dose, and approaching statistical significance at the 6 g dose.

We have presented supportive data demonstrating statistically significant efficacy of the lower doses, and demonstrated statistically significant efficacy in terms of daytime sleepiness, using the Epworth Sleepiness Scale, again at 9 g. In a scale used in the Lammers study at 60 mg/kg daytime sleep attacks were statistically significantly reduced in all 3 studies. We supported the long-term efficacy of Xyrem with return of cataplexy when blindedly assigned to placebo in the SXB-21 protocol.

[Slide]

I would now like to very briefly summarize the pharmacokinetics studies that were conducted by Orphan Medical.

[Slide]

In total, we conducted 8 clinical pharmacokinetic studies, including 2 studies in narcoleptic patients and 6 in healthy human

volunteers. This slide lists the 8 pharmacokinetic studies by their primary objective.

The studies included a single dose pilot study in 6 narcoleptics, and a second study in narcoleptic patients comparing acute and chronic dosing over an 8-week period. Normal volunteer studies were conducted to examine the kinetics of Xyrem with respect to gender differences, dose proportionality and the effects of food. Also, 3 drug interaction studies were performed with Zolpiden, protriptyline and modafinil as representatives of the 3 classes of drugs used commonly to treat the symptoms of narcolepsy. Lastly, an in vitro study, using human hepatic microzymes, was conducted to assess the effects of oxybate.

[Slide]

I will only present the studies that have a significant message, and in very brief summary form. This slide displays the results of the dose proportionality study that compared nightly dose of 4.5 and 9 g given in 2 equally divided doses at bedtime and 4 hours later. A randomized, 2-day crossover design was utilized, and doubling the dose from 4.5 to 9 g resulted in a nearly 4-fold

increase in the area under the time concentration curve. The peak plasma concentration and the time to peak concentration changed significantly with doubling the dose, the latter suggesting capacity-limited absorption. C_{max} was higher after the second dose than with the first nightly dose, as has been seen in other studies with divided dosing.

These findings indicate non-linear kinetics and capacity-limited elimination and absorption, as reported in previously published studies.

[Slide]

The results of the effect of food study are displayed graphically on this slide. In this randomized, crossover study 34 healthy subjects were dosed with 4.5 g of Xyrem on 2 occasions 1 week apart, either after an overnight 10.5 hour fast or immediately following a high fat standardized breakfast. After the high fat meal the peak plasma concentration decreased by almost 60 percent. The median time to achieve peak levels increased from 45 minutes to around 2 hours, and the AUC decreased by 37 percent. All of these differences were statistically significant. The

apparent half-life was not significantly altered. Thus, the presence of food significantly reduces systemic exposure to GHB, a finding not previously reported.

In the 3 volunteer kinetic studies the urinary excretion of Xyrem was measured, and renal excretion was shown to be a minor pathway of elimination, accounting for less than 5 percent of the administered drug.

[Slide]

As an example of the drug interaction studies, on this slide we present the modafinil results. The upper graph indicates that co-administration of 200 mg of modafinil had no impact on the kinetics of Xyrem. The lower graph demonstrates that 4.5 g of Xyrem had no clinically significant effect on the kinetics of a standard dose of modafinil.

Likewise, in the Zolpiden protriptyline interaction studies, no significant kinetic interactions were found. In the separate in vitro study using human hepatic microzymes, sodium oxybate was found to have no effect on 6 cytochrome p450 enzymes either to inhibit or induce their activity.

[Slide]

So in summary, Xyrem oral solution is rapidlyh absorbed and eliminated with a half-life of about one hour. The drug displays non-linear, dose-dependent kinetics, indicative of capacity-limited absorption and elimination. Xyrem kinetics are similar in men and women and do not change with chronic administration at therapeutic doses.

[Slide]

Chronic dosing did not change the kinetics of Xyrem in a patient population, and a high fat meal appreciably delayed absorption and reduced total systemic exposure to the drug. Three separate in vivo drug interaction studies, as well as the in vitro p450 enzyme study, would suggest the probability of significant drug-drug interaction with Xyrem is minimal. Thank you very much.

DR. REARDAN: Thank you. I would now like to introduce Dr. Jed Black, from Stanford University Sleep Center, and he will present on the polysomnographic effects of Xyrem and GHB.

Polysomnographic Effects of Xyrem

DR. BLACK: Good morning, ladies and

gentlemen. I would like to summarize the body of data that has been collected over the past 25 years which characterizes the effects of gamma hydroxybutyrate or sodium oxybate on sleep parameters. I will then speculate briefly on a possible mechanism whereby these effects on sleep result in a robust improvement in daytime narcolepsy symptoms seen with this agent.

This has been a particular focus of my research in sleep over the past years. That is, how does what happens in the brain at night affect various aspects on daytime function and alertness?

It is unexpected that a medication that objectively markedly improves sleep quality also improves measures of daytime alertness as this finding has never been observed with traditional hypnotics or sleep aids. To pursue an understanding of this possible interaction, 6 investigations have been conducted in humans. These studies explored the effect of sodium oxybate on a variety of nocturnal sleep parameters, using electroencephalography during sleep and a laboratory test known as polysomnography.

The first 3 studies found an increase in slow wave sleep. Slow wave sleep, also known as

stages 3 and 4 sleep, is the deepest portion of sleep and correlates positively with functions of daytime concentration, attention and alertness in normal subjects. These studies also reveal a reduction in nocturnal awakenings with GHB.

The more recent studies of Scrima, Lammers and Orphan Medical explored both measures of nocturnal sleep as measured by polysomnography, or PSG, and measures of daytime sleepiness with the Multiple Sleep Latency Test, or daytime alertness with the Maintenance of Wakefulness Test.

[Slide]

These 2 studies, the design of which has been reviewed by Dr. Houghton, again found significant reductions in slow wave sleep, that is to say stage 3-4 sleep or slow wave sleep, and reductions in nocturnal awakenings. Additionally, the Scrima group reported a reduction in stage 1 sleep, a very light stage of sleep, and the Lammers group noted significant reduction in the percentage of time patients spent awake during nocturnal polysomnography.

[Slide]

The most recent study, a multi-center trial performed at 4 sites with an enrollment of 25

patients, was designed to further explore the effects of sodium oxybate on nocturnal sleep parameters and daytime measures of sleepiness and alertness. In this open-label study patients were kept at a stable stimulant dose throughout the protocol. Cataplexy medications were tapered, followed by a 2-week washout and baseline period. Sodium oxybate was initiated at 4.5 g in a divided nightly dose for 4 weeks, then increased to 6, then 7.5, then 9 g for 2 weeks each. Nocturnal polysomnography and the Maintenance of Wakefulness Test, or MWT, were obtained at the time points noted here.

[Slide]

This study revealed the expected increase in slow wave, or stages 3-4 sleep, and increase in delta power. Delta power is the measure of the depth of sleep. It incorporates the combination of the amplitude of the slow frequency waves and the prevalence of those waves through the night to produce a single number called delta power. Delta power is another measure found in a variety of animal and human studies to correlate positively with sleep quality. The calculation of this value requires sophisticated processing which was

unavailable for the prior studies. The increments in slow wave sleep and delta power were found to be dose related. Dose-related improvements in daytime alertness and subjective sleepiness were also observed.

[Slide]

The dose-response increase in the number of minutes of slow wave sleep is illustrated in this slide, with an increase from 6 g up to the 9 g dose. The total duration of slow wave sleep increased to over 5-fold that of baseline at the 9 g dose.

It is important to note that while these results are predicted to be dose related, time on medication cannot be factored out as a potential contributor to these increments.

[Slide]

Delta power, which characterizes slow wave activity throughout the entire sleep period, not just during stages 3 and 4, was also found to increase in a dose response fashion with a 50 percent increase noted at the 9 g dose over baseline.

[Slide]

The Maintenance of Wakefulness Test, or

MWT, is a daytime evaluation which places the patient in a dimly lit room in a semi-recumbent position, with nothing to do and with the instruction to remain awake. The duration of sustained wakefulness was measured in this study over 40-minute intervals across 4 periods, spaced 2 hours apart during the day. Substantial dose-related increases in the ability to remain awake were observed at both the 4.5 g and 9 g doses.

[Slide]

As previously noted, the MWT was not performed at the 6 g nor 7.5 g doses in this protocol. Similar marked reductions were found in the Epworth Sleepiness Scale scores. In this measure the individual rates their own potential to fall asleep in a variety of more sedentary daytime activities.

[Slide]

A post hoc analysis of the possible correlations between sodium oxybate-related changes in nocturnal parameters with changes in daytime measures revealed the strongest correlation occurring with delta power and Epworth Sleepiness Scale scores. This was a negative correlation,

such that the greater the delta power, the lower the daytime sleepiness. In addition, trends toward significant correlations between delta sleep and MWT scores, and between slow wave sleep and Epworth and MWT scores were observed.

[Slide]

In conclusion, studies of sodium oxybate's effects on sleep demonstrate increases in measures of restorative sleep, including dose-related increments in slow wave and delta sleep, coupled with and correlated with improvements in measures of daytime alertness and sleepiness.

It is postulated that sodium oxybate works directly to enhance brain neurochemical activity critical to the restorative mechanisms of slow wave sleep and of slow wave activity during the total sleep period. Such enhanced activity may be the cause of substantial improvement in both subjective and objective measures of sleepiness and alertness observed with sodium oxybate in narcolepsy.

DR. REARDAN: Thank you, Dr. Black. Dr. Houghton will now present the safety summary overview of Xyrem and finish up with a benefit/risk assessment.

Safety Overview and Summary of

DR. HOUGHTON: Thank you.

[Slide]

I am sorry to horrify you with this complex diagram again but it is just to outline the 15 studies that will be referred to today as the updated safety database. The Lammers study was excluded because adverse events were not recorded in the classical way and, as Dr. Katz explained, the Scharf study was separated and will be explained again later.

[Slide]

The safety profile was reported based on exposure of 479 narcoleptic patients and 125 healthy volunteers from the pharmacokinetic studies. This represents an exposure of greater than 6 months in 360 patients in total, and greater than 12 months in 296 patients, which represents a total patient-year exposure of 1328 years with the Scharf database included.

[Slide]

When exposures were restricted to the studies other than the Scharf database, 399 narcoleptics and 125 subjects represent exposure in 524 persons. This represents exposure of greater

than 6 months in 296 patients and greater than 12 months in 223 patients, for a total exposure of 330 patient-years.

[Slide]

In the open-label studies patients were titrated between the doses of 3-9 g in divided dose at night. This slide represents the distribution of patients across this defined dose range and, again, identifies the 6 g dose as the most commonly used, followed again by the 9 g dose. In fact, approximately 80 percent of patients were titrated within the 6-9 g range.

[Slide]

In the updated integrated safety database, composed of 402 patients, 399 of whom were treated with active drug and 3 patients received placebo only, it can be seen that 65 percent of patients completed therapy or were ongoing in the treatment IND study. Thirty-five percent have discontinued treatment for the reasons noted here, with 13 percent discontinuing due to adverse events; 2 percent discontinuing because of lack of efficacy; and there were 2 deaths that occurred in the treatment IND studies, both due to suicide.

[Slide]

Across all of these studies, 82 percent of treated patients reported any adverse event, as did 70 percent of patients exposed to placebo. It is important to note that the placebo exposure represents 4 weeks as compared to active drug treatment over a much longer period of up to 4 years. Hence, severe adverse event discontinuations and serious adverse events are significantly greater in the active treatment groups.

[Slide]

When considered in terms of dose at onset, there seemed to be a slight preponderance of incidence in the 9 g group.

[Slide]

This slide represents the most frequent adverse events reported across the integrated database. There was a consistent pattern of events across the study. Nausea, dizziness, sleep walking, are represented here as a partial representation of the term sleep disorder, enuresis and confusion were most frequently considered dose related, while others represent intercurrent illness.

[Slide]

This profile is reinforced by consideration of the controlled trials in which there is represented a balanced exposure to placebo and active medication. Again, dizziness, nausea, pain, sleep disorder, confusion, infection, vomiting and urinary incontinence separate. A dose relationship was shown introduction eh GHB-2 trial for confusion, nausea, dizziness and urinary incontinence.

[Slide]

In the SXB-21 trial the most common adverse events that were reported are shown here. The incidence was very low in this study of patients on long-term treatment, but what is relevant is the data that looks at the possible presentation of a withdrawal syndrome with the abrupt cessation of long-term therapy.

[Slide]

This is in marked contrast to a severe syndrome that is being described in the abuser population who have significantly escalated both dose and frequency of dosing. When we looked at symptoms that could relate to a withdrawal phenomenon, we saw only 2 patients with anxiety in a circumstance of escalating cataplexy, 1 patient

with dizziness, 1 insomnia, 1 sleep disorder that actually in verbatim terms, was increased awakenings, and 1 patient with somnolence as their narcolepsy worsened.

[Slide]

I would like to now address the Scharf database. This was conducted under an investigator IND commencing about 10 years before Orphan's involvement, without any of the rigors of external monitoring, and really represents over 16 years experience in the use of the drug rather than drug development clinical research with regulatory disciplines.

Patients were scattered all over the country and, hence, the data is based primarily on diary recordings without medical review and interpretation, leading to a significant discontinuation rate for lack of compliance. Dose accountability and titration were less clearly defined and less controlled. Patients had less defined entry criteria and represent a broader profile of associated pathologies. On this basis, the study data has been reported separately to the integrated database, as Dr. Katz had suggested.

[Slide]

We will address the Scharf open-label experience in terms of dosing exposure, patient disposition, adverse event incidence over 16 years, and then to try and establish some parity with the integrated database. We have considered the adverse event experience reporting in just the first 6 months of the study.

[Slide]

Patient disposition in the Scharf database is represented in this slide. At the time of database closure 63 patients transferred into the SXB 7 protocol. The FDA expressed concern regarding the accountability of the 80 patients that did not continue. We provided a narrative account for each individual patient, with updated status where possible, in the form of a major amendment. In addition, FDA requested further clarification of adverse events initially deemed uaevaluable, which we have also provided.

Of these 80 patients, 8 continued in the Scharf trial under his treatment IND. The 71 patients who withdrew had received oxybate for from 5 days to 10 years, and the reasons for early withdrawal of the 71 patients were primarily classified into non-compliance, adverse event and

cost.

[Slide]

The adverse event profile reflects the length of the study. The relatively large numbers of viral infection, flu syndrome, pharyngitis, etc. shouldn't be worrisome considering the 16 years duration of the study. However, of particular interest is the unusual incidence of sleepwalking and urinary incontinence and these will be discussed in some detail later.

[Slide]

The most frequent adverse events in the first 6 months of the Scharf trial are shown here. When compared to the integrated safety database, few adverse events separate in incidence. Most notable are somnolence, infection, viral infection and malaise. There were few new adverse events reported after the first 6 months.

The FDA requested further information regarding the following adverse events of particular interest. They were represented by incontinence and convulsions, confusion, neuropsychiatric events and sleepwalking.

[Slide]

I will address incontinence first. In

their review of the GHB-2 trial, submitted in October, 1998, the FDA requested an analysis of adverse event terms for incontinence in association with central nervous system adverse events suggestive of seizure.

[Slide]

We responded by initiating the following: a questionnaire to all investigators to review the history of abnormal nocturnal observations that could be suggestive of seizures; a detailed urologic history preceding oxybate therapy and any new neurologic symptoms.

Examination of the databases for potential correlation between central nervous adverse events that could be related to seizures and incontinence, either urinary or fecal, was undertaken. Review of both preclinical and clinical data in the literature was performed and an overnight EEG recording after a 9 g dose was conducted in 6 patients who had reported incontinence during their oxybate therapy. An expert opinion was provided by Dr. Nathan Chrone, a neurologist of Johns Hopkins University.

[Slide]

The issue as represented is shown here.

Urinary incontinence was presented by 8 patients reporting 15 events in the GHB-2 study, by 13 patients reporting 51 events over the 2-year period of GHB-3, and in the Scharf study by 33 patients reporting 140 events.

When central nervous system events were analyzed for contemporaneous reporting, 2 patients in each of the GHB-2 and -3 trials recorded such events corresponding to episodes of incontinence, as did 7 patients in the Scharf database. Relatively few incontinence events were temporally associated with the CNS adverse events suggestive of seizure. No potential seizure genesis was reported by bed partners in response to specific questions, and many of the partners reported relevant urinary symptoms such as frequent nocturia preceding the Xyrem treatment.

[Slide]

Single events of fecal incontinence occurred in 4 patients in 4 different trials. Association between these incontinence events and central nervous system adverse experiences were present only in 1 patient in the Scharf trial and 1 in the pharmacokinetic SXB-11 trial. In this patient the event of fecal incontinence was

definitely associated with a seizure in a patient with a known pre-study history of seizures. The subject in the SXB-11 effect of food study was a patient who, while significantly obtunded and with respiratory obstructive symptoms, had a brief episode of fecal incontinence.

[Slide]

In conclusion, there was limited support for a relationship between incontinence and seizures from the clinical trials, the prospective EEGs or from the literature.

[Slide]

The vast majority of events that could have been coded as convulsions were actually recorded under the COSTART dictionary as cataplexy events. One patient in the integrated trial database did not represent this classification and he has been investigated by a neurologist for seizure genesis. His fugue state and automatic behavior episodes have been deemed part of his narcolepsy syndrome.

In the Scharf database two patients with definite seizures recorded history of preexisting disease, and two other patients recorded seizure events without definitive diagnosis but with

complicated polypharmacy.

[Slide]

To now address confusion, in the integrated safety database 30 patients or 70 percent reported 48 events recorded as confusion, leading to discontinuation from study in 3 patients. A possible dose relationship was suggested by a review of the entire database. In the Scharf database, again 7 percent of patients reported 15 such events, with no discontinuations and no dose relationship pattern observed.

[Slide]

The coding of confusion embodied a wide range of verbatim terms, as shown here. These do not represent confusion based on a standard medical status examination. They do not differentiate between nighttime events from those of awakening or arousal parasomnias. These events led to no dosage adjustment in 37 instances, but dose was reduced in 4 events, led to temporary discontinuation following 4 events, and 3 patients discontinued permanently because of a side effect of confusion.

[Slide]

When the GHB-2 controlled trial was considered with respect to confusion, the highest

incidence in the databases is represented in this 4-week study by 10 patients. The highest incidence was seen in the 9 g dose, and 6 of the 10 developed during the first week of treatment. Seven of these 10 events were in patients over the age of 50. The difference in this study, of course, was the assigned doses rather than dose titration. It is important to note that 1 event was reported in a placebo patient.

[Slide]

In conclusion, the term represents a symptom report rather than confusion defined in a medical sense by formal mental status examination, and all resolved usually without interruption of therapy or dose modification. Confusion and other associated symptoms are not unexpected with sedating medications. The blinded, controlled trial results suggest that a higher incidence may result without dose titration.

[Slide]

Neuropsychiatric events will now be reviewed. The adverse event database was searched for terms that could represent neuropsychiatric symptoms, and this led to the classification shown in this slide. Fifty-two patients reported 57 such

events in the integrated safety database, of whom 12 discontinued as a result of these events. In the Scharf database 41 patients reported 84 such events, leading to 2 patient discontinuations.

[Slide]

Of these 57 events, 1 occurred while a patient was on placebo. This slide lists the terms examined and some, such as stupor and coma, failed to represent neuropsychiatric events. Many represented symptoms of narcolepsy such as hypnagogic hallucinations COSTART-coded to the term hallucinations. The most frequent was clinical depression, and this represents a symptom rather than a diagnosis of major depressive disorder. Depressive symptoms are frequent accompaniments in narcolepsy, and this is well recorded in the literature. Suicide was attempted in 4 patients with major preexisting psychiatric history, and resulted in death in 2 of these patients. The other representations of psychotic disorders and the patient with manic depressive disorder also occurred in patients with preexisting major psychiatric disease. As is shown, a similar profile of reported symptoms is found in the Scharf database.

[Slide]

In conclusion, most patients with major events had a preexisting psychiatric disorder. Many events do not qualify as neuropsychiatric disorders, as was represented by the terms pointed out. Assignment of causality is very difficult because narcolepsy is associated with depression and even mechanistically there has been an association between psychosis and the central processes in narcolepsy. As Dr. Mignot mentioned, stimulant medications are associated with central nervous system side effects that are represented by neuropsychiatric symptoms. And, it is true to say that in many patients, particularly in the Scharf database, pre-study screenings were deficient.

[Slide]

To lastly address sleepwalking, in the integrated safety database 7 percent of patients reported such events, whereas in the Scharf database 32 percent of patients reported events that were listed as sleepwalking. In the Scharf trial, however, these reports were primarily data listings in patient diaries in response to a specific leading question, listed as a line item in the diary.

[Slide]

The listing of this term did not receive the benefit of medical consideration of a differential diagnosis of somnambulism, and since most patients were not seen by the investigator no clarification was provided. Post hoc consideration was rendered impossible given the lack of information regarding sleep stage, time of night, relationship to drug dosing, and could be representative of any of the differential diagnoses listed on this slide.

[Slide]

In the controlled trials only 3 sleepwalking events were reported, 2 of which occurred on active treatment and 1 occurred in a patient during placebo treatment.

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Hence, in conclusion, the incidence in the integrated safety database of 7 percent is not particularly dissimilar to the range reported in the literature for normal patients. This was reported by Dr. Mahowald, of Minneapolis, as between 4-10 percent in a publication in 1998, and between 1-7 percent by Dr. Roger Broughton of Canada.

Diary recording without medical classification represents a potential increased reporting in the Scharf trial. The slight increase in incidence over the general population may certainly be representative of Xyrem effects with increase in slow wave sleep, but REM behavior disorder, common in narcolepsy, mayou be a separate consideration.

[Slide]

To summarize the safety profile of this drug, we based our assessment to date on 604 patients, which represents 524 patients excluding the Scharf database. Dosing was between 3-9 g per day in divided nightly dosing. The common adverse events were certainly headache, unspecified pain, nausea, dizziness, and less common but important adverse events were vomiting, confusion, restlessness, agitation, sleepwalking and enuresis.

[Slide]

All events have been reversible. There were no significant changes in lab values or vital signs identified across the studies. There was no evidence of organ toxicity outside the pharmacologic effects in the central nervous system. There was no diversion or consumption of

clinical trial supplies by any family members during the trials, and there was certainly no evidence of Xyrem diversion in our database.

[Slide]

I would like to conclude with the statement that Xyrem was generally well tolerated.

[Slide]

To commence a risk/benefit assessment, I would like to remind you of the indication proposed by Orphan Medical for the use of Xyrem. That is, to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.

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As has been pointed out, narcolepsy is an uncommon disease, with an incidence of around 0.05 percent and, as such, has been qualified for orphan designation. There are no therapies approved for the treatment of cataplexy. Because of this, the FDA were very kind to apply a priority review to our submission and we are very appreciative of that recognition. Current off-label therapies, so well described by Dr. Mignot, are unsatisfactory. Excessive daytime sleepiness has approved therapies but these do not address cataplexy. There is

clearly a medical need existing beyond the therapies available.

[Slide]

The benefits of Xyrem in the trials presented were based on patient diary recordings, investigator ratings of overall clinical improvement in overall disease severity, and objective measures of changes in sleep architecture and daytime response.

[Slide]

Clinical benefit in the short-term reduction in cataplexy was shown by the dose-related reduction in cataplexy in the GHB-2 and Scrima studies and in the long-term efficacy in the SXB-21. Subjective changes in the Epworth Sleepiness Scale have been well demonstrated, and reduction in daytime sleep attacks have accompanied this change. Early objective Maintenance of Wakefulness Test data supported these changes in daytime sleepiness. The global impression of the investigators for overall changes in disease severity also showed a significant dose relationship.

[Slide]

Xyrem was generally well tolerated when

used in the proposed dose range, with the most common side effects reported including nausea, dizziness, headaches, pain and confusion. Less common but important associated effects include enuresis and sleepwalking, with a possible dose relationship suggested. Although there were 11 deaths in the Scharf trial over 16 years and 2 deaths by suicide in the integrated database, no deaths were associated with Xyrem.

[Slide]

In relation to the specific FDA inquiries, there is a possible relationship between Xyrem therapy and somnambulism but further definition is required. There is a marked discrepancy between the reported incidence in the Scharf study of the 32 percent, recorded solely by diary entry in response to a leading question, and the 7 percent in the integrated database, which is really in the range in public literature for the normal population. In the controlled trials there were only 3 such reports in total, 2 recorded in active treatment and 1 during placebo treatment.

[Slide]

Confusion is also an adverse accompaniment of sedative hypnotic drugs and has been identified

as an occasional side effect of Xyrem. Dose titration may assist in limiting this side effect but it remains an important component of patient and physician education.

[Slide]

The incidence of enuresis with Xyrem treatment supports an association that may be dose related, but any association of these events with seizure activity is very weak. In terms of Xyrem causing seizures at the therapeutic doses, there was no reliable support for such causality. In this regard, the coding to the COSTART dictionary terms of cataplexy as convulsion was confusing. However, there were 2 patients recording seizures with preexisting causes. Two further patients in the Scharf database reported seizures where confounding contributions rendered assignment very difficult. One patient in the Orphar studies represented a complex history of symptoms characterized by fugue state and these symptoms have been attributed to his narcolepsy syndrome.

[Slide]

No significant measures were seen in laboratory measures, vital signs or ECG measures and these changes were comparable across the

treatment groups. There was no evidence of organ toxicity at therapeutic doses that were not part of the central nervous system pharmacology of the drug.

[Slide]

We did not identify any evidence of kinetic or dynamic tolerance in the narcoleptic populations studied and the absence of drug-drug interactions in the 3 classes of drugs commonly used in narcolepsy, along with the absence of either induction or inhibition of the oxybate p450 enzyme system make it possible to predict that drug-drug interactions should be minimal.

[Slide]

Although a serious withdrawal syndrome has been described in the abuser population that relates to escalation in both dose and frequency of dosing, no evidence of withdrawal has been demonstrated in patients maintained on long-term therapeutic doses in narcolepsy. Following abrupt discontinuation of long-term dosing in the blinded study, only 2 patients reported anxiety but in the presence of worsening cataplexy, with 1 patient reporting mild dizziness and 1 report of insomnia.

[Slide]

We have not attempted in any way to minimize the issue of abuse with GHB or its precursors. We recognize that this is a serious problem, but stress the fact that this has been peripheral to the development program in narcolepsy. We have detected no evidence of abuse, diversion or self-escalation of dosing in patients in clinical trials. Great efforts have been applied to working with the appropriate expert bodies to plan a restricted distribution system to support in every way the unique bifurcated scheduling legislated by Congress and to plan physician and patient education to minimize the possibility of diversion. This will be greatly facilitated by the documentation centrally of prescribing and patient use. This will be described in detail to you later.

[Slide]

In conclusion, I would propose that we have established statistically and clinically significant evidence for the reduction in cataplexy, and for improvement in daytime sleepiness when used concomitantly with stimulant medications.

Xyrem is generally well tolerated, with a

safety profile well characterized in this orphan population by long-term exposure. The medical benefits clearly outweigh the risks for a therapeutic agent that may be the first single agent to address the multiple symptoms of narcolepsy. Thank you very much.

DR. REARDAN: I would just like to thank the committee and FDA for your attention. I believe Dr. Mani has some comments, or we are now happy to take questions from the committee.

DR. KAWAS: The FDA will give us a response to the presentation, and then we will probably take a break before we have questions, unless the committee has anything burning they need to ask now. Dr. Ranjit Mani will present for the FDA.

FDA Response to the Presentation

DR. MANI: What I propose to do in the next few minutes is address two issues where our views diverge somewhat from those of the sponsor.

[Slide]

The first is the effect of GHB on measures of daytime sleepiness in narcolepsy.

[Slide]

This overhead illustrates how many

measures of daytime sleepiness there were in the GHB efficacy trials. As you can see, GHB-2 had 3 measures of daytime sleepiness; the Scrima study had 2, of which 1 was primary; and the Lammers study had 2. I will draw your attention to the fact that, with the exception of the Scrima study, the remaining measures were all designated as being secondary.

[Slide]

Because what is considered statistically significant does depend or could depend on the number of comparisons made, I think it is also important to illustrate how many secondary efficacy measures there were in each trial. In the GHB-2 trial I was able to count a total of 10; in the Scrima study 17; and in the Lammers study 7.

[Slide]

This is based on data provided by Orphan. As you can see, in the GHB-2 trial the Epworth Sleepiness Scale measure did reveal a fairly clear-but efficacy for GHB but only at the 9 g dose. The p value of 0.001 probably remains statistically significant even when adjustment is made for multiple comparisons.

On the other hand, the frequency of

daytime sleep attacks and duration of daytime sleep attacks should probably be considered negative evidence of efficacy if adjustment is made for multiple comparisons.

[Slide]

Again, in the Scrima study one primary efficacy measure was sleepiness index of the Multiple Sleep Latency Test. Here, the results must be considered negative whether adjusted for multiple comparisons or not.

[Slide]

The other measure was the frequency of daytime sleep attacks, again negative whether adjusted for multiple comparisons or not.

[Slide]

In the Lammers study the severity of daytime sleepiness was 1 of 7 secondary efficacy measures which is probably negative when adjusted for multiple comparisons. On the other hand, the frequency of daytime sleep attacks was positive, but using an ANCOVA which was not a protocol specified analysis.

[Slide]

So, here are the problems as we see them with the proposed claim for excessive daytime

sleepiness. Most measures were secondary. The only measure that was primary was negative. The majority of measures were negative after adjustment of the Type 1 error for multiple comparisons. The effects were inconsistent across studies, and the clearly positive results on the GHB-2 trial on the Epworth Sleepiness Scale were not replicated. As mentioned, the approval of modafinil for the treatment of excessive daytime sleepiness was based on replicated results in 2 efficacy studies. And a minor point, the results on the GHB-2 study were, to some extent, confounded by concurrent stimulant use, raising the question, among other questions, of whether Xyrem is effective as monotherapy for the treatment of excessive daytime sleepiness.

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The second issue that I want to address briefly is that of sleepwalking. As you can see, I have put it in quotes. As Bill Houghton has already emphasized, we do not know what these episodes represent. They have not been clinically characterized.

[Slide]

The term sleepwalking does not correspond to the medical entity of somnambulism. The term is

based entirely on patient diary entries, and there has been no attempt to characterize the episodes further and define what clinical entity they correspond to.

The incidence of these episodes, whatever they may represent, was approximately 32 percent. The majority of patients did list as having more than one episode. A single patient had a total of 346 episodes over a 5-year period. As already said, an adequate clinical description is lacking, and the episodes cannot be said to be completely benign.

There was one patient who is reported to have overdosed twice during two consecutive episodes of sleepwalking. During one episode the patient became comatose and needed to be hospitalized, needed to be on a ventilator for some hours but completely recovered. A second pat had multiple episodes of sleepwalking. She was found by her husband to be smoking, apparently inadvertently. During one such episode her clothes were set on fire. The fire was put out. She was taken off GHB and did not have any further such episodes. A third patient is reported to have swallowed nail polish remover during an episode,

without any serious consequences.

I would also like to add one minor point in response to Dr. Houghton's presentation. That is, I believe that in the Scharf study there was one patient who was withdrawn from the study because he felt that he had benefitted from Xyrem and decided that these benefits could be extended to a circle of friends who also received part of his own supply, again apparently without serious consequences. Thank you. That is really all I have to say.

DR. KAWAS: Thank you, Dr. Mani. Does the committee have any questions they would like to ask before the break? If not, we will reconvene this meeting at 10:30 sharp.

[Brief recess]

Committee Discussion

DR. KAWAS: Will you please have a seat so we can reconvene this session? This meeting of the Peripheral and Central Nervous System Advisory Committee is now reconvened. We appreciate the presentations from the sponsor and the FDA, and the floor is open for questions. The first question is going to come from someone who has been patiently sitting on the phone. Dr. Chervin, can you hear

me?

DR. CHERVIN: Yes, thank you.

DR. KAWAS: Dr. Chervin, we can't year you yet, if you will give us a moment to do whatever it is we have to do?

DR. CHERVIN: Can you hear me now?

DR. KAWAS: Give it a shot.

DR. CHERVIN: I have a question perhaps for Dr. Houghton. In regard to the safety experience with the 1328 patient years, were there any reports that alcohol was taken in the evening in combination with GHB? If so, what was the outcome?

DR. HOUGHTON: It was certainly recommended as a contraindication in our protocols. The advice to the patient was that they not consume alcohol during the studies. I can't vouch for the fact that it was entirely complied with, but we don't have protocol or database record of consumption of alcohol during the trials. There certainly is record of patients having imbibed during the Scharf study and I am not in a position to clarify that.

DR. GUILLEMINAULT: This is Dr. Guilleminault. I have also a question, and it is

for Dr. Mani, about the sleepiness data. Was there the slow wave sleep information looked at for sleepiness? As you know, delta power greatly improves alertness and there are many studies, sleep deprivation studies and investigation into sleep disorders such as obstructive sleep apnea, where it is very clear that decrease in delta power and in slow wave sleep has a big impact on the alertness, and the more delta power you have and the more slow wave sleep you have, the better alertness the next day.

So, one of my understandings is that this drug has an impact on slow wave sleep and delta power. Was there any analysis of that in data looking at alertness?

DR. MANI: To the best of my knowledge, it was not listed as an efficacy measure in any of the controlled studies that I looked at.

DR. GUILLEMINAULT: Okay. The second question is maybe a question about my ignorance. I did not understand exactly the statistic about the ESS because in the investigation of the results of the ESS there was an investigation with negative studies. All the results, when you look at everything there, was there a positive p value?

Was there a statistical difference? Because I don't understand the manipulation which was done. Maybe through poor knowledge, I have never seen this type of manipulation.

DR. REARDAN: Dr. Guilleminault, which study are you referring to when you ask about the Epworth Sleepiness score?

DR. GUILLEMINAULT: I think OMS-2.

DR. REARDAN: Is that for Dr. Mani, or do you want to pose that to the company?

DR. GUILLEMINAULT: No, I was asking that because Dr. Mani reported that he looked at that study and classified the results, and my understanding, and it may be a wrong understanding, is that he made a subdivision in looking at the results and I did not see completely the statistical rationale for that approach.

DR. MANI: Are you referring to the statistical adjustments for multiple comparisons? Is that what you mean?

DR. GUILLEMINAULT: No, the Epworth Sleepiness Scale study in GHB 2, secondary efficacy daytime sleepiness on your slide, and I did not understand exactly how that was analyzed, the type of analysis that was done or redone.

DR. MANI: Perhaps I should ask the Orphan statisticians to explain that in greater detail, but the analysis was an ANCOVA.

DR. GUILLEMINAULT: The microphone must be poorly placed because we cannot hear the response.

DR. MANI: Can you hear me now?

DR. GUILLEMINAULT: Yes.

DR. MANI: The analysis was an ANCOVA. I mean, perhaps I should get the Orphan study statistician to explain the analysis to you in greater detail.

DR. REARDAN: I am just asking Dr. Richard Trout, the statistician, to comment on how the Epworth Sleepiness score was statistically analyzed.

DR. TROUT: Hi. My name is Dick Trout. First of all, the analysis was just as you described, that is to say it was an analysis of covariance which was preplanned. I think the concern that you expressed was the fact that it was listed as a secondary efficacy measure --

DR. GUILLEMINAULT: Right.

DR. TROUT: -- as compared to a primary, and there was a number of secondary efficacy measures, but even if one adjusted for the multiple

testing which I think you were concerned about, the 9 g separation from the placebo group would still be significant. We already adjusted for the multiple testing with regard to the dosing issue, using Dunnett's test, but your concern was with regard to the fact that there were a number of secondary efficacy measures which would then diminish the effect.

DR. GUILLEMINAULT: Okay, thank you.

DR. PENN: I can see that the claim for helping daytime sleepiness is going to be one that we will want to look into very carefully, and I want to ask our FDA statistician a question about that in a general sort of way. If you were a gambling person, which I assume a statistician would not be --

[Laughter]

-- from the data that you have looked at for 9 g, would you say that in a good controlled trial you would bet on it working to decrease daytime sleepiness? It looks like the strongest data is at 9 g and that is what the company is suggesting. I am going to ask you to bet on that, and then I am going to make a point.

DR. MANI: You addressed the question to a

statistician; I am not a statistician.

DR. PENN: Oh, I am sorry. Anybody else want to gamble with this?

DR. REARDAN: Coming up to the podium is Dr. Sharon Yan, who is the FDA statistician that has been working on the Xyrem program.

DR. YAN: Basically we rely on the results that were prespecified, and a lot of results that we looked at -- and you want me to bet -- after looking at those results, most people would bet that the data shown, for example, the 9 g it seems that it is highly positive; it is highly significant, but we rely on the analysis which is prespecified. Without that, the data information -- it is hard to bet on anything.

DR. PENN: But I am asking you how you would bet on that if you had to make a bet now in Las Vegas, and the point I am trying to make is that it seems to me a reasonable bet that it does help daytime sleepiness but that they haven't presented two clean studies that show at 9 g that that is the case. And, is there going to be some middle ground to this where that claim can be put in language that would be acceptable later on? So, I wanted to see if you agree that that analysis

then presenting of the problem is the correct one, that is, that there is very strong suggestive evidence, not as strong as we often want for a claim, that it helps daytime sleepiness. When you sit back and you look at all the data, would you bet on that helping daytime sleepiness?

DR. KAWAS: Perhaps Dr. Katz could help with this response.

DR. KATZ: Yes, again, I will just sort of reiterate something that Dr. Yan has already said, which is that whether or not we personally believe something is true or what we would bet on is not really the standard. The standard which we apply is what the law requires, which is substantial evidence of effectiveness, ordinarily defined, unless there is some compelling reason to do otherwise, as data from at least two adequate and well-controlled trials demonstrating effect. We have adopted by tradition a usual sort of statistical rule by which we decide whether or not a study is "positive" for a particular indication. So, I think that is the standard. Unless there is some, as I say, very compelling reason to apply some different standard, like what would I bet on or what my personal belief is, that is the standard

we need to apply. Again, unless there is a view that there is some compelling reason to apply some different standard, we would ask you as a committee whether you think that the evidence for that particular claim meets that standard.

DR. PENN: So, once again the question should go then to Orphan, whether or not they feel they have met that standard on two separate occasions using their 9 g amount, and I haven't gotten a clear-cut idea in my mind whether they are really claiming that or just showing us data that would be for a good bet.

DR. YAN: May I clarify one thing? For the analysis for daytime sleepiness for GHB-2 the sponsor showed it was highly significant, with a p value of 0.001, and I analyzed the data with the original scale and, as I analyzed it, it shows that the normal assumption was validated and then the log transformation to then improve the data, and I used nonparametric analysis to analyze the p value, and it is not that small. As I remember, the p value is 0.03 or something.

DR. REARDAN: I can comment on the trials. We have GHB-2, obviously, where the trial was very effective. I don't think there is a dispute with

FDA on that. The question is do we meet the standard of two well-controlled trials for that indication. The data in support of that comes from the Lammers study. The sleepiness scale used there was something he developed, not a validated scale but it was statistically significant for daytime sleepiness, albeit in a very small, 24-patient crossover trial.

So, we have a small supportive study. We have the large controlled study, GHB-2. That is the evidence basically. Bill, do you want to comment?

DR. HOUGHTON: Yes. We are not trying to make this something that it is not in any way, and if you apply the absolute, most rigorous standards of normal drug development to our database, we have a small database. We did have the two components that were statistically significant. This was supported by the reduction in daytime sleep attacks which are very clinically significant to the patient, and we had two components of statistical significance there.

The other issue, and I know that this from a pure mathematical sense is problematic, is the evidence of long-term support in daytime sleepiness

claim with the GHB-3 protocol, which showed the Epworth Sleepiness Scale and the daytime sleepiness reduced and maintained over the long period of time. The fact then that the objective data in SXB-20 was so strongly supportive and the change in Maintenance of Wakefulness Test is an objective measure and was clearly positive was very important.

The part that concerns me from a clinical point of view is if you look at the patient profiles as they enter the studies, they are on stable doses of stimulants and, yet, their ratings are very low. The real issue is that daytime sleepiness with current medications isn't well addressed. So, the question is not only have we shown absolute irrevocable evidence of long-term efficacy for daytime sleepiness with the existence of the present treatments for long-term effectiveness, what we didn't do is ask for a claim in daytime sleepiness.

[Slide]

Our proposed indication was to improve the symptom. We didn't attempt to do studies that displaced the stimulant therapies. What we are really looking at is a hand-in-glove approach that

actually makes patients better as an incremental change, and all therapies up to now have been very separate. The symptoms of daytime sleepiness and those of the associated REM phenomena have been treated by entirely separate medications. If there is a component of Xyrem that assists in daytime sleepiness as an incremental change, we think it is very clinically important and that is what we sought to present today. I want to stress very clearly that we are not looking for the claim of daytime sleepiness; we are looking at an improvement in the symptom thereof.

DR. KAWAS: Dr. Houghton, can I ask you then, to my reading, that indication is actually two indications, I mean, cataplexy and sleepiness being a separate one. When I was reading the materials that you very carefully provided us, obviously for cataplexy the GHB 2 and the SXB-21 study speak to that issue as pivotal trials. I was going to ask you which were the two that speak to the issue of daytime sleepiness. Now I understand them to be the GHB-2 and the Lammers small trial with the questionnaire that was developed there. In both of those cases, however, we are talking about subjective sleepiness from the Epworth scale