

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

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Pippa Simpson, Ph.D.
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NON-VOTING:

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

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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.

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1 PROCEEDINGS

2 Call to Order and Introductions

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

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

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

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

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

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

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

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

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

25 DR. WOLINSKY: Jerry Wolinsky, Professor

1 of Neurology, University of Texas, Houston.

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

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

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

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

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

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

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

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

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

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

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

6 Conflict of Interest Statement

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

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

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

1 conflict of interest with regard to this meeting.

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

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

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

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

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

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

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

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

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

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

19 As a result of these reports, the agency
20 withdrew GHB from health food shelves and made it
21 illegal to use. However, illicit use continued and
22 continues to this day, not only with GHB but with
23 two related drugs which are precursors, GBL and
24 1,4-butanediol, and there have been similar reports
25 of serious adverse events associated with the use

1 of those products.

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

18 Just another relevant piece of history, in
19 2000 Congress passed a law which placed GHB in
20 Schedule I and also placed it into Schedule III for
21 any approved uses that may be granted.

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

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

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

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

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

8 We were particularly interested in the 80
9 or so patients that Dr. Scharf treated that did not
10 move on into the company's treatment IND. He
11 treated a total of 143, or thereabouts, patients,
12 60 of whom went into the sponsor's treatment IND.
13 So, we had a good idea of what was happening to
14 those patients but there were about 80 that didn't
15 and who were basically discontinued from treatment
16 under Dr. Scharf's own IND.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

13 Orphan Medical Presentation

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

17 [Slide]

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

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

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

5 [Slide]

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

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

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

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

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

6 [Slide]

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

18 [Slide]

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

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

5 [Slide]

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

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

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

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

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

12 [Slide]

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

21 But GHB is not the only problem. GBL and
22 1,4-butanediol are precursor chemicals that can be
23 easily converted to GHB and are, in fact, converted
24 to GHB in the human body. These precursors are
25 widely available as bulk chemicals and are being

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

3 Federal legislation, enacted in 2000,
4 helped to control the availability of GHB and GBL
5 but not 1,4-butanediol and other precursor
6 chemicals that can be used for the same purpose.
7 In many states, even with GHB schedules, GBL and
8 1,4-butanediol are not controlled.

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

13 [Slide]

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

18 [Slide]

19 Narcolepsy fits the definition of orphan
20 disease in the United States, with less than
21 200,000 patients. There are estimated to be about
22 135,000 patients, of which 55 percent are
23 diagnosed, with about 24,000 seeking treatment for
24 cataplexy.

25 [Slide]

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

7 Medical Need

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

13 [Slide]

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

17 [Slide]

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

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

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

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

1 paralysis.

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

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

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

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

1 are just awake and cannot sleep.

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

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

18 Most cases of narcolepsy start during
19 adolescence but occasionally it starts as early as
20 5 years of age. It peaks around 15 years of age.
21 It is often extremely problematic because I am sure
22 you realize when you have this type of thing
23 happening to you and sleepiness at school,
24 especially when you are 15 years old, when you are
25 an adolescent, it really wrecks your life apart,

1 especially when it is not properly diagnosed.

2 [Slide]

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

10 [Slide]

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

17 [Slide]

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

1 normally people won't fall asleep or nap in the
2 middle of the day, or they would fall asleep with a
3 15-minute latency in the dark. A patient with
4 narcolepsy, as soon as you switch off the light,
5 they are sleeping. In a few minute latency, they
6 are asleep. So, we have objective ways to show
7 that these people have a problem.

8 [Slide]

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

18 [Slide]

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

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

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

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

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

9 [Slide]

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

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

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

5 [Slide]

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

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

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

10 [Slide]

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

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

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

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

19 [Slide]

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

1 conducted in 136 patients in 16 centers.

2 [Slide]

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

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

13 [Slide]

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

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

25 [Slide]

1 The overall study design was divided into
2 5 stages. Firstly, there was a screening period in
3 which the patients were required to qualify for
4 entry criteria and then withdrawn from their
5 existing anti-cataplectic medications over a 4-week
6 period to avoid rebound phenomena which were
7 considered a safety consideration. At the end of
8 this withdrawal period they entered a washout
9 period, which was determined by at least 5 times
10 the half-life of their preceding drug to remove any
11 effects of those drugs. However, if patients
12 weren't on any cataplectic medications, they were
13 still required to remain 5 days in that washout
14 period to familiarize themselves with the use of
15 diaries.

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

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

4 [Slide]

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

10 There was a dose-response relationship
11 across the doses based on median change in the
12 total number of cataplexy attacks that, when
13 compared to placebo, approached significance at the
14 9 g dose, with a p value of 0.0529, and achieved
15 highly significant change at the 9 g dose.

16 [Slide]

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

22 [Slide]

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

1 calculated as the distribution of percentage change
2 values for each individual patient and is again
3 presented as the medians. This representation
4 clearly shows that the major change in cataplexy
5 occurs in the first 2 weeks, but with ongoing
6 change in the subsequent 2 weeks, as represented in
7 2 of the dose groups.

8 [Slide]

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

17 [Slide]

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

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

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

9 [Slide]

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

17 [Slide]

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

24 [Slide]

25 Because of the complexity of presenting

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

9 [Slide]

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

17 [Slide]

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

24 [Slide]

25 Patients entered this blinded, randomized

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

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

19 [Slide]

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

1 placebo. This was highly significant.

2 [Slide]

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

10 [Slide]

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

16 [Slide]

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

23 Following the withdrawal of
24 antiepileptic medications, he recorded a baseline
25 period during which the patients were required to

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

9 [Slide]

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

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

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

7 [Slide]

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

16 Following a 1-week baseline to establish
17 disease severity, the patients were randomized to a
18 4-week treatment period at a dose of 60 mg/kg in
19 divided nightly doses, followed by a washout period
20 of about 3 weeks, and then a baseline period of 1
21 week again preceding a second treatment period of 4
22 weeks.

23 [Slide]

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

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

14 [Slide]

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

18 [Slide]

19 Although not eligible for determination of
20 efficacy since it is an open-label study, I would
21 like to briefly mention three aspects of the
22 follow-on study to the pivotal GHB-2 study. And,
23 117 patients chose to participate entering the
24 study at the 6 g per day dose and then slowly
25 titrating to clinical efficacy between the doses of

1 3 g and 9 g. This study, therefore, represents the
2 proposed clinical use of the drug and, although
3 primarily a safety study, represents some important
4 dynamic information.

5 [Slide]

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

11 [Slide]

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

20 [Slide]

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

25 [Slide]

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

8 [Slide]

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

25 [Slide]

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

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

18 [Slide]

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

22 [Slide]

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

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

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

17 [Slide]

18 I will only present the studies that have
19 a significant message, and in very brief summary
20 form. This slide displays the results of the dose
21 proportionality study that compared nightly dose of
22 4.5 and 9 g given in 2 equally divided doses at
23 bedtime and 4 hours later. A randomized, 2-day
24 crossover design was utilized, and doubling the
25 dose from 4.5 to 9 g resulted in a nearly 4-fold

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

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

13 [Slide]

14 The results of the effect of food study
15 are displayed graphically on this slide. In this
16 randomized, crossover study 34 healthy subjects
17 were dosed with 4.5 g of Xyrem on 2 occasions 1
18 week apart, either after an overnight 10.5 hour
19 fast or immediately following a high fat
20 standardized breakfast. After the high fat meal
21 the peak plasma concentration decreased by almost
22 60 percent. The median time to achieve peak levels
23 increased from 45 minutes to around 2 hours, and
24 the AUC decreased by 37 percent. All of these
25 differences were statistically significant. The

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

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

10 [Slide]

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

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

1 [Slide]

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

10 [Slide]

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

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

24 Polysomnographic Effects of Xyrem

25 DR. BLACK: Good morning, ladies and

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

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

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

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

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

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

12 [Slide]

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

23 [Slide]

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

1 patients, was designed to further explore the
2 effects of sodium oxybate on nocturnal sleep
3 parameters and daytime measures of sleepiness and
4 alertness. In this open-label study patients were
5 kept at a stable stimulant dose throughout the
6 protocol. Cataplexy medications were tapered,
7 followed by a 2-week washout and baseline period.
8 Sodium oxybate was initiated at 4.5 g in a divided
9 nightly dose for 4 weeks, then increased to 6, then
10 7.5, then 9 g for 2 weeks each. Nocturnal
11 polysomnography and the Maintenance of Wakefulness
12 Test, or MWT, were obtained at the time points
13 noted here.

14 [Slide]

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

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

6 [Slide]

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

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

17 [Slide]

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

24 [Slide]

25 The Maintenance of Wakefulness Test, or

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

11 [Slide]

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

19 [Slide]

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

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

6 [Slide]

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

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

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

25 Safety Overview and Summary of

1 Risk/Benefit Assessment

2 DR. HOUGHTON: Thank you.

3 [Slide]

4 I am sorry to horrify you with this
5 complex diagram again but it is just to outline the
6 15 studies that will be referred to today as the
7 updated safety database. The Lammers study was
8 excluded because adverse events were not recorded
9 in the classical way and, as Dr. Katz explained,
10 the Scharf study was separated and will be
11 explained again later.

12 [Slide]

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

21 [Slide]

22 When exposures were restricted to the
23 studies other than the Scharf database, 399
24 narcoleptics and 125 subjects represent exposure in
25 524 persons. This represents exposure of greater

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

4 [Slide]

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

13 [Slide]

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

25 [Slide]

1 Across all of these studies, 82 percent of
2 treated patients reported any adverse event, as did
3 70 percent of patients exposed to placebo. It is
4 important to note that the placebo exposure
5 represents 4 weeks as compared to active drug
6 treatment over a much longer period of up to 4
7 years. Hence, severe adverse event
8 discontinuations and serious adverse events are
9 significantly greater in the active treatment
10 groups.

11 [Slide]

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

15 [Slide]

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

25 [Slide]

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

10 [Slide]

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

18 [Slide]

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

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

5 [Slide]

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

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

25 [Slide]

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

8 [Slide]

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

20 Of these 80 patients, 8 continued in the
21 Scharf trial under his treatment IND. The 71
22 patients who withdrew had received oxybate for from
23 5 days to 10 years, and the reasons for early
24 withdrawal of the 71 patients were primarily
25 classified into non-compliance, adverse event and

1 cost.

2 [Slide]

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

11 [Slide]

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

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

24 [Slide]

25 I will address incontinence first. In

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

6 [Slide]

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

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

24 [Slide]

25 The issue as represented is shown here.

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

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

18 [Slide]

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

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

7 [Slide]

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

12 [Slide]

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

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

1 complicated polypharmacy.

2 [Slide]

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

12 [Slide]

13 The coding of confusion embodied a wide
14 range of verbatim terms, as shown here. These do
15 not represent confusion based on a standard medical
16 status examination. They do not differentiate
17 between nighttime events from those of awakening or
18 arousal parasomnias. These events led to no dosage
19 adjustment in 37 instances, but dose was reduced in
20 4 events, led to temporary discontinuation
21 following 4 events, and 3 patients discontinued
22 permanently because of a side effect of confusion.

23 [Slide]

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

1 incidence in the databases is represented in this
2 4-week study by 10 patients. The highest incidence
3 was seen in the 9 g dose, and 6 of the 10 developed
4 during the first week of treatment. Seven of these
5 10 events were in patients over the age of 50. The
6 difference in this study, of course, was the
7 assigned doses rather than dose titration. It is
8 important to note that 1 event was reported in a
9 placebo patient.

10 [Slide]

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

20 [Slide]

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

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

5 [Slide]

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

1 [Slide]

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

16 [Slide]

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

1 [Slide]

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

12 [Slide]

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

17 [Slide]

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

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

9 [Slide]

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

19 [Slide]

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

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

4 [Slide]

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

7 [Slide]

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

14 [Slide]

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

1 clearly a medical need existing beyond the
2 therapies available.

3 [Slide]

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

10 [Slide]

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

24 [Slide]

25 Xyrem was generally well tolerated when

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

10 [Slide]

11 In relation to the specific FDA inquiries,
12 there is a possible relationship between Xyrem
13 therapy and somnambulism but further definition is
14 required. There is a marked discrepancy between
15 the reported incidence in the Scharf study of the
16 32 percent, recorded solely by diary entry in
17 response to a leading question, and the 7 percent
18 in the integrated database, which is really in the
19 range in public literature for the normal
20 population. In the controlled trials there were
21 only 3 such reports in total, 2 recorded in active
22 treatment and 1 during placebo treatment.

23 [Slide]

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

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

5 [Slide]

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

22 [Slide]

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

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

5 [Slide]

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

14 [Slide]

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

25 [Slide]

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

18 [Slide]

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

25 Xyrem is generally well tolerated, with a

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

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

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

17 FDA Response to the Presentation

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

21 [Slide]

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

24 [Slide]

25 This overhead illustrates how many

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

9 [Slide]

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

17 [Slide]

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

25 On the other hand, the frequency of

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

5 [Slide]

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

11 [Slide]

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

15 [Slide]

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

23 [Slide]

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

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

16 [Slide]

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

23 [Slide]

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

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

5 The incidence of these episodes, whatever
6 they may represent, was approximately 32 percent.
7 The majority of patients did list as having more
8 than one episode. A single patient had a total of
9 346 episodes over a 5-year period. As already
10 said, an adequate clinical description is lacking,
11 and the episodes cannot be said to be completely
12 benign.

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

1 without any serious consequences.

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

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

16 [Brief recess]

17 Committee Discussion

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

1 me?

2 DR. CHERVIN: Yes, thank you.

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

6 DR. CHERVIN: Can you hear me now?

7 DR. KAWAS: Give it a shot.

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

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

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

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

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

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

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

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

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

8 DR. GUILLEMINAULT: I think OMS-2.

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

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

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

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

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

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

6 DR. MANI: Can you hear me now?

7 DR. GUILLEMINAULT: Yes.

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

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

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

22 DR. GUILLEMINAULT: Right.

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

1 testing which I think you were concerned about, the
2 9 g separation from the placebo group would still
3 be significant. We already adjusted for the
4 multiple testing with regard to the dosing issue,
5 using Dunnett's test, but your concern was with
6 regard to the fact that there were a number of
7 secondary efficacy measures which would then
8 diminish the effect.

9 DR. GUILLEMINAULT: Okay, thank you.

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

17 [Laughter]

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

25 DR. MANI: You addressed the question to a

1 statistician; I am not a statistician.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

21 [Slide]

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

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

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