FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

8:03 a.m.

Thursday, September 25, 2003

Holiday Inn
Versailles Ballroom
8120 Wisconsin Avenue
Bethesda, Maryland

ATTENDEES

COMMITTEE MEMBERS:

CLAUDIA H. KAWAS, M.D., Chair
Professor of Neurology
University of California, Irvine
1121 Gillespie N.R.F.
Irvine, California 92697-4550

ANUJA M. PATEL, M.P.H., Executive Secretary
Advisors and Consultants Staff
Center for Drug Evaluation and Research
Food and Drug Administration
5630 Fishers Lane, HFD-21
Rockville, Maryland 20857

JERRY S. WOLINSKY, M.D.
Professor of Neurology
The University of Texas-Houston
Health Science Center
Department of Neurology, MSB7.044
6431 Fannin Street
Houston, Texas 77030

SPECIAL GOVERNMENT EMPLOYEE CONSULTANTS: (voting)

STEVEN EBERT, PHARM.D., Consumer Representative
Department of Pharmacy
Meriter Hospital
202 South Park Street
Madison, Wisconsin 53715

JORGE C. KATTAH, M.D.
Professor, Department of Neurology
University of Illinois College of Medicine at Peoria
530 NE Glen Oak Avenue
Peoria, Illinois 61637

LOIS E. KRAHN, M.D.
Chair, Department of Psychiatry and Psychology
Mayo Clinic
13400 East Shea Boulevard
Scottsdale, Arizona 85259

ATTENDEES (Continued)

SPECIAL GOVERNMENT EMPLOYEE CONSULTANTS: (voting) (Continued)

EMANUEL J. MIGNOT, M.D., PH.D.
Director, Center for Narcolepsy
Stanford University
701-B Welch Road, Room 146
Palo Alto, California 94304-5742

DAVID NEUBAUER, M.D.
Associate Director, Johns Hopkins Sleep Disorders Center
Johns Hopkins Bayview Medical Center
4940 Eastern Avenue, Suite A-456
Baltimore, Maryland 21224

GERALD van BELLE, PH.D.
Professor, Departments of Biostatistics and
Environmental Health
University of Washington
4225 Roosevelt Way NE, Room 301
Seattle, Washington 98195

ACTING INDUSTRY REPRESENTATIVE: (non-voting)

DANIEL AZARNOFF, M.D.
349 Oyster Point Boulevard
South San Francisco, California 94080-1913

FOOD AND DRUG ADMINISTRATION STAFF:

JOHN FEENEY, III, M.D.
NORMAN HERSHKOWITZ, M.D., PH.D.
RUSSELL KATZ, M.D.
ROBERT TEMPLE, M.D.

ATTENDEES (Continued)

CEPHALON, INC. REPRESENTATIVES:

CHARLES CZEISLER, M.D., PH.D.
DAVID DINGES, PH.D.
ROD HUGHES, PH.D.
GEORGE McCORMICK, PH.D.
GWENDOLYN NIEBLER, D.O.
THOMAS ROTH, PH.D.
LESLEY RUSSELL, MBChB, MRCP
JAMES WALSH, PH.D.
DAVID WHITE, M.D.

ALSO PRESENT:

RICHARD L. GELULA, M.S.W.
CHRISTIN L. ENGELHARDT

C O N T E N T S

sNDA 20-717/s-008 Provigil (modafinil) Tablets,
Cephalon, Inc.,
Indicated for Use to Improve Wakefulness in
Patients with Excessive Sleepiness
Associated with Disorders of Sleep and Wakefulness

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P R O C E E D I N G S

(8:03 a.m.)

DR. KAWAS: Good morning and welcome to the September 25th, 2003 meeting of the Peripheral and Central Nervous System Advisory Committee of the FDA. Welcome, everybody. I think we are going to have a very interesting day.

Since some members of the committee are new today, I'd like to remind everybody that the entire session will be transcribed, and so we need everybody who speaks, whether they're from the audience, the sponsor, or the committee, to please speak into a microphone and identify yourself.

We will begin this morning with a conflict of interest. Actually, let's begin with introducing the committee, and I think we can start at that end with Dr. Katz.

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

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

DR. HERSHKOWITZ: Norman Hershkowitz, medical officer, FDA.

DR. NEUBAUER: I'm David Neubauer from the Johns Hopkins University School of Medicine.

DR. KATTAH: Jorge Kattah, University of Illinois, Peoria.

MS. PATEL: Anuja Patel, Advisors and Consultants Staff, executive secretary for the meeting, FDA.

DR. KAWAS: Claudia Kawas. I'm a neurologist from the University of California, Irvine.

DR. WOLINSKY: Jerry Wolinsky. I'm a neurologist from the University of Texas, Houston.

DR. van BELLE: Gerald van Belle, a biostatistician from the University of Washington.

DR. KRAHN: Lois Krahn, psychiatrist, Mayo Clinic.

DR. MIGNOT: Emanuel Mignot, Stanford University.

DR. EBERT: Steve Ebert, a pharmacist at Meriter Hospital and University of Wisconsin, Madison.

DR. AZARNOFF: Dan Azarnoff, clinical pharmacologist, D.L. Azarnoff Associates.

DR. KAWAS: Thank you very much, and we will have a conflict of interest statement, which will be read by Anuja Patel.

MS. PATEL: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude

even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research, which have been reported by the participants, present no potential for an appearance of a conflict of interest at this meeting.

We would like to disclose that Dr. Daniel Azarnoff is participating in this meeting as an acting industry representative, acting on behalf of regulated industry.

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

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

Thank you.

DR. KAWAS: Thank you.

Today we'll be discussing supplementary new

drug application sNDA 20-717/S-008, Provigil, modafinil, Tablets from Cephalon indicated for the use to improve wakefulness in patients with excessive sleepiness associated with disorders of sleep and wakefulness. And Dr. Rusty Katz of the FDA will give us opening remarks.

DR. KATZ: Thanks, Claudia. I want to welcome the committee back, those members who were here yesterday, for today's discussion. I particularly want to acknowledge and thank three experts who have agreed to help us out with this thorny problem that we have in front of us today, and that's Drs. Neubauer and Krahn and Mignot. So thank you very much for coming and we appreciate the help.

As you just heard and as you know, today we're going to be discussing a supplement to NDA 20-717, which was submitted by Cephalon, Incorporated in December of last year, for the use of Provigil in the treatment of excessive sleepiness associated with disorders or sleep and wakefulness. As you probably know, Provigil has been marketed since 1998 in this country to improve wakefulness associated with excessive daytime sleepiness in patients with narcolepsy. Now they're going for a wider claim, a new claim, with which we have no previous regulatory experience, and so that's why we're coming to the committee.

Again, let me apologize briefly to the

committee. We had not had a chance, by the time we sent you the documents, to complete our own independent review of the data, so we haven't sent you our reviews. I suppose, on the other hand, it's less to read, so I won't apologize too vociferously.

We are, again, in general agreement with the results of the analyses that the sponsor has performed, but we, of course, have questions that we want you to discuss. The sponsor, again, will present the data in detail.

So my purpose here this morning, again, is to just really run through the issues that we would like you to discuss on the way towards voting on the formal questions that you have in your package.

Again, the sponsor in their document has briefly recounted the regulatory history. It's been long. It's been characterized by many interactions between the sponsor and us. I won't go into the details here.

But basically -- and this is the fundamental question we think needs to be dealt with first before anything else -- the sponsor is going for a claim for a particular symptom that occurs in multiple clinical settings. In this case, the symptom is excessive sleepiness and the multiple clinical settings are primary sleep disorders associated with excessive sleepiness. This is a somewhat unusual approach. Ordinarily we are

considering approving drugs for a specific indication, a specific disease, but this is a little different.

But there is precedent for this sort of an approach. Typically in such a case, the way it works is that the symptom is studied in several different clinical models or clinical settings in which it occurs. Not all clinical settings can be studied. That would be impractical, but nonetheless, the idea is you study the symptom in several different clinical models and then you hope that you can infer from that that the drug works against the symptom regardless of what clinical setting it might occur in, even in those that haven't been studied.

So an example might be a simple analgesic where a drug is getting approved to treat pain. Pain occurs, obviously, in many, many different settings. They may study post-surgical pain, dental pain, a couple of models of pain, show it works wherever you study it, and then that presumably permits the inference that the drug works against pain regardless of the setting. That's not entirely true, but that's the general approach that's been taken in the past.

Critically, though, before one can reach the conclusion that the drug is effective against a symptom regardless of the clinical setting, one has to be fairly certain that one can extrapolate in that way to settings

that have not been studied. So in a case like this, we'd like to be able to conclude that we understand very well the pathophysiology and the etiology of the particular symptom so that we can be relatively certain that the clinical models that have been studied are actually representative of all the models, including models that have not been studied.

So in the case we're discussing today, the sponsor has proposed to support their claim for excessive sleepiness on the basis of results in three clinical settings or three clinical models. What the sponsor has done is it has grouped the primary sleep disorders that are associated with excessive sleepiness into what I'll call an overarching category which they call disorders of sleep and wakefulness. This category has been further subdivided into three subcategories, each of which presumably has been defined on the basis of the sponsor's understanding of the pathophysiology of those three categories. And those three categories are sleep-wake dysregulation, sleep disruption, and circadian misalignment.

In each of these categories, the sponsor has studied the effect of the drug on excessive sleepiness in a so-called representative disorder. So for the sleep-wake dysregulation subcategory, they've studied narcolepsy. In fact, they have not done any new studies in narcolepsy.

They are relying on the studies that supported the previous approval of narcolepsy. In the sleep disruption category, they've studied obstructive sleep apnea hypopnea syndrome, and in the circadian misalignment category, they've studied shift work sleep disorder. I'm not going to go into the details of what these diagnoses are. The sponsor will talk about that in detail.

But critically again, based on the results of the studies in these three individual disorders, the sponsor wishes to obtain a claim for an effect of Provigil on excessive sleepiness in all the so-called disorders of sleep and wakefulness. And the critical point I think that needs to be made here is that the sponsor has created both the overarching category of disorders of sleep and wakefulness and they have created, again based on their understanding of the pathophysiology, these three subcategories.

As I said before, it's critical if we're going to extrapolate from studies in a few settings to an effect on the symptom in all the categories, that we are able to understand the pathophysiology or the etiology of the symptom across these different categories so that we can conclude that the drug actually works wherever you would see excessive daytime sleepiness, even in disorders that have not been studied. So it's critical for us to ask the

question whether or not we understand the etiology of these disorders sufficiently to be able to make that extrapolation, and I think that's the critical question before us. So that is the first issue that we would like the committee to discuss. So we need to know whether or not you think it was appropriate to create these categories and whether or not it's appropriate to extrapolate from the findings in these three disorders to the larger universe of disorders that are subsumed under the categories that the sponsor has created.

So ultimately we'll want to know whether or not you think that they have submitted evidence to be able to draw a conclusion about it for a general claim for excessive sleepiness. And if the committee concludes that the data don't support such a general claim, we're very interested to know whether or not you think it supports any other perhaps disease-specific claim.

There's one other general issue that I think the committee should discuss as well. The sponsor has assessed the effects of the treatment on excessive sleepiness by the use of several objective measures, the Multiple Sleep Latency and the Maintenance of Wakefulness Test, which assess under different conditions how long it takes a patient to fall asleep or whether he can stay awake under certain circumstances. These tests are objective.

They're timed. They are used widely in this field to assess drug effect, but they are, of course, in a sense artificial. They don't really look at the real-life situations in which these patients find themselves. So we're interested to know whether or not the committee thinks that these tests are appropriate for these settings.

One could, for example, imagine that in these settings there could be more, I'll say, face-valid measures of effectiveness, number of work accidents, for example, in patients who are shift workers, or automobile accidents during the day in patients with sleep apnea who are falling asleep, or number of naps during the day, that sort of thing which are sort of naturally occurring events. So we're interested to know whether or not you think the primary outcome measures were appropriate here.

Those I think are the primary, larger, fundamental, generic questions we'd like the committee to grapple with, but there are a few disease-specific questions that we have. As I said, one of the models that the sponsor studied, narcolepsy, has been the subject of a previous approval, so I'm not going to ask too many questions about that.

But let me start with questions about the sleep apnea studies. The changes in the sleep latencies, as judged by these objective sleep measures, were small, just

numerically small, although statistically significant. And although analyses of other secondary measures were also statistically significant, we're interested to know whether or not the committee thinks that these treatment effects are meaningful clinically.

In addition, the vast number of patients in the sleep apnea studies were CPAP-compliant. The sponsor was intending to enroll patients who were noncompliant or minimally compliant or compliant, but most of the patients were compliant, at least by the sponsor's definition. I'll get to that in a second. So we're interested to know whether or not, if you think the drug has shown itself to be effective in these patients, it would be appropriate to include under any indication or in labeling any effects of the drug on patients who were noncompliant.

We're also interested in your views on the sponsor's definition of CPAP-compliant, which was I think during a run-in period use of CPAP for 4 nights or greater during that period, 4 nights per week I think or greater. I'm sorry. It's 4 hours per night for greater than 70 percent of the nights. That was the definition of compliant. We're interested in your view on this definition because it's the view of some, we're under the impression, that if patients were truly CPAP-compliant, that they wouldn't have an excessive sleepiness. So one

can ask the question whether or not the use of Provigil, if it has an effect on excessive sleepiness, could motivate patients to either become CPAP-noncompliant or to remain CPAP-noncompliant, if they're starting out that way, and what the long-term consequences, if any, are of that. Again CPAP, in effect, treats the underlying at least anatomical problem, and one needs to ask whether or not, if patients become less compliant with CPAP, there are long-term sequelae of that for the patient. So that's an important question that we think you need to address.

Turning to the shift work studies, again here, the numerical treatment effects are small, and we're interested to know whether or not the committee has any particular concern about that point, even though they're statistically significant. Here also, the sponsor had intended to enroll patients who worked intermittent night shifts, as well as patients who worked more chronically or more frequently on the night shift, but actually here again almost all the patients enrolled were, I will call them, more chronic, more steady night shift workers and not very many intermittent night shift workers. So again here, we're interested to know whether or not the committee thinks that any effects, if you determine that there are effects, seen in the more chronic night shift workers are extrapolatable to the people who work much more

intermittently on night shifts. This is sort of a subcategory of the whole relevance of the models studied question that we wanted to ask you before.

In addition, the final issue we'd like you to think about -- and this also leads into a more generic issue -- patients with shift work sleep disorder have difficulty sleeping during the day, which is when they need to be sleeping. So the question is if Provigil decreases their excessive sleepiness at night when they need to be awake, what effects, if any, are there on their hopefully restorative sleep that they are trying to get during the day.

And the larger question is has the sponsor addressed the more global question of the effects of Provigil on normal sleep in a number of these categories that they've studied. So we're interested to know whether or not you think the sponsor needs to address that question, has adequately addressed that question, and what you think about those concerns.

Those are the main issues we'd like you to discuss. Obviously, we're interested to hear your discussions on any other issues or topics of interest to you, as usual.

We've handed out a list to the committee of some of these issues just so you have something in front of

you, as the discussion proceeds, to refer to, but it doesn't list all the questions. It's just sort of a little aid.

So what I'd like to do now is just as I did yesterday in a more formal way read into the record what the questions are that we actually want you to vote formally on. It's a relatively long list, so I'll just sort of run through it so everyone can hear them.

The first question is, using the International Classification of Sleep Disorders, the sponsor has defined disorders of sleep and wakefulness associated with excessive sleepiness. Does the committee agree with this designation?

The second question is, the sponsor believes that the above group can be divided into three categories we discussed, based on the presumed cause of the excessive sleepiness. The categories are sleep-wake dysregulation, sleep disruption, and circadian misalignment. Again, does the committee agree with this classification?

The third question. Does the committee agree that the disorders studied by the sponsor, narcolepsy, obstructive sleep apnea, and shift work sleep disorder, are representative of the three categories described above? As I said, these are the critical questions we need to get answers to first.

The fourth question. Does the committee agree that the sponsor has submitted substantial evidence of effectiveness for their proposed indication, the treatment of excessive sleepiness associated with disorders of sleep and wakefulness?

The fifth question is, has the sponsor demonstrated that Provigil can be used safely for this broad indication?

And then, if the committee does not vote yes on the first set of questions, if you find that this approach is not viable, then we have two additional other questions, and this relates to disease-specific claims.

The first one is, has the sponsor provided substantial evidence of effectiveness to support the use of Provigil in the treatment of excessive sleepiness in patients diagnosed with sleep apnea?

And the second is, has the sponsor provided substantial evidence of effectiveness to support the use of Provigil in the treatment of shift work sleep disorder?

With that, I'll stop and I'll hand the microphone back to Dr. Kawas.

DR. KAWAS: Thank you, Dr. Katz.

The sponsor presentations will occur now from Cephalon, Incorporated, and the introduction will be done by Lesley Russell, Vice President of Clinical Research of

Cephalon.

DR. RUSSELL: Good morning. Madam Chairperson, members of the advisory committee, FDA, we are pleased to be here today to present to you data that we believe supports the use of Provigil as treatment to improve wakefulness in patients with excessive sleepiness associated with disorders of sleep and wakefulness.

I'm Dr. Lesley Russell, Vice President of Clinical Research at Cephalon. I will start off the presentation by making a brief introduction.

Dr. Tom Roth, Professor and Division Head of Sleep Medicine at Henry Ford Health System, Detroit, will give an overview of the symptom of excessive sleepiness and its underlying pathophysiology, the disorders of sleep and wakefulness and how they can be categorized, how the symptom of excessive sleepiness manifests itself and how it can be measured.

This will be followed by a review of efficacy data generated from five principal studies by Dr. Rod Hughes, Director of Sleep Medicine at Cephalon.

Dr. Niebler, Director of Clinical Research at Cephalon, will then give a comprehensive overview of the safety data, following which I will conclude and take questions.

As outlined by Dr. Katz, in December 1998,

Provigil received orphan drug approval for the following indication: to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy. The efficacy and safety for this indication was established in two U.S. multi-center, randomized, placebo-controlled studies.

The recommended dose was 200 milligrams administered once daily, but in addition it is noted in the current label that 400 milligrams was well tolerated but with no consistent evidence for additional benefit beyond 200 milligrams.

Provigil is listed in Schedule IV of the Controlled Substances Act.

I would now like to outline for you some key discussions that have taken place over the past four years between Cephalon and FDA which led us to undertake the clinical program that we are presenting to you today.

In June of 1999, Cephalon first met with FDA to discuss the clinical program that would be required to expand the indication for Provigil beyond narcolepsy to the treatment of excessive sleepiness associated with other clinical conditions. The initial proposed indication for Provigil was for excessive sleepiness secondary to sleep deprivation associated with obstructive sleep apnea hypopnea syndrome. However, FDA noted at that time that

since excessive sleepiness occurs in multiple clinical settings, a general claim for the treatment of excessive sleepiness could be pursued if it could be shown that Provigil had an effect on the symptom regardless of the clinical setting in which it occurred.

Several meetings then took place to discuss a clinical program that could potentially support an indication such as to improve wakefulness in patients with excessive sleepiness associated with sleep disorders. In order to support such an indication, FDA requested data from three representative disorders.

In April 2001, agreement was reached that obstructive sleep apnea and shift work sleep disorder, in addition to the narcolepsy which had already been submitted, were appropriate disorders that could, if positive outcomes occurred, be submitted to support potential approval of such a claim. In addition, further discussions took place and agreement was reached on the design and endpoints implemented in the study undertaken in shift work sleep disorder.

Therefore, in addition to the narcolepsy studies, clinical trials have now been undertaken and completed in obstructive sleep apnea and shift work sleep disorder, and as we will show you today, Provigil was consistently efficacious in improving wakefulness in all

three disorders. In addition and as important, the safety profile of Provigil was similar in all three disorders. Therefore, we believe that the results seen in these three disorders are predictive of Provigil's treatment effect on excessive sleepiness in disorders of sleep and wakefulness.

In December 2002, a supplemental NDA was submitted for the following indication: to improve wakefulness in patients with excessive sleepiness associated with disorders of sleep and wakefulness.

I would now like to highlight some key points which underlie the rationale for the clinical program that was undertaken with Provigil and which will be presented to you in greater detail by Dr. Roth and Dr. Hughes.

Firstly, the symptom of excessive sleepiness is associated with significant morbidity, causing impairment in occupational and social function, and occurs in qualitatively similar ways in many clinical settings. Regardless of the underlying etiology, excessive sleepiness is a consequence of sleep disruption and/or an increased drive for sleep.

Primary sleep disorders that have excessive sleepiness as a primary complaint have been categorized in the International Classification of Sleep Disorders as disorders of sleep or wakefulness, and using this classification, the disorders of sleep and wakefulness can

be grouped into three categories which are operationally definable; namely, disorders of sleep-wake dysregulation, disorders of sleep disruption, and disorders of circadian misalignment. Within these three categories, narcolepsy, obstructive sleep apnea, and shift work sleep disorder are representative clinical disorders that all have excessive sleepiness as a primary complaint.

Importantly, regardless of the underlying cause, excessive sleepiness manifests itself in similar ways and can be measured objectively and subjectively using standardized, validated, and clinically relevant instruments.

And finally, as we embarked on the clinical program, we believed that Provigil would be an effective treatment for excessive sleepiness associated with disorders of sleep and wakefulness regardless of the underlying etiology.

I would now like to hand over to Dr. Tom Roth who will give a review of excessive sleepiness.

DR. ROTH: Thank you, Dr. Russell.

What I would like to do in my presentation is to give you information about three topics.

One is excessive sleepiness has significant morbidity and that manifests itself very similarly regardless of the etiology of that.

Two, excessive sleepiness can and is reliably measured in clinical practice, in clinical trials, and in clinical research on an ongoing basis.

And finally, excessive sleepiness related to sleep-wake disorders is a finite number of diseases which can be defined both in terms of what is included in that category and what is not included in that category.

Those are the three things I would like to cover.

Now, the presentation I'm about to give was offered not only by myself, but by three other people, Dr. Charles Czeisler from Harvard Medical School and Brigham and Women's Hospital, Dr. David Dinges from the University of Pennsylvania School of Medicine, and Dr. Jim Walsh from St. John's/St. Luke's Hospital and St. Louis University. The four of us spent the time developing this presentation. I was chosen to be the one to give it. I'm afraid to ask why, but I was the one chosen.

Now, the presentation I'm about to give will touch on these five points. One, I will try to define sleepiness and, within that context, to define what differentiates sleepiness from excessive sleepiness. Two, I'm going to talk about etiology of sleepiness, what makes individuals sleepy both at a normal level and at a pathological level. Then I will discuss the disorders of

sleep and wakefulness, but not all disorders of sleep and wakefulness, but specifically disorders of sleep and wakefulness which sometimes give rise to a clinical symptom of excessive sleepiness. Then finally, I'll talk about how this excessive sleepiness exhibits itself, why it's clinically important, and how clinicians and researchers quantify it on an ongoing basis.

Now, what is normal sleepiness? Normal sleepiness, like hunger, like thirst, is a drive state, and it is defined very simply by decreased ability to maintain levels of wakefulness or, conversely, an increased propensity to sleep. So it is often referred to as a homeostat, drive state, but we're going to talk about that in the context of sleepiness.

Now, very importantly, like other symptoms Dr. Katz mentioned, sleepiness has adaptive value. It is telling the organism that it is not functioning at maximal capacity and it ought to either expend effort to be more careful or to stop that activity because they are not doing it well. So it has very clear and important adaptive value, and that's why it's become the single most important symptom in the practice of sleep medicine.

Now, what drives normal sleepiness? Two factors normally control sleepiness.

One is sleep drive, and as I mentioned, it's

often referred to as sleep load or the homeostat. It is driven by two things: how long you've been awake, time since sleep, the longer you're awake, the higher the sleep drive; and the duration and continuity of sleep. Once you go to sleep, that sleep drive dissipates and you then start over the next day. So this is a buildup of sleep drive. This is an attention or a diminution of sleep drive.

The second major output is the circadian phase, and by circadian phase, we are talking about your biological time of day. Very importantly, it is a biological time of day. It is not the time of day on your clock. And what's very important is your biological time of day and the time on your clock are often discrepant, and that becomes an issue, which we will talk about, in some individuals.

It's important to understand two things about that circadian clock. One, its primary output is an alerting pulse to the cerebral cortex. That is its primary output. And two, it is primarily governed by light and dark schedules.

Now, in my presentation I'm going to use this slide on several occasions. I'm going to spend about 30 seconds describing it for you. This is a 24-hour day. This is 9:00 a.m., 9:00 p.m. This is when people routinely work. This is when people routinely sleep.

Now, what causes sleepiness? As I mentioned, the first thing is the homeostat or the sleep drive. As you can see, across the day, it increases. Across the night, it dissipates. That sleepiness is modulated by that circadian drive for wakefulness or that cortical activation. You can see this peaks about 8-9 o'clock in the evening. What's very important is at 7-8 o'clock at night, people should be falling asleep while they're eating dinner. They don't, and it is because of this important alerting pulse. These two biological signals result in this wake propensity.

So each of us, across a 24-hour day, have a wake propensity. Right now, we have a reasonably high wake propensity. When we go to sleep, we are able to sleep because you have a decreased wake propensity. So this is the net. When it moves up, we have a greater wake propensity; when it moves down, we have a greater sleep propensity.

Now, this green line is very similar to slides you see in the literature or graphs you see in the literature of measures of sleep tendency. So how do you operationalize wake propensity? You operationalize it or the sleep community or the medical community operationalizes it with the Multiple Sleep Latency Test. So they measure the tendency to fall asleep. So wake

propensity is operationalized and clinically used by measures of sleep tendency.

Now, the difference between excessive sleepiness is that it is a symptom of difficulty in maintaining wakefulness and increased propensity to fall asleep. The difference between normal sleepiness is that it is in inappropriate circumstances and it importantly interferes with activities of daily living. So excessive sleepiness, regardless of what causes it -- regardless of what causes it -- is the level of sleepiness which interferes with activities of daily living. So by definition, it has morbidity almost.

Now, the prevalence of excessive sleepiness, depending on how you define it and the population you study -- and people sort of can define this clinically in the literature, patient-rated scales, clinical scales. Basically if you look at the literature, somewhere between 5 and 15 percent of the population will experience excessive sleepiness. So that is the piece of pie we're going to talk about. We're going to dismiss normal sleepiness.

Now, within that pie, we can trichotomize. We can sort of say there are three causes of sleepiness.

One, the most common, by far the most common, are behavioral, environmental, and other extrinsic causes.

It is not spending enough time in bed. It's not having regular sleep times. There's a series of behavioral causes which give rise to that. That is normal variations which reach an extreme level. That is not what we're going to be discussing today.

The second is excessive sleepiness due to a variety of medical diseases. This is very much a neurological panel. Parkinson's disease gives rise to the symptom of excessive sleepiness. Medications used to treat medical disorders, for example, dopamine agonists, can also lead to that. Seasonal affective disorders lead to symptoms of excessive sleepiness. But again, that is not, as Dr. Katz pointed out, what we're going to discuss today.

What we are going to discuss today is very simply the disorders of sleep and wakefulness. Within the disorders of sleep and wakefulness, currently the sine qua non of that category and the current indication for modafinil is in fact narcolepsy. So that is the sine qua non of that category, and the category is what we're going to talk about today.

Now, when you take that group of disorders which give rise to the symptom, one of the questions becomes how do you dissect that. What we have sort of come up with is, if you look at all those disorders and you look at the mechanisms, more importantly, there are three types

or three groups of disorders which lead to sleep and wakefulness associated with excessive sleepiness. One are disorders of the sleep-wake dysregulation. Two, there are disorders of sleep disruption. And I'll talk about these individually. And three, there are disorders of circadian misalignment. So these three groupings represent that universe.

Now, the next question becomes how do these things lead to excessive sleepiness. So, for example, we'll talk about pathologies in sleep-wake dysregulation in the hypothalamus. But how do they lead to that symptom, that common symptom in all of these disorders? How do they lead to that common symptom?

Basically these three groups of disorders have two pathways to excessive sleepiness. The reason we picked these three groups is they differentially take these two roads to excessive sleepiness in different ways.

The disorders of sleep-wake dysregulation primarily impact sleepiness by increasing sleep drive for impacting the homeostat. So disorders of sleep disruption, obviously, primarily have as their pathway leading sleep disruption in losing the recuperative value of sleep. The third are disorders of circadian misalignment and they impact both of those equally. So you have three groups of disorders and two pathways, all leading up to the symptom

of excessive sleepiness associated with sleep-wake disorders.

Now, the International Classification of Sleep Disorders is developed by the American Academy of Sleep Medicine, and it has developed a nosological system which codifies and provides codes for all the various sleep disorders. They put them into four categories. They're proposed sleep disorders and that's because all researchers always say more research is needed, so that's what that means.

Then there are disorders associated with mental, neurological, and other medical disorders. We dismiss those in that part because we're interested in sleep-wake disorders. We're not interested in those associated with medical disorders.

There are parasomnias, and there are arousal disorders. Now, the reason we're not particularly interested in that is because they don't present with excessive sleepiness. If you look in the nosological system, they don't present with excessive sleepiness.

So we are left with dyssomnias which are defined in the ICSD as disorders of sleep or wakefulness.

Now, within the disorders of sleep and wakefulness, we're primarily interested in intrinsic sleep disorders and circadian rhythm sleep disorders. We're not

particularly interested in extrinsic sleep disorders because those are disorders where, if you treat the source of that extrinsic factor, such as noise in environment and allergy, it goes away. So these are the ones we're primarily interested in.

Now, besides giving this myriad of diagnostic entities, the ICSD provides us with a differential diagnosis, and this has much more clinical utility. So the differential diagnosis of sleepiness falls into two groups that I'm going to call "other," and these are the ones we dismissed now twice. And these are the four which are disorders of sleep and wakefulness, which I sort of had on the previous slide. They are sleep-induced respiratory impairments, sleep-related movement disorders -- sleep-related movement disorders, not other movement disorders -- disorders of timing of the sleep-wake pattern, and neurological, not all neurological disorders, but specifically neurological sleep disorders. So those are the four groups in the nosological system we're interested in.

Now, this slide melds the two nosological systems I just gave you. This is the categorization of sleep disorders we created: sleep-wake dysregulation, sleep disruption, and circadian rhythm misalignment. These are the ICSD classifications in their system which

correspond to these, and they're very tight. So this is a melding of those two systems. In here we have all those things that the nosological categorization associated with neurological sleep disorders. In here we have disorders associated with the timing of sleep and wakefulness. In here in sleep disruption, we have those associated with respiratory impairments and those associated with sleep-related movement disorders. So that is a melding of the ICSD system and the way we broke these up. They're almost identical and almost one-to-one categories, and I'll get back to discussing those. So those are very important.

Now, if you go one step lower or further into the nosological system, within each of these categories, this is the ICSD category which corresponds to it. It's exactly one-to-one, and these are the specific disorders within that category. These are the disorders within that category, excessive sleepiness due to restless leg syndrome, periodic limb movements, or in that category. And these are excessive sleepiness in shift work sleep disorder and other disorders.

So the question really becomes this is the universe of symptoms. This represents the individuals in each category, and this is how we picked the representative nature of all disorders of sleep and wakefulness. So in this slide, you have all of the disorders of sleep and

wakefulness associated with excessive sleepiness. If they're not on this slide, we do not consider them or the ICSD, more importantly, does not consider them a disorder of excessive sleepiness due to sleep-wake disorders.

I'm going to now deal with them individually.

Now, narcolepsy is a disorder which we picked in terms of sleep-wake dysregulation. Now, why do we pick that? Well, we picked it because, one, at this point in time it is the most common one seen in the practice of medicine. By far, of all of these disorders, that is the one most commonly seen in the area of medicine.

Now, what is the pathology in these things? Well, for example, one of the things we know, based on the work of Professor Mignot, is that narcolepsy represents a degeneration of a group of hypothalamic neurons which lead to a down-regulation or diminution of the arousal system. That is the pathology there. Idiopathic hypersomnia, recurrent hypersomnia, post-traumatic hypersomnias have different lesions, albeit it ill-defined at this point in time, but they all have the same exact common pathway. They decrease arousal level.

How do we draw that out? The way we draw it out is by going back to the original slide. This is the normal I showed you before. This would be one of the disorders of sleep-wake dysregulation. Sleep drive, sleep

load -- use those interchangeably -- is significantly increased. That results in an increased sleep propensity or, most importantly, a decreased wake propensity. So this wake propensity is significantly lower than it is in the normal individual.

Now, one of the things that was pointed out by both speakers who preceded me is modafinil is indicated for excessive sleepiness in narcolepsy. And how does it do that? Basically the efficaciousness of the compound is defined by its ability to move wake propensity from here to here. That is the definition of efficacy.

Let's go to the next group of disorders, what we call disorders of sleep disruption. In that, what we have is a group of disorders, all of which have a common pathophysiology, and the common pathophysiology is that they fragment your sleep. So it doesn't make a difference if you have leg movements causing sleep fragmentation. It doesn't make a difference if you have respiratory events causing sleep fragmentation. The commonality is all of these fragment your sleep. That fragmentation of sleep specifically leads to an attenuation of the recuperative value of sleep and leads to the symptom of excessive sleepiness. So they are very common in their pathology. They differ in the source of the stimulus, very much like before. They all lead to a decreased arousal. The site of

the lesion is different. The same thing here. They all lead to sleep fragmentation. The site of the lesion is different.

Why do we pick obstructive sleep apnea syndrome? Because of all of the disorders, it's the one most commonly seen in clinical practice today.

How does that work? Well, the major pathology in these disorders is right here. In other words, this we showed you before, the recuperative value of sleep. Here the recuperative value of sleep is profoundly attenuated. So when you get out of bed the next morning, you still have a very high sleep drive.

Now, the questions in front of you and which the speakers which follow me have to address is the question of this decreased wake propensity associated with disorders of sleep and wakefulness. Does modafinil increase that wake propensity just as it did in narcolepsy? So I drew you a schematic which shows that the effect is exactly the same as in the approved indication. Does that effect in sleep apnea show the same thing?

The other requirement that is important for you to consider is, does it do this without impacting the primary treatment? So the primary treatment for sleep apnea is CPAP. Does this change CPAP compliance? Does it, as Dr. Katz pointed out, disturb nocturnal sleep by making

it more disturbed? Or does it change issues related to sleep apnea such as cardiovascular disease? So two things. It has to increase that level of alertness, and two, it has to do it without changing the primary disease or its therapy.

The third group of disorders are the disorders of excessive sleepiness, for example, shift work sleep disorder. But again, it is no different from time zone change. It's no different than jet lag in the sense that the pathology is these individuals are waking at a time when the circadian pacemaker does not have its maximum output again to the cortical arousal. We keep going to cortical arousal. So we decrease cortical arousal because of fragmented sleep. We decrease cortical arousal because of a lesion in the hypothalamus. We decrease cortical arousal because it is the time of day when the SCN isn't putting out its maximal pulse for cortical arousal. So these are all the same in terms of the fact that that is what's causing the sleepiness.

Why did we pick shift work disorder? Because in clinical practice today, this is the most common one seen on a daily basis.

Now, again, this is the schematic. The only difference here is that when you had sleep here before, you now have sleep here. You had work here before, you have

sleep here. So what one of the things that's happening is in fact when people are waking at this point in time or working, you have a maximum sleep drive because it's the wrong time. We simply flipped that slide.

So what is the challenge, again, for modafinil data? Well, we want to show that like narcolepsy, like sleep apnea, this wake propensity is enhanced, and again, enhanced without the primary therapy. The primary therapy of these disorders is to make sure that nocturnal sleep is adequately managed. So we want to make sure that this enhancement of alertness occurs without disturbing nocturnal sleep as measured by sleep studies, polysomnography as mentioned by Dr. Katz, or without impacting patients' compliance. Specifically, are they reporting an equal amount of time in bed or are they sort of decreasing their time in bed?

Now, one of the things that becomes important to understand is we have these various disorders. We said they have a common pathology, and that common pathology is a decrease in cortical activation. We don't really know what modafinil does at a cellular level, and certainly there are people on the panel who know that better than I do.

But what are we talking about here? Well, basically what we have here are the various mechanisms

involved in the normal arousal system because we have activated the cortex. These are mediated by hypothalamic neurons which then give signals up to the cortex. And there is a variety of transmitter systems, mostly in the hypothalamus, hypercretin, histamine. All have outputs which increase that.

In disorders of sleep and wakefulness, there is a decreased activation of these hypothalamic centers. For example, in narcolepsy, as I mentioned, Dr. Mignot showed that there's an impairment in the hypercretin system, and you wind up with a decreased activation of that system.

How does modafinil work? Well, as I mentioned, we don't know how it works at a molecular level, but work from Professor Jouvet in Lyon has shown that modafinil leads to an activation of hypothalamic centers in the brain, and he demonstrated that by early genes, such as specifically Cfos. So what that activation does is it restores a normal level of cortical activation. So these disorders decreased our level of cortical activation. Modafinil, working through the hypothalamus -- again, I can't specify exactly where or what transmitter systems -- leads to a restoration of that normal cortical activation.

So let us move on to the whole issue of understanding the data. As I mentioned, disorders of sleep and wakefulness which produce excessive sleepiness have

significant morbidity. There's very little question that they have effects on productivity, accidents. They manifest themselves in very homogeneous ways, and that's what makes this a single category. They have comparable morbidity. Decreased productivity is the same in apnea as it is in shift work sleep disorder as it is in narcolepsy. They manifest themselves the same way and they are measured in clinical practice and clinical research in the same ways.

Now, there's a lot of morbidity associated with excessive sleepiness, and in fact today there's a tremendous amount of research on the physiological consequences of excessive sleepiness. People look at things like insulin resistance and a variety of other measures. But without any question, the most clear, most imminent morbidity associated with excessive sleepiness, regardless of the cause that we're talking about, is an impact on behaviors and mood. Behaviors which are impacted are you wind up with undesired sleep episodes, either working, driving, lapses of attention, decreased work productivity, and at its worst, accidents. The impacts on mood are irritability, fatigue, depressed mood, not depression, loss of energy, and very importantly, lack of motivation. So these are the morbidities of excessive sleepiness due to all of the causes I spoke about.

Now, how do they manifest themselves? Well, sleepiness/alertness manifests itself from its highest point, sustained wakefulness. You're able to sit behind the wheel of your car and drive for 10 hours. At the other end is continuous sleep and you go from concentration all the way down to undesired sleep episodes. Disorders of excessive sleepiness are in this part of the continuum. We are going to deal with drowsy wakefulness, sleep-wake instability. What sleep-wake instability means is you're sort awake except for about 100 milliseconds you have a lapse. To sort of put that in context for you, if you're driving your car at 70 miles an hour and you have a 500 millisecond lapse, you stop your car 50 feet later, better known as off the highway. So very clearly lapses are an important measure. And there's undesirable sleep episodes, which are longer than those micro-sleeps, those lapses.

Now, excessive sleepiness is measured regardless of etiology. Again, it doesn't make a difference if you're Dr. Walsh doing studies in shift workers or if you're Dr. White doing studies in sleep apnea, they're measured in exactly the same way. The gold standard of measuring sleepiness regardless of which of the causes is measures of sleep propensity, and there are two measures of sleep propensity originally described by Drs. Mary Carskadon and William DeMint. The first one is the

Multiple Sleep Latency Test and the other one is the Maintenance of Wakefulness Test. In a meta-analysis recently done by the academy, they give very similar results, albeit slightly different numbers, but they functionally measure the same thing and get very comparable results.

It is very important to understand that these are very, very sensitive assays and are very valuable to measuring pathology, very valuable in terms of measuring treatment outcome. There is not a single treatment for any sleep-wake disorder, whether that's apnea, shift work sleep disorder -- and I'm not talking about modafinil -- CPAP -- there's not a single treatment in sleep medicine which does not have a study with a measure of sleep tendency as its primary endpoint. So the big advantage is it's profoundly sensitive.

The problem is how do you translate a 1-minute change in MSLT. If you take an analysis of all the CPAP studies done to date for the treatment of sleep apnea syndrome -- I think Dr. White did this -- the mean change in MSLT is .93 minutes. What does that mean? And since we can't mean that, one of the things that's very incumbent on the clinician is to translate that into real-world clinical outputs, and that is done in a couple of different ways: one, by making clinical judgments. So things like the CGI

are very important. In the sleep and neurology community, the Epworth Sleepiness Scale is becoming a total mainstay for the evaluation of sleepiness. You have physician-rated, you have patient-rated evaluations of sleepiness, Epworth Sleepiness Scale, Karolinska Sleepiness Scale, specifically used in occupational medicine rather than general medicine.

Beyond that, we have measures of neurobehavioral performance. I'm sorry. Since I sort of mentioned that is the most commonly used scale in medicine, I'm going to spend about 30 seconds on the Epworth Sleepiness Scale.

What is it? Well, it is nothing more than having listened to patients with excessive sleepiness for many years. You sort of ask them, what's your problem? My problem is why do they present. I fall asleep driving a car. I fall asleep in meetings. Basically what Dr. Johns has done is he took those symptoms -- I fall asleep sitting and reading; I fall asleep watching television; I fall asleep in a public place, in a theater -- and he sort of quantified those, gave it psychometric properties, and identified a pathological level of 10. That has been shown in a variety of conditions. So it is a self-rating scale which has been validated in a variety of ways, and it is by face value a clinical measure. It talks about do you fall

asleep driving, do you fall asleep while talking to your friends. So very clearly it has clinical face validity.

Beyond that, there are neurobehavioral measures. Originally what was commonly used, especially in the apnea literature, was the Steer Clear, but more recently the PVT, the Psychomotor Vigilance Task, worked on mostly by Dr. Dinges, has become the standard measure of excessive sleepiness in occupational medicine, in sleep medicine, and in normal variations in sleepiness we talked about. That is now the gold standard of neurobehavioral measures.

Finally, there's a series of outcome measures such as the SF-36 and one specifically for sleep, which will be discussed.

So one of the things I want to emphasize to you is in evaluating the efficacy of these compounds, the sine qua non is multiple measurements. It is multiple measurements. This is the continuum that I talked about in terms of the manifestations. These are the measuring instruments. These complement each other. You can't use one without the other. In one case, you wind up with no clinical relevance; in the other case, you lose precision. So these are complementary parallel measures of the impact of the disease state and the treatment of the disease state.

So in conclusion, I want to make two things: one, about the symptom which we're talking about today, and then two, about the disorders we're talking about today. So, in conclusion, excessive sleepiness is associated with significant morbidity, well-defined, well-documented. Excessive sleepiness manifests itself in very similar ways regardless of which disorders are causing it. It manifests itself in similar ways; hence, we can measure it in similar ways. So excessive sleepiness can be measured objectively, subjectively using standard, reliable, validated tools which are used in clinical practice and in clinical research.

Now, in terms of the disorders, excessive sleepiness is caused by increased sleep drive and/or disturbed sleep. Those are the two routes.

Two, disorders of sleep and sleepiness can be defined based upon the underlying pathophysiology. There's a basic impairment of the sleep drive system which we are called sleep-wake dysregulation. It could be due to sleep disruption. It could be due to circadian misalignment. Those are the three routes. Narcolepsy, obstructive sleep apnea syndrome, refractory, and shift work sleep disorder are the most common and most representative disorders in each of those categories.

I want to thank you for your attention. And I

would like to take this opportunity to introduce Dr. Hughes who will be our next presenter.

DR. HUGHES: Thank you very much, Dr. Roth. Good morning, everyone.

As Dr. Roth said, I will be presenting our efficacy data today. In doing that, I will show you that Provigil significantly improves wakefulness in patients with excessive sleepiness associated with narcolepsy, as Dr. Katz correctly pointed out as in our original submission and our current indication, and in addition, in patients with residual excessive sleepiness associated with obstructive sleep apnea syndrome and in patients with excessive sleepiness associated with shift work sleep disorder.

I will show you that these clinical effects are indeed clinically significant, as evidenced not only by the fact that the clinicians can recognize the improvement and judge these patients to having been at least minimally and, in most circumstances, much or very much improved in the severity of their overall clinical condition.

Secondly, the data clearly show that the patients themselves can recognize the improvement and report by subjective scales that an increased ability to maintain wakefulness while they are doing daily activities in their social and occupational settings.

Finally, I'll highlight for you that despite differences in the underlying pathophysiology, as Dr. Roth has described, Provigil consistently improves wakefulness across these disorders of sleep and wakefulness.

I'll start with a few slides that point out the similarities in study design and assessment of excessive sleepiness across the disorders that we have studied. Our inclusion and exclusion criteria led to a patient population, all of whom presented with a subjective symptom of excessive sleepiness, met formal ICSD criteria for one disorder of sleep and wakefulness, either narcolepsy, obstructive sleep apnea, or shift work sleep disorder. All patients had no other sleep disorders, no uncontrolled medical, neurologic, or psychiatric conditions, and were taking no sedating or activating medications.

Of the studies that I'll show you today, all studies employed a double-blind, placebo-controlled, randomized, parallel groups design. In our first two studies, part of our original submission, we studied the effects of a morning dose of 200 or 400 milligrams of Provigil across 9 weeks in patients with excessive sleepiness associated with narcolepsy.

We studied two additional studies in patients with residual excessive sleepiness in OSA. In one study, we assessed the effects of a 200 and 400 milligram dose,

again administered in the morning, across 12 weeks, and in an additional study, we assessed the effects of a 400 milligram dose across 4 weeks.

In our study of shift work sleep disorder patients, we assessed the effects of a 200 milligram dose importantly administered 30 to 60 minutes prior to their shift work, in contrast the two previous groups, in a 12-week design.

Throughout the presentation, I'll spend most of my time talking, however, about the four studies that are highlighted for you here. These studies have in common the employment of co-primary endpoints. Now, as Dr. Roth just described, using multiple measures to assess the clinical effects is important in this condition, as it is in many others. In these studies we, indeed, employed two co-primary endpoints, the first of which was using the gold standard assessments of physiological sleepiness that Dr. Roth has described, the assessment of an objective measure of physiologic sleepiness either by the MWT, the Maintenance of Wakefulness Test, or the MSLT, the Multiple Sleep Latency Test.

For both of these tests, the outcome measure is the latency to sleep in minutes as recorded by polysomnography and as scored according to standardized criteria. And the primary analysis was the change from

baseline in these measurements at the final visit. Analysis was done by analysis of covariance using the baseline as a covariate.

Our second co-primary endpoint was the change in overall clinical condition as assessed by the clinician raters themselves. In discussions with the patients, these raters independently obtained a rating of the severity of their overall clinical condition at baseline and the outcome measure that we will be measuring is the CGI-C, and that is the change in the severity of their overall clinical condition on a seven-category scale, ranging from very much worse to very much improved.

In this analysis, the primary analysis was again done at the final visit and was done upon the distribution for each treatment group in the patients who fell into each of these seven categories. The analyses statistically were done with the non-parametric chi-square test.

Now, it's very important to highlight the use of these co-primary endpoints because, as Dr. Roth said, while the objective gold standard measurements of excessive sleepiness or physiologic sleepiness are necessary for determining the extent to which or the degree to which Provigil significantly led to improvements in underlying physiologic sleepiness, the change in overall clinical

condition is used and has been used primarily as a judgment to the extent to which Provigil treatment is clinically significant.

But as Dr. Roth described, there are a variety of tools that can and have been used to assess sleepiness and the effect of sleepiness in the sleep community. We employed many of these tests in our studies. In three of our studies, we employed a second objective measure of physiologic sleepiness, the MSLT. And in all studies, we employed at least one subjective measure of sleepiness.

In our narcolepsy NOSA studies, we employed the Epworth Sleepiness Scale, which simply, as Dr. Roth described, assesses the extent to which these patients are able to maintain wakefulness in their daily lives while they're in their social and occupational settings. And in the shift work disorder study, we utilized the Karolinska Sleepiness Scale.

We also employed objective measures of performance in these studies, the Steer Clear Performance Test, or in our newer studies, the Psychomotor Vigilance Test. And in addition, we employed the assessment of quality of life, functional status, and diary data to assess the extent to which Provigil improved excessive sleepiness or affected aspects of their daily lives that might be impacted by excessive sleepiness.

Now, throughout the presentation, I will show you data from not all but a variety of these tests. On these slides in which I have data points, I have p values only on those tests, where appropriate, that were either primary efficacy analyses or prespecified secondary analyses.

I'll start with a review of some of the data from our original narcolepsy program. This is important to do for two reasons, the first of which is that we utilized the results of this program as the foundation upon which we built the rest of the program. So the results of these studies were used to predict the results of our subsequent studies in OSA and shift work sleep disorder.

Secondly, as Dr. Roth described and as Dr. Russell described, this disorder, narcolepsy, excessive sleepiness associated with narcolepsy, is included here in our current proposal as our representative disorder of those patients who present with excessive sleepiness associated with sleep-wake dysregulation.

Again, I'll just highlight for you here that in the narcolepsy studies, studies 301 and 302, the primary outcome measures were the MWT and the CGI-C, and that all patients met objective criteria for physiologic sleepiness as indicated by an MSLT score of no greater than 8 minutes.

You can see here that the severity of their

excessive sleepiness and the degree of excessive sleepiness at baseline were balanced across the treatment condition. These individuals demonstrated at baseline, as we would predict because of their disorder, severe excessive sleepiness as indicated by mean MWT sleep latencies of approximately 6 minutes and mean MSLT scores of approximately 3 minutes at baseline.

Similarly, these individuals were judged by their independent clinical raters to be, for the most part, at least moderately ill with respect to their overall clinical condition, and in fact, between 75 and 85 percent approximately were rated as at least moderately ill on this category.

The sleepiness markedly interfered or severely interfered with their activities of daily living and their social and occupational settings can be seen here by a mean Epworth Sleepiness Scale that is of the highest that have been reported. 24 is the highest on this scale. So clearly, these individuals had at baseline a difficulty, a substantial difficulty in maintaining wakefulness.

Again, these individuals also demonstrated at baseline significant sleep disruption as evidenced by a greater than 30 minutes of wakefulness in their sleep episode.

You can see here the results of our first co-

primary endpoint at final visit for the MWT. Provigil significantly increased the ability of these patients to maintain wakefulness on this task. I'll remind you that statistical significance here is based upon the change from baseline for each of the active groups compared to the change from baseline in placebo. The nearly 3-minute increase or the 3-minute difference between active and placebo demonstrated in study 301 was nearly identical in study 302.

The independent raters of overall clinical condition also judged and were able to recognize the improvement in sleepiness. Here statistical significance is based upon the distribution, as I said, of the treatment groups across these seven categories, and that Provigil significantly improved these patients' overall clinical condition can be highlighted by the percent of patients who were rated as much or very much improved at the final visit in the active groups compared to the majority of patients who were rated in the placebo group as having not changed. Again, these results were remarkably consistent in study 302, highlighting the fact that the independent raters judged these individuals to be predominantly at least minimally improved and more so in the active groups to be much or very much improved.

That these individuals were able to recognize

that sleepiness and demonstrate by their subjective assessment of their sleepiness that Provigil was improving their wakefulness in their daily lives can be seen here by a significant reduction at the final visit in the mean Epworth Sleepiness Scale score, strongly suggesting that Provigil treatment significantly improved their ability to maintain wakefulness in their daily lives.

Provigil treatment was also associated with an improvement in performance in this case on the Steer Clear Performance Task as denoted by a reduction in the percent of objects hit while they were performing this task. This effect, similar in study 302, did in fact achieve statistical significance in our second study in narcolepsy.

Here I'm going to show you just some of the diary data that we had collected in this study and, in fact, the most important data with respect to the degree to which sleepiness affected these individuals' daily lives. Now, in narcolepsy patients, unlike in other patients, and in fact, thankfully, unlike in most patients, on a daily basis they, as most of you know, can and often do experience unintended sleep episodes if not unintentional naps. If you look at those patients who experienced unintended or undesired sleep episodes at baseline and look by diary data at the percent reduction, you can see that between 33 and 38 percent in study 301 experienced a

reduction in the percentage of unintended sleep episodes and a nearly 50 percent, approximately 50 percent decrease in these unintended sleep episodes in study 302.

So to summarize our effects in narcolepsy, Provigil significantly improved wakefulness as evidenced by the objective measure of physiologic sleepiness, the MWT; significantly improved overall clinical condition as assessed by the CGI-C and as specifically highlighted by the higher percent of patients who reported to be very much or much improved. Provigil improvements were supported by the results of the secondary outcome measures that demonstrated improvements in MSLT in their ability to sustain wakefulness in their daily lives, reductions in the number of errors on the objective performance test, and a reduction in the unintended sleep episodes by sleep diary. And again, similar results were seen in this study between the 200 and 400 milligram treatment groups.

As you recall, residual excessive sleepiness associated with OSA is the disorder that we chose to be representative for those individuals who report with excessive sleepiness associated primarily with sleep disruption.

Just to take a few moments to talk about excessive sleepiness in OSA, of course, the primary treatment for obstructive sleep apnea is nasal CPAP or some

similar mechanical device designed to treat the underlying sleep-disordered breathing. In fact, as Dr. Roth described, it is well accepted in the sleep and pulmonary communities and, indeed, the medical communities that treatment of this underlying disruption can lead to important and clinically significant improvements in alertness or wakefulness as evidenced by a reduction in the amount of sleepiness in their daily lives, as measured by the ESS, or just as we've done in narcolepsy, an increase in the MSLT.

As Dr. Roth described, a recent meta-analysis of every study that's been reported on the effects of CPAP on excessive sleepiness shows that a combined MSLT and MWT difference on treatment from placebo in most cases or in many cases is about a 0.93 minute change in objective sleep latency and that these improvements, not all in the same studies -- CPAP improvement is indeed associated with a slightly less, about a 2.9 decrease in the mean Epworth Sleepiness Scale score.

Despite the clear clinical benefit in reducing excessive sleepiness associated with nasal CPAP, some patients, despite regular use of this therapy, still experience excessive sleepiness. The CPAP therapy fails to fully resolve these symptoms. And this residual excessive sleepiness has been associated and can be associated with

moderate impairment in social and occupational function.

In study 303, I'll remind you that we assessed a 200 and 400 milligram dose of Provigil and utilized again, like narcolepsy, the MWT and the CGI-C as our co-primary endpoints. All patients met formal criteria for a diagnosis of obstructive sleep apnea syndrome and demonstrated residual excessive sleepiness as indicated by an Epworth Sleepiness Scale score of greater than or equal to 10.

Importantly, these individuals had to demonstrate in nocturnal polysomnography that their CPAPs were indeed effective as operationalized by an apnea-hypopnea index while on treatment. An apnea-hypopnea, for those of you who may need reminding, is simply just the number of apneas or hypopneas, the number of sleep disordered respiratory events, per hour. So while on treatment, their apnea-hypopnea index had to be less 10 and had to have demonstrated at least a 50 percent reduction or improvement in their sleep-related breathing disorder compared to historic AHIs.

We also stratified in this study according to CPAP use at baseline as assessed nightly on a minute-by-minute basis for approximately 2 weeks prior to the study. That stratification was based upon in the literature the prespecified definition of regular use, which as Dr. Katz

rightly pointed out, is greater than or equal to 4 hours per night on approximately 5 nights or more. Partial users were simply those individuals who were using their CPAP but not for the amount of time that would quite meet the formal criteria for regular use.

Originally 18 patients were enrolled into the trial who demonstrated no use on their CPAP at all. But importantly, upon discussion with our advisors and upon further reflection, we made the decision to amend the protocol to exclude those individuals who were not using their CPAP. We did this because of the importance of CPAP in treating the underlying pathology and in the ongoing clinical difficulty in the sleep community about CPAP compliance. Those 18 individuals are not presented in the efficacy data that I'll show you in a minute, but are presented in the safety data that Dr. Niebler will be describing for you soon.

At baseline you can see approximately an equal number of patients were randomized to each of the treatment groups. There was a low withdrawal rate due to adverse events. However, I'll highlight indeed a higher withdrawal rate due to adverse events in the Provigil treatment groups.

The treatment groups were balanced with respect to age and race. More males than females were enrolled

into the 200 milligram group. However, I'll point out for you that we looked at this in our statistical analyses and found it to have no effect on our efficacy analyses.

Like in narcolepsy, the severity of excessive sleepiness and the degree of sleep disruption was balanced across the treatment condition. Unlike in narcolepsy, however, these individuals did not, as we would expect based upon the fact that they were being partially treated, they were having residual sleepiness and not sleepiness -- we found that these individuals had moderate excessive sleepiness at baseline as indicated by a mean MWT of approximately 13 minutes.

About 65 percent or so of these individuals were judged to be at least moderately ill in overall clinical condition by their clinicians, and the patients themselves rated approximately a 16 on the Epworth Sleepiness Scale, suggesting that there was a moderate, at least a moderate, impairment in their ability to maintain wakefulness at baseline while performing daily activities.

As in the other study, these individuals did still demonstrate significant sleep disruption as indicated by a greater than 30 minutes of wakefulness within their sleep episode.

Finally, I'll highlight for you that these individuals, although the criteria for inclusion in the

study maximally could have been the greater than 4 hours per night on 5 nights, the mean average use was very high and well above the national average. So these individuals were using their CPAPs on average about 6 hours per night, which is quite high if you look at the literature.

Provigil treatment was associated with significant improvement in wakefulness on the objective measure of physiologic sleepiness. Again, I'll remind you that statistical significance was based upon the change from baseline in the active groups compared to the change in baseline in the placebo group.

As in narcolepsy, clinicians not only noticed the change, but significantly rated these individuals as having statistical and clinical significance in overall clinical condition, as denoted by the shift in the two active treatment arms towards the at least minimally improved category and highlighted by the greater number of patients who were rated as at least much or very much improved in the active groups compared to the majority of patients again who were rated as having no change in the placebo group.

As in narcolepsy, still, these individuals were able to recognize that Provigil was improving their wakefulness and indeed demonstrated on the Epworth Sleepiness Scale that Provigil improved their ability to

maintain wakefulness in their daily lives as denoted by statistically significant reduction in the mean Epworth Sleepiness Scale score at final visit.

Now, in this test, we used the Psychomotor Vigilance Test not only in this study but in the subsequent studies. As you may know, the narcolepsy studies were done in the early to mid-'90s, and at this time, the Psychomotor Vigilance Test had clearly replaced the Steer Clear Performance Test as the gold standard assessment in the sleep community of performance.

The PVT is a very boring task I'll highlight for you. One just simply watches a computer monitor for 10 minutes and waits for a stimulus to occur. Once it occurs, they just press a button as quickly as they can. Now, you and I should be able to press this button in approximately 250 milliseconds, probably on average maybe 300 milliseconds as a high, and we should be able to perform this 10-minute task with about 1 lapse. A lapse is defined as responding or failing to respond to the stimulus within 500 milliseconds and typically either in the best case represents a lapse of attention, or in the worst case represents a micro-sleep episode or an unintended sleep episode.

You can see that the two active groups were unequal at baseline. However, statistical significance was

achieved in both groups, and more importantly both groups represent approximately a 50 percent decrease in the number of lapses.

So to summarize our results in study 303, Provigil significantly improved wakefulness as assessed by the objective measure, improved overall clinical condition, significantly improved wakefulness as assessed by secondary outcome measures, and again as in narcolepsy, similar results were seen for the 200 and the 400 milligram dose.

In our additional 4-week study in these patients, we used the Epworth Sleepiness Scale score as the primary outcome measure, but notably included an objective measure of physiologic sleepiness, the MSLT, and of course, the CGI-C.

The patient population was very similar in that they all had a diagnosis of OSA. All demonstrated residual excessive sleepiness. All had to demonstrate that their CPAPs, when they were being used, were effective in treating their underlying sleep-disordered breathing, but this study only included those individuals who were regularly using their CPAP.

As in the three previous studies I showed you, Provigil was associated with significant improvement in these patients' ability to maintain wakefulness in their daily lives as denoted by statistically significant

reductions in the mean Epworth Sleepiness Scale score at the final visit.

And Provigil was associated with significant increases at the final visit in the latency to fall asleep on the Mean Sleep Latency Test.

And the clinicians rated statistically significant improvements in overall clinical condition, although I'll point out for you that in this study alone, of all the studies I'll show you, statistical significance was driven primarily by the increase in the percentage of patients who were rated as at least minimally improved compared to those patients, the vast majority of whom, were rated as having at least no change in the placebo condition.

So here again, in our second study of OSA, we found very similar results to study 303, suggesting that Provigil significantly improves wakefulness on objective measures of physiologic sleepiness. This improvement in wakefulness is recognized both by the clinicians and by the patients.

In the last study I'll show you today, I'll highlight for you the results of what you may recall is our representative disorder of those patients who present with excessive sleepiness associated with primarily circadian misalignment. But I'll spend just a few moments talking

about the differences between shift work and shift work sleep disorder.

Approximately 20 million Americans work nonstandard schedules. It could be arbitrarily defined between the hours of 7:00 a.m. and 7:00 p.m. Many of these individuals would change their work schedule if they could, as denoted by a recent study that was done by Dr. Ohayon.

Working nonstandard hours has, for many, many decades, been associated with increased morbidity, most notably excessive sleepiness and insomnia. In fact, approximately 2 to 5 percent report a sleep-related difficulty associated with working nonstandard hours, and these individuals have, in many instances, been shown to have significantly increased risk for errors, lapses of attention, near misses, and accidents, particularly during the commute home. This risk has been recently reported to be significantly greater in those patients with a formal diagnosis of a circadian rhythm sleep disorder or shift work sleep disorder. But it's important to recognize that while all patients with shift work sleep disorder are shift workers, not all shift workers have shift work sleep disorder.

The highest assessment of the prevalence of shift work sleep disorder has recently been published in a very rigorous way assessing the minimal diagnostic

criteria, and in this study, Dr. Ohayon found that approximately 19 percent of individuals working the night shift report moderate to severe excessive sleepiness, and approximately 23 percent of these individuals would meet minimal criteria for shift work sleep disorder.

But what is shift work sleep disorder? Shift work sleep disorder is simply a circadian rhythm-related sleep disorder in which the primary complaint is either insomnia or excessive sleepiness. I've highlighted excessive sleepiness because this is what we're here to talk about. The primary symptom is temporally associated with working the night shift and that simply means that on their days off, they're not excessively sleepy.

PSG and MSLT demonstrate loss of normal sleep-wake pattern. That's just a very roundabout way of saying that when you assess their sleep during the daytime by daytime polysomnography, you see significant sleep disruption, and when you assess their sleepiness at night by the MSLT, you see significant sleepiness. These individuals, of course, have no other mental, neurologic, or psychiatric condition nor have another sleep disorder.

In our study, I'll highlight for you that we assessed the effects of a 200 milligram dose administered 30 to 60 minutes prior to their work shift on those nights that they worked the night shift. The primary outcome

measure for the physiologic sleepiness was the MSLT, and we also included, of course, as our co-primary the CGI-C. The MSLT was included in this study primarily because of the predominance of evidence in the literature validating the MSLT assessment of sleepiness at night at the time that we designed the trial, and because this was the very first clinical trial of this nature done in patients with shift work sleep disorder, we wanted to choose the most conservative of the two objective measures of physiologic sleepiness, both with respect to the predominance of evidence in the literature, but also with respect to modafinil's effects.

We also included the Karolinska Sleepiness Scale for very similar reasons as our subjective measure of sleepiness. The Karolinska Sleepiness Scale is the predominant scale of excessive sleepiness used in occupational medicine and in occupational settings and has been widely validated in assessing sleepiness subjectively across the day and particularly at night.

With the important help of the FDA -- thank you -- and with our advisors here, we took great pains to design a trial that would allow individuals an opportunity to adapt to their night shift but still include patients who, despite that opportunity, met very rigorous definition and formal criteria for shift work sleep disorder. In

doing that, these individuals were either fixed-night workers or rotating night workers who had to work at least 5 nights a month, not individuals who just simply worked 1 night every 3 months and were sleepy. They had to work at least 5 nights per month. We originally stratified by the number of nights that they worked, between 5 and 10 nights or greater than 10 nights. At least 3 of these nights had to be consecutive, and the work shifts themselves had to be no greater than 12 hours with at least 6 of those hours falling in between the nighttime hours, as we defined, 10:00 p.m. to 8:00 a.m.

All individuals met formal criteria for a diagnosis of shift work sleep disorder, but also reported excessive sleepiness for at least 3 months, so they clearly had the opportunity to adjust, if they would have, to working this schedule.

In addition to these, we had the independent clinician raters judge them to be at least moderately ill with respect to excessive sleepiness on their work nights and including the commute home.

And finally, all patients met objective criteria for excessive sleepiness as indicated by a mean sleep latency of no greater than 6 minutes and objective measure of disrupted sleep during the daytime, as indicated by no greater than 87.5 percent of sleep efficiency.

I'll take a moment to describe the clinic visits because they were somewhat more complex given the nature of how we assessed sleepiness. The clinic visits occurred on the first night immediately following their final night of working the work shift. So if they had a work week that was 3 nights long, then this clinic visit would occur on night 4. If it was 5 nights long, the clinic visit would be on night 6.

The clinic visits began with a dose of Provigil administered at 10:00 p.m., with objective measurements beginning and continuing throughout the night, beginning about 3 hours after. The MSLT was done between 2:00 a.m. and 8:00 a.m. every 2 hours, as is standardized. PVT was done between 1:00 and 7:00 a.m., with the Karolinska Sleepiness Scale being done hourly just before each of those.

Importantly, the CGI-C assessments were done after the last MSLT but prior to the daytime sleep episode in which we assessed at the final visit polysomnographically their daytime sleep which occurred between 10:00 a.m. and 6:00 p.m.

A roughly equal number of patients were enrolled into each of the treatment groups, and again, there was a low discontinuation rate due to adverse events, approximately equal between the two treatments. Again, the

two treatment groups were balanced with respect to age, gender, and race.

As in our previous trials, the severity of excessive sleepiness and degree of sleep disruption was balanced across the two treatments and unlike in those patients with residual excessive sleepiness in OSA and in fact more so, at least at the time that we looked, than the patients with narcolepsy. These individuals were, as you can see by the highlighting here, significantly and severely sleepy as evidenced by a mean MSLT of approximately 2 minutes.

The clinicians rated them also to be moderately to severely ill, as indicated by the approximately 50 percent of the patients who were rated as at least markedly ill in overall clinical condition. And again, these patients could recognize this sleepiness and rated it themselves as moderately to severely ill on the Karolinska Sleepiness Scale score.

Now, because of the nature of the disorder, these individuals did, indeed, have a greater degree of sleep disruption, which has been characterized many, many times and as Dr. Roth described, as a consequence of the misalignment that they are living under.

Provigil significantly improved wakefulness on the MSLT test at final visit, as indicated by significant

increases in the mean sleep latency of this test, and these effects and the Provigil treatment was judged by the clinicians as having significantly improved their overall clinical condition, as indicated by a greater number of patients shifted to the improved category in the active group and as highlighted by the greater percentage of patients who were rated as much or very much improved in overall clinical condition.

As in our other trials, these data provide strong support for the clinical significance of this treatment, as do the data from our secondary outcome measures. Shown here is the improvement in subjective sleepiness at the final visit on the Karolinska Sleepiness Scale and the improvement in lapses from the Psychomotor Vigilance Test again at the final visit. Here you can see that we employed a 20-minute test, not a 10-minute test, which is one of the reasons why these individuals, along with their greater impairment compared to the OSA patients, were having at baseline greater than 1 lapse per minute. That Provigil significantly improved performance in this task can seen by -- again I'll highlight statistical significance was based upon the improvement in the active group compared to what was a worsening in the placebo group, and that the difference between these two groups at final visit represents about 10 lapses. So in fact

Provigil treatment on this task was associated with approximately 1 less lapse every 2 minutes.

We also measured subjective sleepiness by use of electronic diaries assessed every 2 hours during the night shift and during the commute home, not during the home, rather, but for the commute home. You can see that Provigil was associated with a reduction in subjective sleepiness while they were at work on the night shift, as well as a reduction, using the same scale we used in the clinic, of their sleepiness during the commute home.

If one looks at the percent of patients who reported at least one mistake, near miss, or accident during the night shift throughout the treatment period, you can see that there was a reduction in the percent of patients who reported at least one of these events throughout the entire treatment period for the night shift and about a 15 percent reduction in the percent of patients who reported an unintended sleep episode during the night shift.

Similarly, there was a reduction in the percent of patients who reported a mistake, near miss, or accident during the commute home, as well as approximately a 9 percent reduction in the percent of patients who reported at least one unintended sleep episode during the commute home.

So to summarize our shift work sleep disorder data, again, as in our other models, we demonstrated consistent and significant improvements in objective measures of physiologic sleepiness using, in this case, the MSLT gold standard measure of objective sleepiness. Provigil treatment was recognized by the clinicians and judged to have been associated with improvements in overall clinical condition. Provigil treatment also in our secondary outcome measures was associated with improvements in subjective sleepiness, improvements in performance, and importantly, improvements in subjective sleepiness in their social and occupational settings.

So I've talked about within each disorder the effects of Provigil on wakefulness on most of the measures that we've used. Now I want to spend just a few moments summarizing the effects of Provigil across these disorders.

What's shown for you here are the MWT data in those studies in which we assessed the MWT, and notably in each of these studies, it was a primary endpoint. I've included a lot of the data, but what I want to highlight for you is that in all instances statistical significance was reached in each of these studies for both doses and in the far right-hand column, if you compare the difference on active, the net difference from placebo, what you see is in the narcolepsy studies, between a 2.7- and 3.0-minute

change, and in the additional study in which this assessment was done in OSA, between a 2.6- and a 2.7-net minute change.

If you look at the data in which we utilized the Multiple Sleep Latency Test, you see very similar effects. Again, statistical significance was reached in nearly all cases except for the 200 milligram group in which there was a trend but didn't reach statistical significance in our original narcolepsy program. And if you look at the net difference in the far right-hand column, the variability in treatment effect outside and across these disorders were in fact less than the variability within narcolepsy. So in narcolepsy, the net difference was between .7 minutes and 1.4 minutes, while in OSA and shift work sleep disorder, we demonstrated a 1.2-net minute change and a 1.4-net minute change, respectively.

If one looks at the overall clinical condition, you can see up here the percent of patients who were rated as at least minimally improved in overall clinical condition, which clearly shows a consistent improvement in the percent of individuals who the clinicians could recognize the treatment and judged this treatment to be clinically important.

You can also notice the remarkable similarity

in the percent of patients who were judged to be at least minimally improved in placebo.

Again, I'll highlight for you that in all studies except one, there was a striking effect for those individuals who were rated as at least much or very much improved in their overall clinical condition.

If you look at the Epworth Sleepiness Scale score, finally, the subjective measure that at least in OSA and in narcolepsy represents a quite face-valid assessment of the extent to which these individuals are able to maintain wakefulness in their daily lives, you can see again remarkable consistency in the effects where Provigil treatment is associated here with significant reductions in the Epworth Sleepiness Scale score and quite consistent across those two disorders in which we employed this measure.

Plotting on the same scale -- and again, this is a different scale I'll highlight -- you can see that the effect size was quite similar for the subjective scale that we employed in our other measure of excessive sleepiness associated with disorders of sleep and wakefulness, shift work sleep disorder.

So, in summary, Provigil significantly improved wakefulness in patients with narcolepsy, obstructive sleep apnea, and shift work sleep disorder.

Provigil improvements were judged by the clinicians to be recognized and clinically significant as indicated by significant improvements in overall clinical condition.

Too, the patients were able to recognize this improvement and judged that Provigil was associated with a significant improvement in their ability to maintain wakefulness in their daily lives.

And finally, despite the differences in the pathophysiology associated with these three disorders, Provigil consistently improved wakefulness across these disorders of excessive sleepiness associated with sleep and wakefulness.

I'd like to thank you for your time and your attention, and I'd like to turn the podium over to Dr. Wendy Niebler who will be describing our safety data.

DR. NIEBLER: Good morning.

Dr. Roth and Dr. Hughes have highlighted for you the commonality of the symptom of excessive sleepiness across the disorders of sleep and wakefulness, as well as the consistency of the wake-promoting effects of Provigil in three representative disorders of sleep and wakefulness, specifically narcolepsy, OSA, and shift work sleep disorder. I will now show you the safety data for Provigil.

As you have heard, Provigil has been approved to treat the symptom of excessive sleepiness associated with narcolepsy since 1998 in the United States and is actually approved in 27 countries worldwide. Extensive worldwide experience and clinical trial data have shown us that Provigil is well tolerated.

The key message that I want to leave you with today is that the safety profile of Provigil treatment for the symptom of excessive sleepiness associated with OSA and shift work sleep disorder is the same and in some cases better than the safety profile already outlined in the current Provigil package insert, with no new safety concerns identified. Therefore, because the safety profile is so consistent across the three representative disorders studied, it is reasonable to conclude that the safety profile can be generalized to the other disorders of sleep and wakefulness.

During the clinical development program, a significant number of patients and subjects have received Provigil. As highlighted for you here, over 1,000 patients have received Provigil for at least 6 months, over 700 for at least 1 year, and over 300 for at least 2 years in clinical studies. I want to point out that there has been long-term exposure to Provigil in all three of the representative disorders. This safety presentation

includes information on over 480 narcoleptics, over 160 patients with OSA, and 90 patients with shift work sleep disorder who have been treated with Provigil for at least 12 months in clinical studies. Of note, the open-label treatment extension of the shift work sleep disorder study 305 is still ongoing, and as of the end of August, actually over 120 patients with shift work sleep disorder have been treated with Provigil for at least 1 year. Altogether, there have been over 2,000 patient treatment-years in clinical studies.

For the purpose of the safety review for this supplemental NDA, studies were grouped into populations and data integrated. I will now walk you through these study groupings.

The briefing document provided details on the six principal studies across the three representative disorders of sleep and wakefulness. The number of patients who received Provigil or placebo within each disorder is presented for you here. As you have heard earlier, these studies ranged between 4 and 12 weeks in length.

The integrated population of the six principal studies includes almost 1,000 patients who have been treated with Provigil and almost 600 who have been treated with placebo. This population was referred to as the principal studies in the briefing document.

When the long-term, open-label extensions of the six principal studies, as well as a few additional supportive studies in narcolepsy and OSA, are added to the data from the principal studies, an expanded population that includes information on over 2,100 patients is created. This population was referred to in the briefing document as all narcolepsy, OSA, and shift work sleep disorder studies.

With the addition of data from studies done in other therapeutic areas, as well as pharmacology studies to the previous group, we create a population that contains information on nearly 3,800 adult patients and subjects treated with Provigil. This population was referred to as "all studies" in the briefing document.

The last two populations include patients treated with Provigil in clinical trials for well over 2 years. The studies by disorders and the integrated principal studies population form the basis of this presentation because of the availability of comparator arms.

Over the next three slides, I will review the adverse event profile, the serious adverse events, and the adverse events leading to study withdrawal from the principal studies and highlight the similarities between the disorders.

Presented here is the adverse event profile for the treatment of excessive sleepiness associated with narcolepsy from the current Provigil label. The adverse events can be conceptualized as occurring in two clinical areas, those related to the central nervous system, such as headache, nervousness, and dizziness, and those related to the gastrointestinal system, such as nausea, diarrhea, and anorexia. Headache and nausea are the most common adverse events, and other adverse events occur at a low frequency.

The important point here is that with the addition of the adverse event profiles from the OSA and shift work sleep disorder studies, the overall type and incidence of adverse events seen in OSA and shift work sleep disorder patients treated with Provigil are similar to those seen in narcolepsy patients treated with Provigil. Headache and nausea are the most common adverse events in both of these disorders with Provigil treatment as was seen in narcolepsy.

The incidence of headache actually declined in the OSA and shift work sleep disorder population, and this is not surprising because an association between headaches and narcolepsy is well established in the literature.

Over 90 percent of the adverse events were judged by the investigators to be mild to moderate in severity and most of the adverse events occurred within the

first month of treatment for all three of the disorders.

Presented here is the serious adverse event profile by body system seen with Provigil treatment for the currently approved indication of excessive sleepiness associated with narcolepsy. Serious adverse events occurred at a low rate, and there were no trends as to the types of serious adverse events.

With the addition of the data from the OSA and shift work sleep disorder studies, you can see that serious adverse events occurred at a low frequency of 2 percent or less in these disorders as well. As with narcolepsy, there were no trends or patterns as to the types of serious adverse events seen within each disorder or between the disorders. The only serious adverse event that occurred in all three disorders with Provigil treatment was chest pain which is included as part of body as a whole on this slide and was reported in 1 patient each with narcolepsy, OSA, and shift work sleep disorder out of 934 Provigil-treated patients. Of note, there were no deaths in the principal studies in any of the disorders.

Adverse events leading to withdrawal can be examined in a similar manner. Specific adverse events leading to withdrawal occurred at a low rate in narcolepsy. The most frequent reason for withdrawal that was at a higher incidence in the Provigil group than in the placebo

group was headache, which is included as part of body as a whole on this slide.

Similarly, in patients with OSA and shift work sleep disorder, there was no predominance of any one adverse event leading to withdrawal from the study. As with narcolepsy, headache was one of the most common reasons for study withdrawal both in patients with OSA and shift work sleep disorder. However, again like narcolepsy, it was the cause for withdrawal infrequently, specifically in only 3 percent of OSA patients and 2 percent of patients with shift work sleep disorder.

The other most common adverse event leading to withdrawal in patients with OSA was dizziness and in patients with shift work sleep disorder was insomnia, each reported in 2 percent of patients. These are included as part of the nervous body system on this slide.

I have now demonstrated for you that Provigil was well tolerated when compared to placebo treatment across the principal studies which, as you will recall, were up to 12 weeks in length.

Since many of these disorders are chronic in nature, I want to now show you the adverse event profile of Provigil when it was administered over a 1-year period.

Longer-term treatment with Provigil for excessive sleepiness associated with narcolepsy did not

reveal patterns of adverse events different from that in the principal studies, and the incidence did not significantly change compared to the principal studies. Over the first year of treatment with Provigil, headache remained the most common adverse event. In general, the adverse events occurred early in treatment except for infection which occurred at a steady rate throughout the year.

When the adverse event profiles seen in the first year of treatment from the OSA and shift work sleep disorder studies are added, you can see that the type and incidence of adverse events are similar to narcolepsy over the same time period, as well as similar to what was seen in the principal studies.

In addition, as I mentioned earlier, studies in this supplemental NDA were integrated into expanded populations that included patients treated for well over 2 years with Provigil. The adverse event profile seen in these populations is similar to that already outlined for you and Provigil continued to be well tolerated with longer treatment.

Across all the studies with Provigil, again with some of them involving years of treatment, a total of 13 deaths have been reported. All of these deaths were considered unrelated to Provigil treatment. No trends were

seen in the cause of death, and no deaths occurred in patients with OSA or shift work sleep disorder.

On the next slide now I will summarize the lack of clinically relevant changes on vital signs, ECGs, and laboratory measures seen with Provigil treatment.

In the clinical studies, there were no changes in vital signs or ECGs including intervals with Provigil treatment. No changes in laboratory values were seen with Provigil treatment except for alkaline phosphatase and GGT variables. Mean values for alkaline phosphatase and GGT showed small increases with increasing duration of exposure to Provigil. However, few patients had elevations outside of the normal range, and there were no effects seen on other liver function tests. An important point here is that all of these results are similar to those already described in the current Provigil label.

To end this section of the safety presentation, I want to show you the adverse event profile from the principal studies integrated across all three disorders of sleep and wakefulness. As discussed, the type and incidence of adverse events was similar between the disorders studied and there was no concerning trend within any disorder or between disorders with regard to serious adverse events or adverse events leading to withdrawal. Therefore, it was felt that the adverse events for Provigil

could be integrated as a way of presenting the adverse event profile across the disorders of sleep and wakefulness.

When the current Provigil label for the treatment of excessive sleepiness associated with narcolepsy is shown next to the integrated profile, it is possible to see the similarities between the two. Both the types and incidence of adverse events are comparable between the two profiles. Headache and nausea remain the two most common adverse events, but the incidence of headache is actually less in the new integrated profile. As in the current label, other adverse events occurred at a low frequency in the profile from the integrated principal studies.

The next several slides will now focus on specific topics of interest with regard to the use of Provigil in the disorders studied. In this section, I will review for you Provigil's effect on blood pressure in patients with residual excessive sleepiness associated with OSA, nasal CPAP use in patients with residual excessive sleepiness associated with OSA, and sleep when sleep is desired.

I mentioned earlier that there was no effect on vital signs with Provigil treatment. However, I want to specifically highlight the lack of effect of Provigil on

blood pressure in patients with OSA because OSA is known to be an independent risk factor for hypertension, and you may recall from the briefing document that an adverse event of hypertension was reported in a few patients in the OSA study.

Blood pressure was obtained at each visit during the principal studies, and the mean systolic and diastolic blood pressure over time is presented for you here for the two principal studies in OSA. As you can see, blood pressure did not change during the studies with Provigil treatment.

Besides evaluating the mean changes, it is useful to look for specific changes. The percentage of OSA patients with a clinically significant change in blood pressure at final visit in the clinical studies is presented here. A clinically significant change was defined as either systolic blood pressure of at least 140 millimeters of mercury or a diastolic blood pressure of at least 90 millimeters of mercury and a greater than 10 percent increase. As you can see, the percent of patients with a clinically significant change is comparable between the Provigil and placebo treatment groups.

As you have heard, as part of managing excessive sleepiness, the treatment of the underlying disorder should be optimized and the treatment for

excessive sleepiness should not interfere with the primary treatment. In the case of patients with OSA, as you have heard, nasal CPAP is considered the primary treatment. Because of this, I want to highlight for you the lack of effect of Provigil on nasal CPAP use in patients with residual excessive sleepiness associated with OSA.

The results of nasal CPAP use seen during the principal OSA studies are presented for you here. Study 303, the 12-week study, is on the left and study 402, the 4-week study, is on the right. Hours of nasal CPAP use are presented on the y axis. As you can see, nasal CPAP use was high at baseline, above the national average of 4 to 6 hours per night, and that level of use was maintained throughout both studies.

It is well established in the literature that nasal CPAP use decreases over time, and if you are wondering what happened to nasal CPAP use with long-term Provigil treatment, here are the results from the 1-year long-term treatment extension of OSA study 303. Presented here are patients who completed the study with mean nasal CPAP use for the same group of patients presented for each interval of time. There was a small decrement in mean nasal CPAP use over the first 9 months and none after that. Of note, the decline in nasal CPAP use is similar to that reported in the literature and mean use over the year of

treatment remained well above the average nightly use of 4 to 6 hours established in the literature.

Next I will show you the lack of effect of Provigil on sleep when sleep is desired. As you will recall, Dr. Roth mentioned that a wake-promoting agent should not adversely affect sleep when sleep is desired. You may also recall from the briefing document and earlier in my presentation that insomnia was reported as an adverse event in a few patients in the Provigil clinical studies. In the clinical studies, polysomnograms were conducted at night in patients with narcolepsy and OSA and during the daytime in patients with shift work sleep disorder to objectively assess whether Provigil treatment adversely affected sleep when sleep was desired.

One measure of disturbed sleep from the PSG is sleep efficiency which is the percent of time in bed spent asleep and which is presented for you here with narcolepsy studies across the top and OSA and shift work sleep disorder studies across the bottom. As you can see, there was no change in sleep efficiency in any of the three disorders with Provigil treatment.

Another measure of disturbed sleep from the PSG is the time awake after sleep onset, which is presented for you here with narcolepsy studies again across the top and OSA and shift work sleep disorder studies across the

bottom. As you can see, there was no deleterious effect on the patient's ability to stay asleep in any of the disorders with Provigil treatment.

I want to further highlight the lack of effect on sleep when sleep is desired, specifically in patients with shift work sleep disorder, because as many of you know, these patients have difficulty sleeping during the daytime. Therefore, besides assessing sleep with daytime PSGs, subjective evaluation of daytime sleep was undertaken in the shift work sleep disorder studies with the use of diaries.

Of specific interest in these patients is whether nighttime administration of Provigil led to patients spending less time in bed during the day, and this data is presented for you here. As you can see, Provigil treatment did not lead to a decrease in the amount of time patients spent in bed during the day after working night shifts. These data all support the conclusion that there appears to be no adverse effect on sleep when sleep is desired with Provigil treatment for any of the disorders of sleep and wakefulness.

I want to end the safety presentation by briefly highlighting for you the data collected through pharmacovigilance surveillance since the approval of Provigil. As I mentioned earlier, Provigil is approved in

27 countries worldwide. Nearly a quarter million patient treatment-years have occurred with Provigil since the first approval through February of this year. Postmarketing adverse drug reactions have been reported with a low frequency similar to adverse events in the clinical studies. Also consistent with the clinical studies, the most common postmarketing adverse drug reactions reported have been headache and nausea. These results from real-world use validate the safety profile from the clinical studies that I have presented to you today.

So, in summary, Provigil has been extensively evaluated and Provigil is well tolerated.

In the clinical studies, Provigil treatment did not result in any clinically relevant changes in laboratory measures, ECGs, or vital signs, did not interfere with nasal CPAP use in patients with residual excessive sleepiness associated with obstructive sleep apnea, and did not interfere with sleep when sleep was desired in any disorder.

The safety profile of Provigil for the treatment of excessive sleepiness associated with OSA and shift work sleep disorder is the same as the safety profile in the currently approved Provigil label for narcolepsy with no new safety concerns identified.

Lastly and most importantly, because the safety

profile of Provigil is so favorable and consistent across the three disorders studied, we can conclude that Provigil will be well tolerated for the treatment of excessive sleepiness associated with other disorders of sleep and wakefulness.

Thank you for your time, and Dr. Russell will now provide concluding remarks.

DR. RUSSELL: Thank you, Dr. Niebler.

So, in summary, what you have heard today from Dr. Roth and Dr. Hughes is that excessive sleepiness is a prominent and disabling symptom of disorders of sleep and wakefulness and that narcolepsy, obstructive sleep apnea, and shift work sleep disorder are representative disorders of sleep and wakefulness which have excessive sleepiness as a primary complaint. In clinical studies conducted with Provigil, Provigil treatment significantly and consistently improved wakefulness across the disorders and across both objective and subjective efficacy measures.

The safety profile of Provigil was comparable across all disorders studied with no population-specific safety concerns noted. And importantly, the safety profile of the expanded patient population is comparable to the safety profile in the current Provigil label with no new trends emerging.

So, in conclusion, Provigil is consistently

effective and well tolerated, and therefore the treatment effect of Provigil can, we believe, be generalized to disorders of sleep and wakefulness. And therefore, Provigil should be indicated to improve wakefulness in patients with excessive sleepiness associated with disorders of sleep wakefulness.

Thank you for your attention and we're now happy to take questions, but before doing that, I just would like to highlight that we have several advisors sitting with us who would be happy to answer questions too.

DR. KAWAS: Thank you very much, Dr. Russell and the company.

The floor is now open for questions to the sponsor.

DR. AZARNOFF: In view of one of the questions, I wonder if either in the protocol or in discussions with the FDA a clinically significant difference in the endpoints was determined.

DR. RUSSELL: Sorry. I didn't quite catch that question.

DR. AZARNOFF: Was there a definitive decision in the protocol stating that so much change was clinically significant or was a discussion with the FDA done in which a clinically significant endpoint was determined?

DR. RUSSELL: The discussion with the FDA

revolved largely around the use of two primary outcome measures for all of the populations studied. They wanted us to include an objective measure of sleep latency, so either the MWT or the MSLT, and a clinical measure, which was the CGI-C. Those were largely the discussions that took place around endpoints.

DR. KAWAS: Dr. Katz?

DR. KATZ: Yes. I just want to ask a question related to the fundamental issue that we are particularly concerned about which has to do with how we know that the disorders studied actually are representative of the various categories that have been created and in which they presumably are the most common. And of course, the next critical question is how do you know that the drug is going to work the same in those. So I don't know whether or not you want to have that discussion now, but I thought maybe we could ask the sponsor.

The categories you've created are constructs, and for that matter, the pathophysiology, the description, the sleep drive, the circadian drive, the wake propensity, these are concepts that have been developed or constructed or created. They don't necessarily, I don't believe, represent actual truth, and there are ways that people have tried to understand these conditions. The pathophysiology of these categories or even of the specific conditions you

studied, let alone the ones that weren't studied, isn't known with certainty, is it? I think that's probably a fair statement.

So what allows us to conclude, other than the fact that there is an assertion that the pathophysiology is the same within a particular category, reliably that in fact these diseases are interchangeable within a given category? And how do I know that if the drug works in shift work that it must, perforce, work in jet lag? Again, the pathophysiology, the etiology of these things are all not known completely, and so I'm wondering how we make that leap. We could either talk about that now or --

DR. RUSSELL: Dr. Czeisler?

DR. CZEISLER: Thank you very much, Dr. Katz.

The question about these constructs that you've raised and the question about the pathophysiology, you've said that they don't necessarily represent actual truth. While that may be literally correct, there has been extensive work on looking at the pathophysiology and the concepts that Dr. Roth talked about in terms of length of prior waking, in terms of the duration of the nightly sleep episode and the buildup of the sleep drive and the sleep load versus the impact of circadian phase that have been formalized into mathematical models. And these mathematical models have been reviewed at a series of

international workshops that began first in Switzerland, continued with the workshop that we sponsored at Harvard, and most recently with a workshop that was sponsored by NASA and organized by Dr. Dinges.

At those workshops, these models that Dr. Roth described of this physiologic and pathophysiologic system have been subjected to rigorous comparisons with data from laboratory investigations. The model that Dr. Roth showed of these different factors and specifically the way that they interact to drive changes in sleepiness and sleep tendency have been validated by those kinds of studies in direct comparison with the predicted results from the model. I don't exactly know what actual truth is, but in comparison with the results of carefully conducted trials, those constructs that Dr. Roth presented have been systematically validated.

The way they interact to produce disease has also been studied in laboratory investigations in which, for example, the interruptions of sleep that are associated with sleep apnea have been simulated even in individuals who don't have sleep apnea but whose sleep is similarly interrupted, producing similar levels of increased sleep tendency.

With respect to the way circadian misalignment interacts with both acute and chronic sleep deprivation,

those have also been systematically investigated by recreating what occurs in the clinical situation in the laboratory and demonstrating the same kinds of deficits.

So in every way that we know how to investigate these conditions, what we understand about them is that they go through this final common pathway to produce excessive sleepiness in the manner that Dr. Roth described.

DR. KATZ: And those studies have been done -- I'm not exactly sure I understand what those studies are -- in all of the disorders that are subsumed under these various categories, let's say, circadian misalignment -- I forget the other two. So there have been studies done? Let's say in circadian misalignment, there's a number of -- I forget how many entities are subsumed under that. Six or seven or eight, whatever it was. There have been the studies of the sort you're describing that have demonstrated, in quotes, a similar final common pathway for all of those?

DR. CZEISLER: Yes, that's true, Dr. Katz. If we look, for example, at the category of circadian misalignment and we look at each of the specific disorders that are associated with circadian misalignment, these have each been systematically investigated in not just one or two, but hundreds of laboratory studies in which delayed sleep phase syndrome has been simulated by shifting, even

in individuals who don't have delayed sleep phase syndrome, their sleep to the same phase relationship that a patient would have with delayed sleep phase syndrome with respect to the output of their circadian pacemaker. And the same kinds of symptoms can be created in normal healthy individuals without this complaint simply be recreating the misalignment of circadian phase that was illustrated in the slides that Dr. Roth gave. Importantly, in patients with delayed sleep phase or advanced sleep phase or non-24-hour sleep-wake syndrome by changing the timing of their sleep-wake schedule, with respect to known markers of the output of the circadian pacemaker, all of their symptoms can be completely resolved.

So, for example, if you take a patient -- and this has been done in laboratory studies -- with non-24-hour sleep-wake schedule and put them in an environment where the period of the timing of their sleep-wake schedule, instead of being 24 hours, is put on a schedule so that it is consistent with the period of the circadian pacemaker that they are exhibiting on the outside world, their clinical condition goes away. So we can take patients and have taken patients with delayed sleep phase syndrome, shifted the timing of their sleep in the laboratory, had them sleep at a properly aligned phase relationship to their output of their circadian pacemaker,

and again the clinical condition goes away.

So we believe that we do understand the pathophysiology of these disorders and that shift work sleep disorder is representative of these conditions and produces, through the same final common pathway, the symptoms that are observed of excessive sleepiness.

DR. KAWAS: I need to understand this a little bit better, Dr. Czeisler, because I do agree this is a crucial point today.

While I certainly understand that all those people might be sleepy and while I also understand that you can put people in the lab and do things to make them sleepy, what I still don't completely understand is how you know from mathematical modeling or systematic studies, which are the terms you keep using, how that tells us that all of these people will respond equivalently to treating their sleepiness in the same way.

DR. CZEISLER: My understanding of the question that Dr. Katz asked originally was taking these heuristic models that Dr. Roth presented, how do we know that these models of the system represent the final pathophysiologic pathways to produce excessive sleepiness. What I said or tried to say was that the mathematical models that have been developed have systematically investigated by, for example, to answer your question, changing the duration

chronically of nightly sleep episodes, shifting the phase of sleep episodes with respect to the time at which they ordinarily occur, and through investigations of that nature have tested mathematical models, a series of different ones, that have been proposed. We have been working on the development of these models for over two decades in our own group, and the model that Dr. Roth presented is consistent with the best of the models and consistent with models in which there is consensus worldwide among investigators at many different institutions looking into this question that it is an interaction between increasing sleep drive that is associated with length of time awake. So just as we all learn when we were children, the longer that you're awake, the greater will be the drive for sleep, this increasing homeostatic sleep drive. That is one important factor that has to be considered in determining how sleepy we are.

The second is how long we sleep at night because this restorative value of sleep reduces homeostatic sleep drive when we are asleep if the sleep is consolidated and not interrupted, as it is, for example, hundreds of times per night potentially in sleep apnea, but if you are able to maintain consolidated sleep without interruption, then the increasing homeostatic sleep drive should dissipate when you are asleep.

And the third principal interacting factor is

this circadian drive for wakefulness, and it is the circadian drive for wakefulness that helps us to maintain a consolidated bout of waking throughout the day because unlike other mammals, we don't take little rat naps and cat naps throughout day and night. We have a consolidated bout of waking and a consolidated bout of sleep.

The way that is achieved is by the interaction of two opponent processes, and those two opponent processes are illustrated here. The circadian system has its maximal drive for waking just before we go to sleep at night, which is paradoxical, and its maximal drive for sleep just before we wake up in the morning. That opposes what would otherwise be an increasing drive for sleep that occurs during the daytime, as we are awake for an extended number of hours, and it is that interaction that allows us to maintain a relatively stable level of wake propensity in the normal consolidated waking day.

But this interacting system is fragile so that if we don't get the restorative sleep that we need at night, this doesn't decline, and then you begin the next day, as Dr. Roth said, with an increased homeostatic drive for sleep which drives down your wake propensity and leads to excessive sleepiness. If you have sleep that is too short during the night, the same thing happens. If you have it shifted, the same thing happens.

DR. KAWAS: Okay. You got me more than halfway there. I now have a better appreciation of the mathematics of that model and how the balance is relevant for the outcome of sleepiness.

So now the part I need to better understand, though, is how do I know? That's a mathematical model as opposed to physiologic disease processes because we're not talking about normal sleepiness now. We're talking about disease. So how do I know that if an individual has excessive sleepiness because something is wrong with the sleep drive, the blue lines up there, that they will respond equally and equivalently and just as well as somebody who has a problem with the yellow lines? That is, their pathology is in the circadian drive for wakefulness. How do I know that a drug will work on a disease no matter how it's affecting the left side?

DR. CZEISLER: So the model has been tested by simulating the pathologies in the laboratory and showing that it produces a similar level of increased sleep drive. Some models can't be tested in the laboratory that way. For example, narcolepsy, because that is a disorder of sleep-wake regulation that can't be simulated by recreating the abnormalities of the hypocretin producing neurons in the brain.

In each of those clinical instances, clinical

studies, such as the ones that Cephalon has presented here, have been conducted in which predictions of the impact of modafinil have been evaluated, and the outcome in each of those clinical conditions is consistent with a reduction in either homeostatic sleep drive or the adverse impact of misalignment of the circadian phase that is consistent with a common mechanism.

If we could show slide 30, as Dr. Roth pointed out, the drive for wakefulness that is coming to the cortex from these hypothalamic regions -- modafinil, by a mechanism that is not completely understood, as Dr. Roth pointed out, increases that drive for wakefulness and helps to overcome the excessive sleepiness that is produced in each of these three different categories of sleep disorders by what we think is a common mechanism.

DR. KAWAS: We think it's a common mechanism, again, because of this mathematical modeling --

DR. CZEISLER: No.

DR. KAWAS: -- or because of some other reason I'm missing here?

DR. CZEISLER: We think that it's a common mechanism because of what is known about, as Dr. Roth pointed out, modafinil increasing the drive from these hypothalamic areas that produces cortical arousal.

DR. KAWAS: And you would then predict, if a

patient's problem has nothing to do with reduced wakefulness drive, but rather has to do with excessive sleepiness drive, that the drug still should work equivalently in the same effect size?

I mean, to bring it down to a different level, to explain my confusion, obesity, for example, is either because you eat too much or you exercise too little or you have a thyroid problem or whatever. But a drug to suppress appetite will only work presumably in the people who have obesity on the basis of increased appetite, not on somebody who has it on the basis of thyroid dysfunction or whatever.

DR. CZEISLER: Right.

DR. KAWAS: So I'm trying to understand to what extent we understand that the mechanisms really are the same in these disorders.

DR. ROTH: I'm just going to repeat what was said. Basically, there are two questions. One, what are the units within each one, and then how do they go to the same thing? How does modafinil then work?

How the units work, very simply as I tried to show and as Dr. Czeisler just pointed out, those groups, for example, sleep-related breathing disorders, periodic leg movements -- it's very clear if you fragment sleep, whether that's due to leg movements, whether that's due to respiratory events -- and in both of those instances

clinically, there are publications which show that the degree of sleepiness is directly correlated with the degree of sleepiness. So there is a one-to-one relationship with that.

Similarly, if I experimentally do that -- as Dr. Czeisler said, Dr. Bonnet has published that; our laboratory has published that -- you then increase sleepiness in a normal individual. If you decrease arousal in an apnea patient, in the leg movement patient, or in that experimental situation, you get rid of that sleepiness. So these systems -- Dr. Czeisler said that very elegantly in the area of circadian rhythm disorders.

You know, again, one of the things that's very important is what is the reality of these categories fitting together. Well, they fit together because they're exactly one-to-one with what the ICSD has. You have circadian rhythm disorders. We call them misalignment. They're called neurological sleep disorders. We call them sleep-wake dysregulation. The only thing we collapse are these sleep-related movement disorders and respiratory disorders. So very clearly, they all fit into that category.

Now, what do those three have in common? I think, again, what we just pointed out. What they have in common is the major output of the SCN, the major output of

all the hypothalamic areas is to produce cortical activation. All of these disorders decrease cortical activation.

What modafinil does -- again, this data comes from Jouvet -- in terms of where it does it, it does it at the hypothalamus. But also very good imaging data that shows that regardless of the cause, if you give modafinil, you wind up with greater activation of cortical activity. So they all lead up to cortical activity. That's what the final effect of modafinil is on cortical activity.

So you're absolutely right. There are 15 different ways you get up there, but you wind up in the same place, a decrease in cortical activation, and that's what you're treating.

DR. KAWAS: Yes, please. Dr. Krahn and then Dr. Mignot.

DR. KRAHN: I'd appreciate it if you'd comment on the choice of sleep diaries, subjective data, for assessing total sleep time in patients with shift work sleep disorder. One issue is whether people will voluntarily restrict their sleep even though they may have the capacity to sleep when having access to an alerting agent for a condition like that.

DR. RUSSELL: I think that's why we looked specifically at the total time in bed, and so if they were

taking a wake-promoting drug, would they therefore say, oh, I don't need to go to bed anymore during the day in the shift work sleep disorder population. I think what Dr. Niebler showed you is that that really wasn't the case. Despite taking modafinil, or Provigil, they actually spent the same amount of time in bed that they did before, highly suggesting that they weren't neglecting the time in bed because they were taking the drug, and that's depicted for you here again.

DR. KRAHN: My concern is that that's subjective data based on the participant's self-report, and that's the issue I'd like to just hear more about.

DR. RUSSELL: This is from diaries, so yes, it's their self-report.

What we also did was daytime polysomnograms at the end of the study where they had a fixed time in bed, and that was where the sleep parameters, in terms of sleep efficiency, and wake after sleep onset were shown from.

DR. MIGNOT: I have two small questions. One of them was regarding the adverse events leading to stopping the treatment in the sleep apnea group. It looks like there were more people stopping treatment in the sleep apnea group than in other groups due to adverse events. I was wondering, it looked like the profile of the effect of the drug was slightly different in that group. I was

wondering if you can comment on that in terms of dizziness or --

DR. RUSSELL: The actual overall adverse event profile was pretty similar in the obstructive sleep apnea patients, specifically the adverse events leading to withdrawal, as outlined by body system here. The profile is kind of the same. Perhaps there's a little bit more in the nervous system. If I could have the breakdown of the actual OSA adverse events, I'll be able to show you that.

DR. MIGNOT: These are body as a whole, for example.

DR. RUSSELL: Body as a whole includes a number of adverse events, and I just need to get you the actual adverse events leading to withdrawal.

DR. MIGNOT: And the other question -- maybe during that time you can answer -- I had was regarding restless leg syndrome, obviously another cause of sleep disruption that's fairly common. I think in your presentation, you're indeed touching the three main areas of sleep medicine, but another very common sleep disorder is indeed periodic leg movements during sleep or restless legs syndrome. Obviously, I'm sure you had some data in terms of leg movements in your population because it's fairly common.

I know the data in narcolepsy because I've

looked at it when it was published. With modafinil, there was no effect, I think, on leg movements during sleep in patients with narcolepsy that have also periodic leg movements. But I'm wondering what happened in these other groups. I'm sure you looked at that.

DR. RUSSELL: Just like in narcolepsy, we saw really no incidence of increased leg movements when it was looked at by PSG.

DR. KAWAS: Are you concluded, Dr. Mignot? Do you have the ASEs waiting for right now, or should we go on to another question while you're looking?

DR. RUSSELL: Can I have the actual adverse events leading to withdrawal please? I'm sorry. They're just getting it. I'm sorry for the delay.

These are the actual adverse events that led to withdrawal in the OSA studies. As you can see, the actual numbers for each particular adverse event are really pretty small, and similar to those that we've identified in the other programs as adverse events that may lead to withdrawal.

DR. MIGNOT: Thank you.

DR. KAWAS: Dr. Temple?

DR. TEMPLE: You've made the case that the normal attempts to sleep in all of these conditions are not adversely affected, but they're also not improved. If a

shift worker has trouble getting a good night's sleep, this doesn't change that, right, because the total sleep was about the same in both cases?

DR. RUSSELL: That's correct.

DR. TEMPLE: So if I were to say the only thing you need to postulate is that this stimulates your drive for wakefulness and there's no reason to presume anything else, would there be something wrong with that conclusion?

I ask that because that's not an unfamiliar property of drugs, as you probably can see me I'm trying to make sure of this morning. It seems to me that's probably the best basis for your argument, that whenever whatever is going on, whether it's apnea, shift work, or narcolepsy, and you might add, sleep deprivation, if you take this stuff at the time you want to stay awake, it probably helps you stay awake, not unlike coffee, but maybe better than coffee and without as much tachycardia or something.

DR. RUSSELL: That's certainly our conclusion.

DR. TEMPLE: Okay. Now, why doesn't it keep you awake at night? Is that a pharmacokinetic thing? Is the effect of the drug gone by that time? I probably should remember this from the original submission, but I don't. There are all these tests of wakefulness and things like that. I presume that by the time it's time to go to bed, the drug isn't having an effect on those things. You

don't have increased sleep latency, and is that just simply because the drug is gone?

DR. RUSSELL: Yes, pretty much so. From the pharmacokinetic parameters we can say that you've fallen well below the plasma level of modafinil required for wakefulness by the time you go to bed.

DR. TEMPLE: Presumably if you took this at the wrong time and you got screwed up and took it just before bed, that would probably not be a good thing.

DR. RUSSELL: That's probably not a good thing to do.

DR. TEMPLE: I noticed in the shift work thing, you take it before you go to work or just before. So that's right at the time you want to do it. Well, with narcolepsy, you take it in the morning I suppose.

DR. RUSSELL: Yes.

DR. KAWAS: Dr. Ebert?

DR. EBERT: Just a follow-up related to the pharmacology of the drug. Most of the studies, of course, have used long-term therapies in patients with persistent problems. Is there evidence that the drug works after just one or two doses in activating the cortex so that if you were going to use it, for example, on a time zone change syndrome where you might only need to take this for 1 or 2 days, that its onset would be rapid enough that it would

work in that circumstance?

DR. RUSSELL: I'd like to ask Dr. Dinges to answer that because he specifically looked at this.

DR. DINGES: I'm David Dinges from the University of Pennsylvania.

We have done laboratory studies on how rapidly the drug affects people who are performing, as well as recording EEG, et cetera, and the effect is very rapid. It's certainly within an hour and actually even shorter than that. You begin to see benefits from it. By 2 hours, it looks like it's up at whatever you're going to get and then it sustains for its half-life of about 12 hours.

DR. KAWAS: Just for my information, can you tell me what kind of study you did to show the effect in an hour?

DR. DINGES: These were studies in which healthy adults were kept in a laboratory for 10 days in double-blind placebo-controlled trials, were given the medication at different times or given placebo at different times, and the placebo group always got placebo, and were being tested on test bouts, and had EEG continuously recorded and a series of other biological markers, cardiovascular, et cetera, and blood levels for key hormones, catecholamines, et cetera, in part because we were interested in how this drug compared to caffeine and

some other substances we had studied.

DR. KAWAS: And the specific outcome that showed a difference between placebo and --

DR. DINGES: Some of those that you saw here, as well as others. So the lapses on the psychomotor vigilance task, cognitive throughput on the digit symbol substitution task, mental arithmetic performance, all showed fairly rapid responses. Critically important are the number of lapses drop off dramatically if the drug is given to someone who's healthy but sleep-deprived.

Obviously, if you give it to people before they're sleep-deprived and they're otherwise healthy, you don't see anything at all in the performance. There's no additional improvement in performance. It looks pretty much like they looked in the placebo group. There's no fundamental difference.

DR. KAWAS: So those studies were done in sleep-deprived people, but most people on jet lag aren't necessarily sleep-deprived. They're just trying to sleep at a completely different time and wake at a completely different time. So can you relate your results to the jet lag issue for us?

DR. DINGES: Well, as Dr. Czeisler said, this heuristic model -- it's true that in jet lag you're trying to be awake at a time your brain is trying to go to sleep

and vice versa in that sense, but because the circadian system also influences sleep duration, you can actually build up a sleep debt in jet lag as well, and it's really both of those things. That's really why the slide showed the two together. It's the two processes interacting in the neurobiology that sort of determined the cortical level of capability, the ability to sustain the wakefulness, et cetera.

In fact, just to be thorough, we do studies. We've run more than 100 people where we flip their circadian time. We simulate jet lag and shift work and have them live chronically on that. We, in fact, do that in the laboratory as well where we'll give the sleep during the day and keep them up at night, and we've looked at this. Again, you get pretty much an immediate, within an hour response in neurobehavioral functioning if there is sleep pressure in the system or if they're at an adverse circadian phase.

DR. RUSSELL: I think Dr. Jim Walsh has also got a comment on this aspect too.

DR. WALSH: This is Jim Walsh from St. Louis.

Let me just add that we did a study of simulated shift work, the first night or two of which you could call simulated jet lag. We used the PVT, the MWT, the Karolinska scale and compared in a double-blind,

placebo-controlled fashion at night from approximately 11:00 p.m. at night to approximately 7:00 a.m. in the morning and showed robust differences between modafinil 200 milligrams and placebo all night long and in fact for 5 successive nights.

DR. KAWAS: Dr. Kattah?

DR. KATTAH: I want to explore a little further the presence of headache in these patients. If you look at the studies 303 and 402, the incidence on modafinil of headache was about twofold that of the baseline. These patients, because of the body habitus, obesity and so forth, are propensed to have pseudotumor cerebri, and I wonder if you can tell us more about the nature of the headache. You showed a slide saying that not many withdrew from the trial because of the headache, but it makes me wonder. In all the other groups, although headache is present, it's not as much as the patients with sleep apnea. You have 25 percent of 292 patients; whereas, the placebo was 12 percent of 188 patients.

DR. RUSSELL: We have looked at headache. The incidence is as you describe. Very generally, the headaches are mild to moderate in severity, start early on in the course of treatment, and are of short duration. So they go away with continued dosing. This is the same across the treatment groups.

DR. KAWAS: Dr. Katz?

DR. KATZ: Yes. I just want to go back to the fundamental approach that we're dealing with here today. I just want to make explicit, in particular for the new committee members and our guests who will be voting, how this situation differs in part in a very fundamental way from what we ordinarily do.

Typically when we approve a drug, it's for a specific disease or a symptom of a disease in that one setting and we're very empirically driven. If the patients are better on the drug compared to placebo for that particular condition, Parkinson's, epilepsy, whatever it is, we approve the drug. We don't usually have or perhaps we never have a complete understanding of the pathophysiology of the disease and we certainly never have a complete understanding of all the possible mechanisms of action of the drug. We just know that the patients were better. We rarely are in a position to extrapolate beyond the condition that was studied. So if you study a drug in patients with Parkinson's disease, for that matter, we make distinctions between early and late Parkinson's disease. If it works, we say it works. It's indicated for that condition.

Here, obviously, there's empirical data. They've studied several different settings and the drug has

been shown to be effective I believe. But we're being asked to do something else as well. We're being asked to extrapolate those results beyond the conditions studied. As I said before and as you're hearing, typically when you do that -- it doesn't happen that often, but when we do that, we have to pretty much believe we understand the pathophysiology of the disease and the mechanism of action of the drug so that we can predict with a reasonable high level of certainty that the drug is going to work in those situations in which it has not yet been studied. Those are predictions and we usually don't make those sorts of predictions and we usually don't have that kind of detailed understanding about the pathophysiology or the mechanism of action of the drug, as I said.

So this is unusual. It's certainly not that it can't be done, and it's been done in the past. But we have to acknowledge explicitly the fundamentally different approach we're being asked to take here. You may find, of course, that the argument has been made, that the case has been made that we really do understand the pathophysiology at least of the symptom of excessive sleepiness across this universe of disorders and we understand enough about how the drug works to be able to say, oh, yes, it's going to work in all these conditions that have not yet been empirically studied. But I think it's important to get on

the table the fundamentally distinct nature of the question we're being asked compared to what we usually ask.

DR. TEMPLE: It's worth thinking about some of the cases where we do at least seem to treat a symptom or a condition that has many origins. As everybody knows, we ask people to study a few pain models, and then you get a general pain indication. However, not everybody agrees on what the right models are, and not all pains are the same. Nobody thinks migraine is the same as other pains, and it turns out menstrual pain, menstrual cramps don't exactly track perfectly either. So even within probably the most established place where we treat a symptom, there's at least a little bit to worry about, although maybe not that much.

Another example actually is all the cases where we treat a surrogate like blood pressure. Well, we just ask that a drug be shown to lower blood pressure. We don't ask what the origin of the blood pressure is, but there are members of the hypertension community, probably a minority, who think we're all wrong and that drugs should be targeted toward whether you're high renin or low renin and a bunch of other things like that. So even in a well-established place like that, there's at least some potential debate, although nonetheless, we still do it.

And then we treat elevated cholesterols and we

don't actually care what your enzyme deficiency is whether you over-eat. Well, we do care. We say you should try lifestyle alterations, and then after they fail, you treat them.

(Laughter.)

DR. TEMPLE: Yet, within that category, there are a lot of different reasons for having an elevated LDL cholesterol.

So there are some cases, and I think as Russ says, is this one of those cases where that's reasonable or is it not? That's really the issue. But there's some precedent for all of those things.

DR. KAWAS: Dr. Wolinsky.

DR. WOLINSKY: Yes. There are a couple of questions I'd like to be educated on. One of them actually has to do with side effects. You've shown us a lot about the side effects that occur in patients who are exposed to the drug and, for that matter, for patients who are exposed to this drug for quite a long period of time.

What I'd like to know is whether or not there have been any studies or data that you can share with us about what might happen to sleep-wake cycles or excessive daytime sleepiness in either patients or individuals who have been on the drug for X period of days, months, or years and then stop it.

DR. RUSSELL: That has been specifically looked at in a couple of studies. One was a study done in Canada, a double-blind, placebo-controlled study, where they had an open-label extension of 16 weeks and then randomized discontinuation at the end of the study. What happened during the discontinuation of the drug was that no adverse effects in terms of side effects, but they went back to their normal level of sleepiness that they experienced before they went on that study.

In addition, we had done a double-blind withdrawal phase in one of the narcolepsy studies, and I have the data here which again shows during the withdrawal phase -- this was done in a double-blind fashion -- that those patients who withdraw from the drug revert back to their original level of sleepiness.

DR. WOLINSKY: So I guess I'm a little bit less concerned about whether or not patients -- "patients" -- and I'm going to be very specific with at least the way I think I'm using that term -- revert back to their primary target symptoms and I guess you're showing me without rebound.

DR. RUSSELL: That's correct.

DR. WOLINSKY: Now I'd like to know about people and what happens to their problem complex.

DR. RUSSELL: In terms of --

DR. WOLINSKY: Let me go for a little bit more background. In this model that's been presented, at least the kind of clinician I am, I think that your Venn diagrams define two categories which include within them groups of patients with pathophysiologic disorders which we do or do not understand fully, but I think most of us would agree they have something that's out of the normal physiology. Then there's another part of the diagram which represents something that can happen to anyone depending upon what they've done tomorrow going to England or going to work tomorrow night or whatever it is. Within that, there is a spectrum of response to that shift of circadian rhythm. So I'm not sure I consider this to be a pathophysiologic mechanism, but rather a shift on the normal physiology.

So I'm particularly concerned about people who might be using this medication for their perceived problems and whether or not that would in any way accentuate the problems either with continued chronic use or with withdrawal from that chronic use. I think the question perhaps is resonating with some of the experts. So perhaps you could give us some insight into that.

DR. RUSSELL: Dr. Roth?

DR. ROTH: I think that's a very important distinction that I may have failed to make. But again, we're not talking about shift work. The numbers from

Professor Ohayon's study was that 23 percent of those people who do shift work wind up with that condition, and why do they wind up with the condition? Because they wind up with the symptom of insomnia or excessive sleepiness. So again, not everybody. The minority of people. The majority of people, as you point out, make that circadian adjustment very, very well, or at least well enough not to be symptomatic.

So the answer to the first part of your question, which I think is outstanding, is it's not a variant on physiology. It is a variant on some vulnerability not to adjust in that 23 percent of the population. It would be very nice if we can sort of figure out prospectively what is that vulnerability. We don't know the answer to that.

But getting relevant to the question you asked in the second part of your question, in all of these situations the discontinuation of medication did not lead across studies to take the medication more frequently across the 12 weeks, nor did it lead to a discontinuation syndrome where you wind up with the PSG on the last night being significantly worse than it was. So, one, medication usage didn't change, and two, PSG didn't change.

Very much like Ohayon's data, by the way, which I'm not sure was presented, of the people who volunteered

for the study, only about a third met diagnostic criteria to get into the study. So it was a very large number of people who answered the ad. First screening, and then of those people who came into the laboratory with their criteria. So again, it's not shift work. It's somewhere about 15 to 25 percent. Again, those are the people who sort of take it as the need it, don't escalate it, and don't have withdrawal syndromes.

DR. KAWAS: Then can I ask, regarding that vulnerability that you mentioned, do we know that's a biological vulnerability or is that an environmental difference? Particularly, in light of the fact that you planned on bringing in individuals that had both chronic and intermittent shift work and yet you ended up almost completely with chronic shift workers, does that mean that there's some difference between those two people in terms of all these things we're talking about?

DR. RUSSELL: Dr. Dinges first and --

DR. KAWAS: I would have thought that an intermittent shift worker would -- why did they not end up in the study I guess is what I'm trying to figure out.

DR. RUSSELL: There are two questions here. I think Dr. Czeisler should answer the one about the intermittent versus permanent night shift worker, which is one of your questions.

DR. DINGES: Well, let me just say briefly regarding the biological vulnerability, we've been studying this trying to understand why people have such literally an order of magnitude, a 10-fold greater difference, in response to being kept up at night. What we found fairly consistently now -- and this is NIH-supported work -- is the interclass correlations when you repeatedly look at these people are very, very high, on the order of .8, .9. In other words, this is trait vulnerability. It looks very biologic. It's very stable. We don't understand. We're still looking for predictors. We're trying to understand where does this begin in life. Are you born with it, et cetera? It may be modified by development; that is to say, as you get older, we don't know if that characteristic diminishes or gets worse. But this is a very new area of science, but it looks very biological and we have enough data now to say that with certainty.

DR. RUSSELL: If Dr. Czeisler could answer the second part of that question.

DR. CZEISLER: The distinction between what the individuals labeled themselves as to whether they were rotating shift workers or, quote/unquote, permanent night shift workers is a bit of an artificial distinction insofar as, if you could show slide 768, the rotating night shift workers, quote/unquote, worked an average of 10 nights per

month on overnight shifts, whereas the, quote/unquote, permanent night shift workers worked an average of 15 overnight shifts per month. So it is not as if one is working all the time at night and the other is not working all the time at night, and their distributions very significantly overlap or substantially overlap I should say. It is a matter of degree. So that's one issue.

The second issue is that the workers, even when they are working 15 nights per month, 15 nights per month they are not working at night, and we know from extensive studies of shift workers that when they are not working at night, they invert their schedule and sleep at night. So even the, quote/unquote, permanent night shift workers are rotators in the sense that on all of their days off, which is half of the days per month, they are inverting their schedule and scheduling themselves to be awake during the day and asleep at night. So all are rotators in that sense.

Then if we also look at and compare these different groups, as you can see in the upper panel to this slide, in terms of their MSLT levels, their KSS scores, and their CGI scores, you can see that the MSLT levels were comparable between the two groups, the KSS levels were comparable between the two groups, and the percentage of individuals reporting themselves as markedly severely ill

are very comparable between the two groups. So we don't see that there is any real difference between them other than their self-identified labels.

DR. KAWAS: Dr. Neubauer?

DR. NEUBAUER: I'm still wondering who these people are who are defined in the shift work study as having the shift work sleep disorder in terms of any sort of criteria. The best example of trying to define a sleep disorder would be with narcolepsy, and even there, there is some debate with some patients. And shift work sleep disorder must be at the other end of the spectrum because even the ICSD criteria are extraordinarily broad, simply saying that the patient has a primary complaint of insomnia or excessive sleepiness and that is temporally associated with the work period.

Well, that's an awful lot of people who do shift work, and Dr. Dinges tells us that he can identify certain individuals who have much greater difficulty in a laboratory setting with sleep deprivation, but how does that relate to the real-world population and those people who would be diagnosed with something called shift work sleep disorder, and how does that relate to the people that were included in this study?

DR. RUSSELL: In our study, we clearly looked at the ICSD criteria for shift work sleep disorder but

really didn't want a population that just only met the minimum criteria. They had to meet other criteria too. So that was why, in conjunction with discussions with Dr. Katz, we really wanted to make sure that these patients were not only significantly sleepy at night, so we implemented that objectively looking at an MSLT. But they really truly had objective evidence of disruptive sleep during the day, so we ran data on PSGs. So in addition to meeting the minimal criteria in terms of having a complaint of excessive sleepiness, we obviously were more interested in that component than the insomnia component there to also have some objective criteria that they were truly suffering from shift work sleep disorder too.

DR. KAWAS: Just to give us an idea of the magnitude of the clinical effect in terms that we can relate to, I note on the MSLT that the range of improvement in all the studies is from .7 minutes to 1.4 minutes. If somebody did a couple of cups of coffee, what would that be expected to result in in an MSLT?

DR. RUSSELL: Dr. Walsh? Sorry. Dr. Roth.

DR. ROTH: That's a very important question. Let me give you the direct answer to that. How many cups and whose coffee? But 600 milligrams will give you that kind of change. CPAP 6 hours a night will give you that kind of change.

One of the things that some people are perplexed by, especially in the sleep community, is how does that 1- to 2-minute change give you this dramatic clinical change. The answer to that actually comes from Dr. Krohnauer at the Brigham and Women's Hospital who has done extensive research on this. It turns out these tests of sleep tendency are psychometrically nonlinear. So that 2-minute change going from 2 to 3 is geometrically much greater than going 15 to 16.

So again, 600 milligrams of caffeine would give you just the same thing. 6-and-a-half hours of CPAP would have given you the same thing. It translates to big clinical effects probably because these tests, as Dr. Krohnauer showed, are not linear at that part of the scale.

DR. MIGNOT: If I can comment on this because I agree with what was just said. I think even though the changes look very small on both the scale and the MSLT, I think they are clinically significant. It's very well known that in narcolepsy you start from a very sleepy background and that the tests never normalize completely. I think that may be a message that's important. I think even in shift workers that take modafinil, they may not be completely normal at night taking the drug. That's another matter. But in terms of improving them substantially, I think that's not an insignificant effect.

Also the fact that two different types of approaches were used, both sleep tests like the MSLT or the MWT, and Epworth that are known to not correlate that well actually and showing efficacy on both of the objective and subjective measures I think is very reasonable.

DR. KAWAS: Dr. Wolinsky?

DR. WOLINSKY: So given those effects of caffeine, how was coffee ingestion controlled for in these studies and especially in those patients on modafinil who may have had an increased incidence of headache? When the modafinil worked, did they stop their coffee?

DR. RUSSELL: Specifically in the shift work sleep disorder study, we had an entry criteria that on a routine basis these patients shouldn't really drink more than 600 milligrams of caffeine, which equates to 100 milligrams a cup, so 6 cups of coffee during their night shift episode. In fact, actually the population that were enrolled in the study really drank only very moderate amounts of coffee. They on average drank 2 cups a night or whatever. That was the average consumption.

In the laboratory clinical assessments where the MSLTs were done, caffeine was actually controlled so that neither groups drank coffee during the nights of their assessments.

DR. KAWAS: Dr. van Belle, and then maybe after

that, we'll try and fit in a brief break because I'm sure some people would like that.

DR. van BELLE: I just have some questions about some of data presented just to make it clear to me. If I give you the page number of your overheads, can you give me the actual slide? It would be helpful.

Let's go to page 92.

DR. RUSSELL: Is that the right slide?

DR. van BELLE: Yes, that's one of them.

I see no statistical test there. So can I assume that these results were not significantly different between 200 milligrams and placebo?

DR. RUSSELL: Actually in reality the statistical tests haven't been done on the diary data, and we specifically said that in the protocol and in the statistical analysis plan that on the more exploratory endpoints, such as the diary data, statistical analyses would not be run.

DR. van BELLE: Okay, because this is one of the endpoints that has kind of practical implications in terms of the number of errors that one would make during the night shift. So that's one.

So on page 93, you haven't done that either?

DR. RUSSELL: Page 93, which would be during the commute home. No, statistical tests were not done on

this parameter either.

DR. van BELLE: Then there are a whole series of presentations starting with page 116. Again, was this prespecified that none of, for example, the CPAP use -- these tests were not done at all?

DR. RUSSELL: Statistical analysis was done on this I think during the double-blind treatment period, which you see here. There was no statistical difference between CPAP usage or --

DR. van BELLE: That also goes for page 117. There is no trend there?

DR. RUSSELL: There actually is a trend statistically here, yes.

DR. van BELLE: There was a trend, okay.

For page 118, no differences were significant?

DR. RUSSELL: These were not statistically significant.

DR. van BELLE: And 119?

DR. RUSSELL: Likewise.

DR. van BELLE: And 120?

DR. RUSSELL: This was diary data, so no statistical analysis was performed.

DR. van BELLE: Thank you.

One of the issues that I haven't heard discussed yet is a dose-response kind of issue. You had

some trials with 400 milligrams and some trials with 200 milligrams. The effects are very similar. What are your inferences with respect to the dose response aspects?

DR. RUSSELL: In terms of between 200 and 400 milligrams, as you rightly point out, there was no statistical differences between the two doses. That's correct.

DR. van BELLE: So you would recommend 200 if this were to be approved?

DR. RUSSELL: I think in our current label, as it stands at the moment for narcolepsy, 200 milligrams is the recommended dose, but it does say that 400 milligrams has been studied, has been well tolerated, but with no consistent additional benefit beyond 200.

DR. van BELLE: My last question deals with the PVT measures. I'm not sure that I have the page numbers here, but the levels in the 305 study were about four times that in the 303 and the 402 studies. Now, I understand that part of it is due to the fact that in 303 and 402, the intervals were 10 minutes, and in the 305 study, the interval was 20 minutes.

DR. RUSSELL: That's correct.

DR. van BELLE: But it still strikes me that even adjusting for that, the 305 levels are substantially higher at baseline than in the other two studies. Can you

give me some clinical explanation for that?

DR. RUSSELL: If Dr. David Dinges could answer that.

DR. DINGES: The reason I'm answering it is because my laboratory developed the PVT and we spent 15 years validating it.

There are two things to remember in answer to your question. The first is a clinical issue and that is that the MSLTs and some of the other data indicated that the shift work sleep disorder patients had a higher level of sleepiness than did the 303 apnea patients.

But there's a second point, and it's equally important. As you increase duration on the PVT, if you have sleepiness, the number of lapses increase. It's not a linear increase. It doesn't double. It goes up very dramatically. Now, you might argue, well, why not do 20-minute PVT's in every study? Because this is an onerous task to do. It's very monotonous. It demands sustained attention. It's punishing in that way. We titrated down to 10 minutes because in validity studies that's about the limit of what you can use and still get sensitivity across a range of homeostatic drive.

But one point I'd like to make about it, in case it doesn't get said. The reason that we're interested in these lapses is the sleepier you are, you have more of

these and they get longer. Now, the real-world relevance of this, the reason that we like this metric in my laboratory is driving down the highway at 60 miles an hour in a 12-foot wide lane with an 11-foot wide breakdown lane, the standard U.S. highway, at a 4 degree angle of drift, which is what drowsy driving crashes occur at, 4 to 10 degrees, you only need a 4-second lapse to be completely off the road. You need a 2-second lapse to hit the car that's broken down in the breakdown lane or less. You get the idea here that these lapses really do matter in everyday life, and the more you have of them and the longer they get, the greater risk posed to you when you're attempting to do something, particularly a vigilance-dependent task like driving.

DR. KAWAS: Thank you.

I think we should take a 15-minute break. So we'll reconvene at 11:30 with the continuation of the questions and discussion.

(Recess.)

DR. KAWAS: Thank you. We're reconvening this session of the Peripheral and Central Nervous System Advisory Committee for the FDA discussing Provigil for excessive sleepiness.

At this point, I'd like to begin the discussion of the committee on some of these issues. We've been given

two major lists from the FDA, which are partially overlapping lists, on questions that they want discussed. On one of the lists, we will be taking a formal vote on the specific questions. On the other list, we have questions for discussion that I think will actually lead very straightforwardly, hopefully, to the voting questions. So I'd like to open the floor for discussion from the committee members about some of the issues.

I want to remind you that one of the major issues involved in this committee deliberation, which is really quite different from virtually any committee that I've been a part of, is that we are talking about an indication for a symptom across a wide variety of diseases and not specifically for the treatment of a specific illness as defined in some way pathologically and clinically. So the floor is now open for anybody who would like to begin telling us some of their thoughts on this.

Our questions for discussion begin with are the selected primary endpoints, that is, the MSLT, the MWT, combined with the CGI-C, used in the two new pivotal trials, which are the trials that are for sleep apnea and shift workers, appropriate for the identification of a therapeutic effect. We're going to rely very heavily on some of our sleep experts particularly for some of these questions. So please share your thoughts with us.

DR. NEUBAUER: Well, I think certainly the MSLT and the MWT are very appropriate because these are both clinically and in research our best way to identify sleep propensity. There is some thought that, well, let's look in the real world at numbers of accidents, numbers of mistakes at work, and they're really sentinel events, which would be extremely difficult to capture in terms of an endpoint for a study. So I think that these particular standard measures are very appropriate and very familiar to us.

DR. KAWAS: And the effect size is the next question for discussion, but I think you can interject it here. The effect size in the two new pivotal trials. Do you have any thoughts on that?

DR. NEUBAUER: Well, the effect size in the change with the MWT and the MSLT I think is a very problematic issue. We've heard this morning already that 1 or 2 minutes of change in the MSLT or the MWT may be more significant than it looks like numerically and that also may be different during different ranges, that is, if somebody is going from 2 to 3 minutes on either of those tests up to something in the teens. But, nevertheless, the changes aren't big and they're still within the ranges where we would consider for people to be impaired.

DR. MIGNOT: Yes. I think I already mentioned

this earlier. I think I feel comfortable about also the MSLT and MWT. They have been used both clinically and in other drug studies and in a number of settings.

I think, indeed, I would have been not so comfortable if only the MSLT or the MWT had been used because there is increasing evidence that sleepiness is not just the MSLT or the MWT and that there is a subjective aspect to it which doesn't exactly capture the same construct. For example, there are a number of studies that have shown that the Epworth Sleepiness Scale, which reports how sleepy people feel, doesn't correlate always very, very well with the MSLT and MWT. It correlates but not as well as you may predict. But in this trial, they have used both subjective and objective measures for sleepiness, and I feel confident they reflect the outcome.

Now, in terms of the size of the effect, I think I would also agree. I think even though they look small, there is indeed, for example, meta-analysis that has looked at the effect of CPAP on sleep apnea that was done recently and shows that the effects that you get on the MSLT are indeed relatively small as well. I think that small magnitude of effect is clinically significant based on other interventions that have been used in sleep medicine.

I would, however, point out that definitely I

think these drugs do not normalize completely sleepiness in these disorders, and I think that's this indication and I think that's important to note whether it's narcolepsy or shift work, et cetera.

DR. KAWAS: Thank you, Dr. Mignot. Actually that's a very good point.

DR. NEUBAUER: If I could follow up a bit. I remain worried, though, particularly with the shift work patients that while there may be a statistically significant increase, still when we think about the MSLT, it's easy to think broadly of somebody having an average sleep latency under 10 minutes as being sleepy and somebody with an average sleep latency under 5 minutes, which would be typical with narcolepsy patients, for those people to be profoundly sleepy. And while with the modafinil, their subjects clearly did better -- they went from 2.1 to 3.8 on the MSLT -- still they're in that range of profound sleepiness, and I wonder if we would be giving them a false sense of security to think that here they're sleepy, they're taking a medication, and they're still in that range where there would be considered to be some impairment.

DR. WALSH: I'd like to address that point, if I could. The patients we studied that had a mean latency of approximately 2 minutes or so during the night shift

were individuals with shift work sleep disorder. If you look at individuals, for example, in the simulated shift work models where you don't pick them to have the shift work sleep disorder, they average in studies approximately 6 minutes or so on the night shift. So the closer we can get them to "normal," the better from my perspective. Once again, at that end of the scale, a minute-and-a-half, 2-minute, 2-and-a-half-minute improvement in the MSLT I think most of us would agree does have true clinical significance.

DR. KAWAS: Could you please give us your name and title?

DR. WALSH: Jim Walsh and I'm from St. Louis University.

DR. CZEISLER: May I also make a comment about that? Dr. Charles Czeisler from the Harvard Medical School.

I think that one of the things that's clear from what Dr. Walsh said is that these patients don't represent -- we all, if we stay up all night to work, will be sleepy, but these patients are profoundly sleepy. These patients with shift work sleep disorder are sleepier than even the narcoleptic patients. So they represent a very vulnerable subset. I think what speaks to the clinical significance of the improvement is the reduction during the

80 minutes that we tested them during the night, the reduction in the number of lapses as compared to the placebo-treated group of an average of 1 lapse every 2 minutes. These people are doing everything from driving to operating power plants and so on. If you think of the impact of somebody working all night and having a reduction in their lapses of attention on average of 1 every 2 minutes, that could be a very profound and have important safety implications as well.

DR. KAWAS: Dr. Krahn.

DR. KRAHN: I think that it is important to keep in mind the patient perspective. We have a subjective scale that's a clinician-rated one, and I hope that the patient perspective is something that's kept in this picture. I think that the endpoints used in these studies is satisfactory, but there is room for improvement in the future with just having a more direct patient report, as well as some of these other secondary endpoints we've been hearing about, perhaps being employed in future work a little bit more so.

DR. KAWAS: Thanks.

Just to focus us a little bit on question number 2 with regard to the magnitude, the agency has noted that the magnitude of change in the drug group as compared to the placebo group in the MSLT in the shift worker study

appears to be particularly small as compared to the magnitude of change in the MWT for both narcolepsy and the apnea studies. I would also point out that in regard to the apnea studies, the significance of the MWT really largely is dependent on the fact that the placebo group declined significantly in this 12-week study, generating a large part of the difference between the two groups.

So the agency has requested that we comment on this, the difference in magnitude in the different studies. Dr. Mignot?

DR. MIGNOT: Again, I want to stress that the MWT and the MSLT are measuring two different things. The MSLT is the ability of allowing yourself to sleep. You are in a dark room and it's how fast you fall asleep when you want to sleep. Whereas, the MWT is how hard, when you try not to sleep, you don't fall asleep. I think to have merged the MWT effect and the MSLT is a bit misleading in a way because I think they measure slightly different things.

In fact, in general, when you look at drug effect on the MWT, they have larger effects than on the MSLT, and a very small effect on the MSLT is much more significant and would translate in a larger effect on the MWT. In fact, you see that too in the, for example, sleep apnea studies in the meta-analysis of Dr. Patel where they have looked at the effect of CPAP treatment on MSLT and

MWT. The magnitude of the effect on sleepiness as measured on the MWT was larger than on the MSLT. I think it partially answers your question that the difference in these studies are partially due to using the MSLT versus the MWT.

DR. KAWAS: In casual observation, it looks like the difference in the two studies is about a twofold difference. You tend to get about a 2-minute change for every 1-minute change in the MSLT. Is that --

DR. MIGNOT: Yes. I have to look here, but I think indeed in that meta-analysis, it was about right.

DR. KAWAS: I also note that the 200 milligram dose in the narcolepsy 302 study is not even significant even though it's one of the largest effect sizes.

DR. WHITE: I'd just like to comment. I'm David White from the Harvard Medical. It was our meta-analysis that looked at this.

If you look at the effect size, the effect size, forgetting the placebo group, on the MSLT and MWT were bigger even on CPAP. If you get a 1-minute change on CPAP and you put on top of that a 1-and-a-half to 2-minute change that they observed with modafinil, the effect size is larger than CPAP, and you've already got the CPAP in place, which suggests to me that the effect size, although again the numbers are relatively small, is clinically

meaningful.

DR. KAWAS: Okay. That serves as a good introduction for question number 3 for discussion which has to do with CPAP.

In the pivotal sleep apnea trial, the sponsor has studied both patients who were either partially CPAP-compliant or CPAP-compliant. Most patients were in the CPAP-compliant category. We're interested in knowing if the committee agrees with the sponsor's definition of compliance. That's the first part of this question. I think we have to rely very heavily on our sleep experts here for their thoughts.

If the committee concludes that the drug is an effective treatment for patients who are fully compliant, we'll discuss where we go from there.

DR. KRAHN: The definition used by the sponsor is certainly one that's widely used. I think many clinicians feel that that degree of usage still indicates room for improvement on the part of patients. So I think there is some discomfort in general with that definition, although it is a widely used one for research studies in other settings. But that represents a lot of room for patients to use CPAP more on a single night or more consistently.

DR. KAWAS: In a previous life, I had some

sleep experience. The one thing that was very apparent to me was that CPAP is not particularly well-liked by patients in many ways. Just like we'd all rather have a pill to lose weight than exercise, I think that if patients with apnea were given the opportunity, they might not look at this as an additional therapy or an adjunctive therapy but actually as a replacement therapy.

Do our sleep experts have any thoughts on this?

DR. MIGNOT: I think my concern would be more to make sure that people that have sleep apnea know that they have sleep apnea and are treated. I think what would be more worrying is people with sleep apnea would take a drug like this without knowing they have sleep apnea.

DR. KAWAS: Right. That's a very good thought.

Yes, Dr. Krahn.

DR. KRAHN: I also believe it will be important that patients' use of CPAP be monitored so that neither clinicians nor patients forget about the importance of CPAP and its demonstrated role in reducing other things like high blood pressure. I think that would have to be emphasized and be a very important issue.

DR. KAWAS: Dr. Neubauer?

DR. NEUBAUER: I think part of the good news here is that at least looking at the studies, most of the patients were using the CPAP about 6 hours and it would be

much more worrisome if it was down around 4 hours. Clinically if a patient comes in saying, at least with evidence from their equipment, that they're just using it for 4 hours and they're complaining of sleepiness in the daytime, we're certainly going to work very hard to increase that compliance and see what we can do to have them be able to tolerate it for a longer period of time rather than turning to some other measure to maximize daytime alertness.

DR. KAWAS: But as the sponsor very appropriately and rightly pointed out to us, the individuals in the study were not typical of individuals out in the community in the number of hours per night that they actually used CPAP. In fact, they used CPAP more than we typically see.

Furthermore, as the FDA would like us to comment on, if somebody is fully compliant on CPAP, do we think that this drug is an effective treatment for them, as well as partially compliant or not compliant? Have we had enough ideas from the data we've seen to discuss this rather thorny issue?

DR. HERSHKOWITZ: Can I make a comment about that, one of those questions? The fully compliant issue has more to do with the fact that some sleep experts are of the opinion that if there's true full compliance, there

shouldn't be any sleepiness, and if there's residual sleepiness, the patient has an alternative diagnosis.

The partially compliance question has more to do with concern about -- or the noncompliance, that is, perhaps the physician isn't pushing compliance sufficient, which I think was commented by one of the panelists.

DR. KATZ: Claudia, the particular question that we've asked in this list of discussion topics related to noncompliance has to do with -- because there is so little information from the trials about how the drug works or doesn't work in noncompliant or partially compliant patients, the question is if you think it's been shown to work in sleep apnea, what can we say, if anything, about its effects in patients who aren't really very well compliant. Is it appropriate to include them in the conclusion that the drug is effective or can we not say anything about those patients, that sort of thing?

DR. KAWAS: Any thoughts from the committee on this issue? It was pointed out by the agency that stratification on the MWT efficacy data and to people who were partially compliant indicated little or no effect of Provigil. Obviously, we don't have any data at all on people who are not compliant with CPAP.

Yes.

DR. ROTH: The most relevant data is if you

look at narcolepsy, you wind up with a mean MSLT of about 2, and we saw what the effects are. Patients who are totally nonusers of CPAP will wind up with a comparable MSLT. So there's no reason to believe that the response in a nonuser will be the same.

But Dr. Katz raises an interesting question: should we say anything about that? The concern, which I think is again related to what Dr. Mignot said, is one shouldn't be using it unless one is, in fact, using the primary therapy and it's not intended as an alternative therapy.

So will it work? Yes, it will work because the level of sleepiness will be that which we see in narcolepsy, and you've seen several studies to show that it works and it's indicated for that.

Should it be used in that condition? I would have to agree with Dr. Mignot. No, it shouldn't. In other words, I think that's what we want to say is if you're not being optimally managed with CPAP therapy, then you shouldn't.

In terms of fully compliant patients, the best answer we have there is the data in children who have sleep apnea, secondary to hypertrophied tonsils and adenoids, and there after surgery their apnea goes away totally and you still get refractory symptoms. So even fully compliant,

some individuals get refractory symptoms.

DR. KAWAS: Thank you, Dr. Roth.

Dr. Mignot?

DR. MIGNOT: Yes, I would agree with that. It will work, I'm sure, and in fact it may be a bit part of the worry.

I guess in general the question is I think people need to have a sleep evaluation so that you know that these patients, if they have sleep apnea, are treated. I would be also concerned, for example, people could be concerned in the shift work area where people could have sleep apnea and being a shift worker, for example. I think it would be very important to make sure that whoever is suspected of sleep apnea is treated for the primary diagnosis before using the drug.

DR. KAWAS: That's very easy for us to say here. Do you have any suggestions, though, on how to make that actually translate into clinical practice?

DR. MIGNOT: They can be studied or there can be a screening tool.

DR. KAWAS: Dr. Wolinsky.

DR. WOLINSKY: So this is not a cottage industry for me, but it would seem that given the range of conditions that were displayed so nicely for us, that those which are disease-associated probably require chronic

therapy and those that are something that's not necessarily -- may possibly be trait-associated but also normal-conditions-of-life-associated probably don't need chronic therapy, one wonders whether or not there should be a suggestion -- I don't know what actually can go into the labeling -- that patients on chronic therapy need to be evaluated in a sleep lab.

DR. KAWAS: I think in many ways we've actually been discussing also question number 4 right now which is the gold standard of treatment for apnea is CPAP and it may ameliorate some of the secondary morbidities such as hypertension. The division is concerned that symptomatic treatment may decrease CPAP compliance, and I think that there has been some concern -- correct me if I'm wrong -- on the part of the committee that there is some truth to that.

I think there has been even more concern, if I'm hearing correctly, that individuals who need CPAP will never find out that they do because of symptomatic treatment.

Yes, Dr. Krahn.

DR. KRAHN: I think technology makes this easier. For patients who have an established diagnosis of obstructive sleep apnea, there are many more ways to monitor their compliance now than there were 10 years ago,

and I think that it's important that compliance monitors and the like be utilized to determine that they are using CPAP as much as possible before a trial of an alerting agent is added. So for the patients where the diagnosis is understood, that should be part of the recommendation.

DR. KAWAS: Most patients right now with sleep apnea, as I understand it, have not been diagnosed anyway. So when the diagnosis is not understood, it actually affects even more people than what we're concerned about in those who already have it.

I guess I don't understand completely the long-term sequelae of not diagnosing these disorders, but I am under the impression that there's concern that the long-term sequelae without diagnosis and treatment may be an issue.

Question number 5, has the sponsor adequately --

DR. WHITE: Can I comment on that last one? I don't mean to interrupt you. Sorry.

The company is not advocating just treating generic sleepiness. 80 percent of sleep apnea patients are not diagnosed. That's the current estimate on the street right now. But they don't present as shift workers or they don't generally present as shift work disorder. They don't present as narcoleptics because every narcoleptic is

diagnosed formally in the sleep laboratory or certainly should be. So for an apnea patient to simply be treated with modafinil without making the diagnosis would imply the doctor is just taking a sleepy patient and putting him on a drug to prevent sleepiness without doing any workup or evaluation whatsoever. And that is not in any way what the company is advocating relative to the use of this drug.

DR. KAWAS: Dr. Katz.

DR. KATZ: I had a question for the company about the long-term data with regard to CPAP compliance. We saw in the controlled trials, which are short, that there was no decrement in compliance. And there was sort of a histogram presented for data out to a year I think, and there was a slight decrement which was said to be consistent with what's reported in the literature about decrements over time in compliance.

But I had a question about this specific cohort that was studied. How long were patients on CPAP before they got into that long-term extension? I assume a lot of those were in the controlled trial. Do you know what the average, let's say, the mean duration of CPAP use was before the trial? I have a reason for asking that, which I'll get to.

DR. RUSSELL: All the patients who went into the open-label extension had obviously been on the double-

blind --

DR. KATZ: No, no, no. I'm asking how long had they been on CPAP before they got into the double-blind on average. Years?

DR. RUSSELL: We'd need to try and find that out.

DR. KATZ: The reason I'm asking is because I don't know the literature about long-term compliance. I assume they followed cohorts forward in time, at best I suppose. But the cohort you're following from the time that you started following them, they had already been on CPAP for years. I don't know if that's true but let's, for argument's sake, say that's true.

So what I'm trying to figure out is if you took a cohort who had already been on CPAP for years and then you followed them forward in time, would they also have a decrement in compliance? In other words, if they've been on it for years already, they've sort of declared themselves as users, let's say, and they may not have the same decrement in compliance over time as a de novo cohort followed forward from the day they started CPAP. So if that isn't too tortured.

DR. WHITE: That's a very fair and astute question actually, and there's not a lot of data on it. The longest CPAP follow-up study to date was done in

Scotland by Neal Douglas. It was a 3-year follow-up protocol. Clearly the rate of decline in CPAP use is steeper at the beginning of the time you use CPAP and flattens out over time, but even out 3 years, it was still deteriorating somewhat. Now, I've not gone back and looked at that study to see exactly how much did the deterioration out 2 or 3 years correlate with what was seen in the Provigil study, but deterioration in CPAP utilization does continue at least out 3 years, and we don't have any data longer than that.

DR. RUSSELL: Just to clarify, for the people going on the protocol, it was a minimum of 2 months. They had a diagnosis of a minimum of 2 months, but the range was actually from months to many years pre-study. So you have a real wide range of people with a diagnosis ranging back years as well.

DR. KAWAS: So the minimum was 2. The range was infinite. Do we know a mean or median or anything like that that would give us an idea of the distribution between those two points?

DR. RUSSELL: No, I'm afraid we don't.

DR. KAWAS: Has the sponsor adequately demonstrated that Provigil does not interfere with normal scheduled sleep, daytime sleep during shift work, for example, or nighttime sleep in obstructive sleep apnea?

Here I think the sponsor showed us some data along those lines. How convinced is our committee, recognizing fully that anyone who's in a study doesn't necessarily represent the real world out there in a variety of different ways, but we had some data to look at?

DR. NEUBAUER: Although the stated elimination half-life I believe is 15 hours, still it seems to be reasonable in not promoting problems with insomnia or disrupted nighttime sleep in the studies and in clinical experience with the narcolepsy patients as well.

DR. KAWAS: Finally, most patients studied in the pivotal shift worker study were permanent non-rotating shift workers. With this is mind, is it appropriate to generalize treatment to all shift workers, including rotating shift workers?

DR. MIGNOT: Based on my understanding of the interaction of the homeostat and the circadian clock mechanisms that were eloquently presented, I don't see this being a real problem personally. I don't see why the drug would be less efficacious in permanent versus temporary.

DR. NEUBAUER: I agree that it probably doesn't make too much difference in a general sense because people can be sleepy at nighttime from permanent night shift or occasional night shift or rotating schedules. It doesn't really answer the question of whether or not there is a

special population of highly sensitive individuals who have more difficulty. An awful lot of people doing rotating night work or shift work and other schedules are still going to have difficulty with sleepiness. So I think it will be hard to tell who those people are who would be most appropriate from a particular physiological vulnerability as opposed to that which all of us would experience with a rapidly changing or a slowly changing schedule.

DR. KRAHN: I do think that we have to be careful because there isn't a lot of data available about the rotating night shift worker. So although scientifically we can see the issues are fairly similar, there hasn't been a lot of data for us to look at concerning that important segment of our population. So I feel somewhat cautious about that group.

DR. KAWAS: I'm still having trouble wrapping my brain around some of this. So for me personally, the rotating shift workers really aren't problematic. I almost view them as just another version of jet lag. They intermittently try to shift into a completely new schedule. And for that matter, maybe even the jet lag people aren't that much of a concern for me.

But what does concern me still is that we're talking about treating a symptom without understanding one of the many possibilities that may lead to this symptom.

When we treat pain, we know the pain is from post-op, we know it's from dental, we know it's from whatever, and our treatment of the pain does not keep us from treating the underlying illness.

In this case, it seems to me that we've got a potentially large issue here for the majority of people getting a potentially serious symptom treated and that their underlying disease might even be exacerbated by ameliorating this symptom, just in the same way that if we treated pain in an appendix or something, we would be doing the patient a disservice in the long run.

Can I get some of the committee members to weigh in on this area for us?

DR. MIGNOT: I think the difference with pain -- and I think pain may not be the perfect example -- is that everyone experiences sleepiness, whereas not everyone experiences pain, and I think that's something to keep in mind.

DR. KAWAS: Could you take that a little step further? I mean, keeping it in mind, then what does it make you think about the whole issue? Not to put you on the spot or anything.

(Laughter.)

DR. MIGNOT: I think since everyone can experience sleepiness, the need for defining the symptoms,

evaluating the symptom is very important.

DR. KAWAS: Dr. Krahn?

DR. KRAHN: I think that because sleepiness is a normal state of being and there certainly are some people who have excessive sleepiness that's pathologic, this is going make it harder for the practicing clinician to decide when to prescribe a medication, and I think that's going to be the challenge. Many physicians don't have a lot of education in sleep medicine and they're going to be presented with patients who are sleepy, and it is going to be difficult for them to know where the threshold should be to prescribe a medication for sleepiness associated with a sleep disorder. For something like shift work sleep disorder, we have heard that that is distinct from shift work, but how possible will it be for the ordinary clinician to make that distinction? I have some concerns about that.

DR. KAWAS: Dr. Czeisler.

DR. CZEISLER: Yes. Dr. Czeisler from the Harvard Medical School.

I think that the most important thing is that physicians be educated as to the diagnosis and treatment of sleep disorders so that that primary treatment is the first step that is taken. I would draw the analogy with insomnia. This field of sleep disorders medicine has been

encouraging the education of physicians so that they treat the underlying cause of the insomnia.

But I would say that the issue that the committee has before it is not that dissimilar from the use of hypnotic medications for insomnia. In fact, I would argue that the symptom of excessive sleepiness is much more homogeneous than the symptom of insomnia with respect to what causes it. Yet, many, many different compounds have been approved and are used for the treatment of insomnia and, by the way, in shift workers. Shift workers are given hypnotic compounds because of difficulty with insomnia during the day. People are given hypnotic compounds for treatment of insomnia associated with loss of a loved one, with the situation with travel across time zones, many of the things that we are talking about, and the agency has repeatedly approved the use of compounds without requiring the specific understanding of the pathophysiology of each of the insomnia conditions.

And this is the flip side of that whole question, and it is the treatment of the symptom of excessive sleepiness which we know much more about what generates it than we do of the symptom of insomnia and which the company has demonstrated with these studies is effectively treated with modafinil.

DR. KAWAS: Thank you.

Dr. Neubauer.

DR. NEUBAUER: I agree entirely with Dr. Czeisler's comments, although I'll point out that while the hypnotics may be useful in treating insomnia and represent a fairly general treatment, with using a stimulating medication in the daytime to counter excessive sleepiness, there may be greater danger of missing what the underlying problem might be. Now, effectively educating all doctors about sleep medicine would allow them to properly diagnose people.

But if this approval for disorders of sleep and wakefulness opens up the door considerably for the range of sleep complaints that might be treated, there are many insomnia patients, for instance, who will come in complaining of being sleepy in the daytime, putting together their daytime symptoms and their nighttime symptoms, and I wonder if, fairly quickly, they may be given symptomatic treatment with a medication like Provigil without adequate evaluation as to whether or not it might be apnea. There are many patients out there who are not overweight and snoring loudly or at least have a bed partner to identify that. We see many patients coming in complaining of insomnia who turn out to have bad apnea, and of course, we're in a good position to be able to evaluate that. I would worry about somebody too quickly being given

a stimulant to treat that symptom, their being happy with the results and go on for a long period of time without effective evaluation and treatment.

DR. MIGNOT: I think the parallel with insomnia is a fairly good one. I think there are similar problems with treating insomnia patients indiscriminately. Clearly depression has been a very longstanding example of that where insomnia can just be a sign of depression, and if it's treated symptomatically, it's a catastrophe. Similarly, I think sleep apnea as well. I agree with Dr. Czeisler.

DR. KAWAS: I want to poll the committee a little bit. It's 12:15 and although normally we would break for lunch now, it looks to me like we're moving along at a rapid clip here, and I wondered if the committee would like to break for lunch of if you'd like to try and work through and see if we can get this done in a reasonable period of time and break for good.

Any thoughts, feelings? I heard one go for it. I think many people are trying to get a plane out, so I think that would be a vote in favor of continuing. Is that interpreted correctly? Okay, let's get started and see what happens then.

The questions for the advisory committee to vote on.

DR. WOLINSKY: Madam Chairman?

DR. KAWAS: Yes.

DR. WOLINSKY: Before we get into the voting questions, there's an issue that I know is bothering me and maybe some others that wasn't addressed in terms of potential toxicity for good reasons I suspect because this is a drug which is already licensed. And I didn't go back and read the package insert. So could the sponsor enlighten me about the pregnancy category for this drug and its recommendations for use in breastfeeding? Because if we go to more general use of the drug, I suspect we might have an interest in that.

DR. NEUBAUER: I wonder if we could add drug-drug interactions to that list as well.

DR. RUSSELL: It's currently listed on the package insert as a pregnancy category C and therefore, the benefit of use in pregnancy should outweigh its risks. That's how it's currently written in the label, and we don't propose that any change in that labeling should occur as a result of this potential expanded approval.

DR. NEUBAUER: So it got to category C because there was some preclinical concerns for abortogenic effect or teratogenic effect, or how did it get to C?

DR. RUSSELL: In fact, I'll ask my toxicology colleague to explain the toxicology finding.

DR. McCORMICK: Hello. My name is George McCormick. I am the Vice President of Drug Safety and Disposition with Cephalon, Incorporated.

The company received a pregnancy category C rating based on results of a segment 2 rat study, and a segment 2 study is also known as a teratology study. In this study, the pregnant animals or presumed pregnant animals are dosed during the period of organogenesis, at which time the offspring are delivered by cesarean sectioning and are examined for skeletal or soft tissue malformations.

In the study that we're referring to, there appeared to be a slight increase in the incidence of hydronephrosis, as well as a delay in the ossification of certain vertebrae in some of the offspring. I would like to note that this study was conducted under non-GLP conditions, but it was the study that was incorporated into the Provigil NDA. The pregnancy C was recommended from the agency, and we accepted that category.

However, as part of our phase IV commitment, we repeated the teratology or segment 2 studies in both species of rats and rabbits. In this study, we used significantly higher doses under GLP conditions, and in that study there was no evidence of any teratologic response in the animals.

The findings that I referred to, the hydronephrosis and the delay in ossification, are frequently referred to as developmental delays rather than true teratogenic responses. This may have an effect on the time that the offspring are taken away from the pregnant animals. Therefore, they should not be viewed as teratologic manifestations, but that is why we have the C category rating.

DR. KAWAS: Any comments on drug-drug interactions for Dr. Neubauer's question?

DR. RUSSELL: Yes. Currently written in the label, it is noted that Provigil has been shown in vitro to induce hepatic metabolizing enzymes, specifically CYP3A4, and also is a reversible inhibitor of CYP2C19, and in one study has shown in vitro to be a suppressor of 2C9. There are currently appropriately worded cautions regarding co-administration of drugs that are either CYP3A4 as a substrate, and in 2C19, it appears to be that those people who are also CYP2D6 deficient, which is roughly 7 to 10 percent of the population, if they were administered a drug that's a substrate of that enzyme, which would then use the CYP2C19 as an adjunctive pathway, may have higher levels than you would otherwise expect. So that's all worded in the label at the moment.

DR. KAWAS: For those of us who are completely

naive, can you tell us what drugs would fall in that category or give us some examples?

DR. RUSSELL: For the CYP3A4, it appears to be clinically significant interactions may occur really with those compounds that use CYP3A4 as a substrate which have high first-pass metabolism and compounds that fall into that category include things like cyclosporine.

For the CYP2D6 deficient population, which I said is around 7 to 10 percent of the population, you might be concerned about things like tricyclic antidepressants.

DR. AZARNOFF: What about MDR1 transporters in the intestines?

DR. RUSSELL: There's nothing there.

DR. KAWAS: Did that take care of your question, Dr. Neubauer? Okay.

Before we move on to the votes, we're running ahead of schedule, but the public forum, which is scheduled for 1 o'clock, we're going to try and put in next. To begin with, I need to read a statement from the agency.

Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes it's important to understand the context of an individual's presentation

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral presentation to advise the committee of financial relationships that you may have with the sponsor, its product, or if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

We have two people who have requested speaking during the public forum. The first one is Richard Gelula. Is he available? He's Executive Director of the National Sleep Foundation.

MR. GELULA: Thank you and good afternoon. My name is Richard Gelula. I'm Executive Director of the National Sleep Foundation, a not-for-profit organization established in 1990 by the organization now known as the American Academy of Sleep Medicine.

I know the panel has received my remarks and I'm going to skip over some of the description of the

foundation and our activities and just jump to the disclosure statement, though I will also say the remarks I'm about to give are about 10 minutes in length and there is apparently some overlap with prior presentations, but with a different focus and viewpoint.

The work of the foundation is supported by contributions and grants from a variety of sources, including individual donors, patients, memberships of nearly 600 sleep center affiliates, project grants from several federal agencies, foundations, and corporate contributions or sponsorships from a range of industries. Of the latter, within the last year, Cephalon joined other contributors to be an unrestricted sponsor of our National Sleep Awareness Week program and of our fund raising dinner. Their contributions amounted to less than 4 percent of our total income. We have not received travel reimbursement or any other compensation from any source to appear here today.

All of our work is guided by a 25-member board of directors. Our standard is to solely rely upon scientifically validated information or scientific consensus for our public guidance or policy positions. We accept no grants that are not unrestricted, meaning the foundation creates all the content of our educational materials independently.

Our purpose in briefly addressing the panel today is to advocate for only one thing: a greater concern and focus on the key problem of sleepiness. Although our concern pertains to the panel's consideration, we are not testifying with specific regard to modafinil. While we are aware of the benefits the medication has produced, we leave it to those most familiar with the clinical data to comment on its safety and efficacy for the new indication.

We address sleepiness because both observation and research have shown that it is a lead symptom for compromised attention and alertness, cognitive and mood disorders, and illness. Sleepiness is clearly the harbinger of danger for those with critical attention responsibilities, including all 190 million drivers in the U.S.

I don't mean to take away from the seriousness of this consideration, but I'm going to point out that it is for good reason that hearings such as this are not conducted between midnight and 8:00 a.m. They're conducted during the daytime, and that is when most of us have our optimal alertness.

The view of the National Sleep Foundation is that sleepiness, though widespread, is no mere social artifact, something we should joke about and accept. It should be recognized as a serious signal that every

individual and authority in our society understands as a risk factor and precursor to accident, injury, destruction, and death.

Clearly, sleepiness in our society is a byproduct of a number of different phenomenon with a range including reckless behavior, poor sleep hygiene, lifestyle choices on one hand, and economic and social forces, medical treatment and illness on the other hand, conditions that people can't always change.

At the National Sleep Foundation, we seek to establish a widespread dialogue about sleepiness within and among key institutions, including the workplace, health care, schools, criminal justice, and among community and civic organizations, and we are working to do this.

We also seek to establish a dialogue about sleepiness between doctors and patients so that the work can begin of distinguishing whether sleepiness is an indicator of disease, whether it results from economic and social factors, or whether it is due to personal choice. And such distinctions should not only be made, but they should be treated differentially as well. But currently these distinctions are, in truth, generally not made at all.

Dr. Carl Hunt, Director of the National Center for Sleep Disorders Research at the National Heart, Lung,

and Blood Institute, made this point this week in a statement reported in the New York Times. He said -- and I quote -- "People today are so accustomed to being sleepy because they don't get enough sleep, that when they develop a real sleep disorder, they don't recognize it as a medical problem."

Another way of saying this is that the prevalence of sleepiness due to poor sleep hygiene degrades our understanding of its significance and the threat it poses, and it masks pathology resulting from disease or societal forces such as employment patterns and institutional schedules, all of which may be unavoidable for the individual patient. Our objective at the National Sleep Foundation is to encourage greater clinical consideration of the root cause of sleepiness so that it can be treated differentially and effectively. We advocate for this because sleepiness is a morbid condition with a high risk of mortality to self and others. In some circumstances, such as for people whose work is in transportation, nuclear power, industrial operations, armed services, medical care, public safety, and other professions, the inattention that accompanies sleepiness -- or actually falling asleep on the job -- can have dire effects on the health and safety of people in entire regions, communities, and within families. This makes

sleepiness a significant public health issue.

For example, just one worker on an overnight shift, a nurse working double shifts, a truck driver getting his perishable load to destination by morning, or even an intern or resident working around the clock in their training, for any of them a single brief episode that experts call micro-sleep can kill them and also take away the lives of any of us or any of our loved ones as we make our way to work or to school in the morning. This is no fantasy. It is happening daily across America.

I'm going to skip again and just say we conducted the first-ever National Summit to Prevent Drowsy Driving at the National Academy of Sciences and in partnership with the National Academy this past November. We heard testimony from people who were affected as perpetrator, as victim in a variety of ways, and we heard from experts as well. Our findings reinforce the view that today the medical perspective on sleepiness as a pathological conditions is entirely inadequate. This has occurred for many reasons, but that is not the topic or the focus of today's meeting.

Overall, we need to recognize that sleepiness is a medical concern, one that is not entirely unlike the problem of controlling contagious diseases because its morbid and potentially mortal effects extend to the public

health and can have their greatest peril for other individuals and communities who are not necessarily sleepy themselves. These secondary patients and victims are endangered because of their contact with others who are, to extend the analogy, not only sleepy but also contagious.

To foster a more aggressive medical approach that is commensurate to the level of individual and community risk caused by undiagnosed and untreated pathological sleepiness, we feel that doctors and the patients too who are treated for sleepiness that is not responsive to behavioral change or other treatments need access to and deserve safe and effective treatment options. New treatment options ideally will have useful characteristics, including ability to foster alertness, low risk for abuse, side effects, addiction, or tolerance, and do not make other disease symptoms worse, do not worsen them, and they should not disrupt or degrade the quality of sleep.

Successful treatment of sleepiness and its causes has enormous positive effect. We clearly see this among patients who are diagnosed and treated for sleep disorders. Patients with obstructive sleep apnea who are successfully treated with continuous positive air pressure devices and who do not suffer residual sleepiness are frequently heard to say, it changed my life. They regain

vitality, interests, social relations, have restored libido, more positive marital and home like, become more productive at work, and begin exercise programs.

A second example now, combined pharmacotherapy and behavioral therapy permits people with narcolepsy to manage their symptoms and lead apparently normal lives. Previously for many, their pathological and unpredictable sleepiness made normal manifestations of life, including education, employment, career, driving, and social relations an impossibility. I would note today that you can have your driver's license withdrawn in many States if you have untreated or unresponsive narcolepsy, but no one has suggested taking away the driver's license of shift workers or people being treated for cancer or other diseases where fatigue is a byproduct.

Such pathological sleepiness and compromised alertness do not necessarily stem from sleep disorders alone, and others are similarly affected. Circadian effects, whether due from disrupted sleep schedules, jet lag, or shift work, may cause the same manifestations. Disease and medical treatments are another common source of sleepiness, particularly in aging Americans.

Again, the National Sleep Foundation just held a terrific two-day workshop on sleep, health, and aging where this was pointed out in presentation after

presentation. This was conducted in partnership with the National Institute on Aging.

These conditions and certain economic and social factors are not always options that people can change or they are not necessarily responsive to behavioral or environmental alterations. We must also recognize that people who suffer from profound sleepiness and its effects and who do not even like to work overnight or who recognize how it endangers themselves or others will continue to choose shift work and overnight work if the choice is between shift work and unemployment.

In conclusion, we feel that sleepiness is a very important public health challenge and is deserving of a robust medical response. We feel this response should differentiate the causes of sleepiness and match treatment to the cause. We don't suggest that people who are behaving recklessly be treated by their doctors with modafinil or, just the same, that an overnight truck driver try to treat his sleepiness with caffeine. Both need the appropriate intervention, and the medical response should be fully commensurate to the risk that untreated sleepiness can pose to the health and safety of all the people in the communities in which our patients live. I think this panel needs to consider the community and public health perspective of this issue. This is how we would frame the

context of your decision today, and I thank you.

DR. KAWAS: Thank you.

Is Christin Engelhardt available? She is Executive Director of American Sleep Apnea Association.

MS. ENGELHARDT: Good afternoon. My name is Christin Engelhardt, and I am the Executive Director of American Sleep Apnea Association, a nonprofit organization dedicated to seeing that all with sleep apnea are diagnosed and treated properly. Thank you for letting the ASAA present its view on Cephalon's application at today's hearing.

In the interest of full disclosure, I first want to acknowledge that the ASAA has received some support from Cephalon for our activities over the last four fiscal years but only less than $4,000 per fiscal year. All activities, such as exhibiting at medical meetings and National Sleep Awareness Day, have been initiated by the ASAA, never by any company. I personally hold no stock in Cephalon or any other company in the sleep field other than what may be in the retirement mutual fund.

Sleep-disordered breathing, including sleep apnea and upper airway resistance syndrome, is a common disorder that affects millions of Americans of all ages. Yet, it is relatively rarely diagnosed in part because the most common symptoms, snoring and falling asleep easily

and/or sometimes inappropriately, are not recognized by society as symptoms of a potentially serious medical disorder. Consequences of untreated sleep apnea may be significant and include sleepiness, high blood pressure and other cardiovascular disease, morning headaches, feelings of depression, impotence, and memory problems. Once diagnosed, the patient can be prescribed a course of treatment. Treatment options include oral appliances, weight loss, positional therapy, surgery, and the use of a continuous positive airway pressure, or CPAP, device. Medications may also be prescribed for central sleep apnea. Which treatment option is best for the patient depends upon the severity of the sleep apnea and other aspects of the patient's medical history.

As you have heard, the gold standard and most consistently effective therapy is the CPAP machine. CPAP works by pushing air, via tubing that connects the CPAP to an interface that touches the patient's face, through the airway passage at a pressure high enough to keep the airway passage open during sleep. The pressure is set according to the patient's sleep apnea. Pressure that is too low will not be as effective in eliminating the apneas and hypopneas. While effective, CPAP may be difficult to use. Hence, published compliance rates may be suboptimal. Of course, adherence to any therapy for any chronic disease is

typically suboptimal. For example, adherence to pharmacological therapy is approximately 50 percent. Moreover, it is possible and important to improve adherence to CPAP. Our publication, If Your Patient is Not Complying with CPAP, was written for professionals precisely for this purpose. And I should note that Cephalon has, through support of our presence at medical meetings, helped us to distribute this to physicians and other health care professionals. Education of the patient can also help improve compliance.

Comfort is often an issue with CPAP, and sadly patients may not get all the equipment and/or assistance they need to utilize this effective treatment all night, every night. For example, patients need access to all available options in the mask and machine features so they can find the best one for them, hence the ASAA publications, Choosing a CPAP and Choosing a Mask and Headgear, among others. There are many masks on the market now and manufacturers constantly work to develop more comfortable masks, but there is no one best mask or machine. Each patient has different personal preferences.

In addition, some patients need to be desensitized to the mask. It often takes a skilled and experienced health care professional to enable a patient to adhere to CPAP therapy. Yet, unfortunately, it can be

difficult, if not impossible, for all patients to gain access to this expertise. Even patients who are assertive and persistent have been known to give up on the treatment before they find a comfortable option.

Thus, proper treatment of sleep-disordered breathing does not always follow the diagnosis. The ASAA finds the state of affairs unacceptable.

The three main causes of sleepiness are sleep deprivation, endemic in this country, untreated sleep disorders, and circadian rhythm misalignment caused by factors such as jet lag and night work. Alcohol and certain medications may also cause sleepiness, as can depression and certain illnesses. Numerous studies show that untreated sleep apnea causes sleepiness and that CPAP, even when not used all night, every night, reduces sleepiness. Likewise, there are studies that show that patients with inadequately treated sleep apnea are likely to remain sleepy. One may also have treated sleep apnea and be sleepy from sleep deprivation or night work. Studies also show that patients who appear to have well-treated apnea may also have residual sleepiness. Regardless of the cause, sleepiness can have adverse consequences and requires attention.

Modafinil was originally approved by the Food and Drug Administration to improve wakefulness in patients

with excessive daytime sleepiness associated with narcolepsy. It has also been investigated, as you have heard, to treat residual sleepiness in patients with treated sleep apnea, defined in one study as using CPAP on a regular basis at least 4 hours a night on 5 nights per week, not all night, every night. Modafinil has been shown to be safe in clinical studies and in clinical use. It is thought to be safer than amphetamines which have also been prescribed for residual sleepiness in sleep apnea. But still it is not benign. No drug is.

As noted earlier, some sleep apnea patients experience residual sleepiness despite getting sufficient sleep and having effective therapy for apnea. Because of this, based on the limited available data, the American Sleep Apnea Association can support the narrow use of modafinil in patients whose sleep apnea is being treated appropriately and sufficiently and whose other causes of sleepiness, including sleep deprivation, insufficient CPAP pressure, or mask leak, have been addressed or excluded. It is worth noting that to our knowledge, no published study looked at the role of sleep deprivation in the sleepiness. Yet, the ASAA believes that modafinil has a role, albeit a minimal one, in managing sleep apnea, and the absence of a relevant indication for the drug can be a barrier for patients to get insurance coverage for

medically necessary medication.

Still, we cannot emphasize enough that prior to prescribing medication for sleepiness after a patient has begun treatment for sleep apnea, the physician must examine and address all possible causes of the patient's sleepiness, particularly CPAP adherence. As Dr. Jed Black wrote in his editorial, Pro: Modafinil Has a Role in Management of Sleep Apnea, published in the American Journal of Respiratory and Critical Care Medicine, one unpublished study found that two-thirds, or 31 out of 46, of CPAP patients who were sleepy after being on CPAP for at least 6 months were no longer sleepy "following 30 days of subsequent upgraded CPAP use." At the same time, 15 of the 46 subjects still had residual sleepiness and underwent a trial of modafinil. It, however, must be remembered that this pharmacological approach treats only the symptom of sleepiness, not the underlying cause of sleepiness. It does not prevent apneas and the consequential oxygen desaturation and sleep fragmentation that may lead to cardiac disease and other health problems.

So while it may be easier for physicians to prescribe and for patients to take modafinil, both must know that taking modafinil does not render CPAP unnecessary. This point must be made clear on the labeling and in any advertising, particularly as one study found a

statistically significant reduction in CPAP use among subjects given modafinil compared to the control group.

In addition, in cases of extreme sleepiness thought to be from untreated sleep apnea, modafinil may have a short-term role to minimize the direct risk of sleepiness until definitive treatment is initiated and found to be effective. While we are aware of no formal studies on the use of modafinil as bridge therapy, the doctor must make a clinical judgment on the potential benefits and risks of prescribing modafinil and of not prescribing modafinil. Sleepiness does carry risks. Yet, modafinil must not be seen as a panacea. The drug must not hinder appropriate diagnosis and treatment of the underlying cause of the sleepiness.

The ASAA is clearly committed to seeing that modafinil, should it be approved for additional indications, be prescribed appropriately. We believe Cephalon as the manufacturer must vigilantly educate the public and prescribing physicians about the appropriate role of modafinil. The ASAA remains willing to continue to work with Cephalon and with other interested parties on our common goal of helping people with sleep disorders.

Again, thank you very much for this opportunity to speak to the panel today, and I do just want to note that we've limited our comments to the use of modafinil for

sleep-disordered breathing given the mission of the American Sleep Apnea Association. Thank you.

DR. KAWAS: Thank you, Ms. Engelhardt.

Anyone else who would like to speak in the public forum section?

(No response.)

DR. KAWAS: Okay, this section is now over.

Since we're going to try to do without a lunch break, it's been requested that we have another bathroom break. So if we can have a very quick break, I'm going to start sharply in 10 minutes.

(Recess.)

DR. KAWAS: We're reconvening this session which hopefully will not extend to a dinner break, but I can tell everyone is hungry. So if it comes down to everyone wanting a break for lunch, please holler and let me know.

I'd like to reconvene this session and open with a final opportunity for anybody on the advisory committee who has any other questions, comments, or thoughts, questions either for the sponsor or for the agency, to take this opportunity now before we proceed to the formal vote for the different questions that they've given us. Yes, Dr. Krahn.

DR. KRAHN: I have a question for the agency.

If Provigil gets this indication, I'm concerned that it will be used in a very widespread way for patients who may have shift work issues rather than shift work sleep disorder. I'm wondering what suggestions or comments you may have on ways to limit its usage to ensure that it is provided to patients who have appropriate needs and not used in a more widespread way.

DR. KATZ: Usually in a case like this, we would basically rely on labeling to describe in whom the drug is safe and effective, who should get it. We can't be completely directive, but we can spell all this out in labeling and not just professional labeling for the prescriber but patient labeling, the so-called patient package insert which is something that can be given to the patient each time they get a prescription filled, which will tell them this shouldn't be taken for just routine -- you stayed up a couple of nights and now you're sleepy, but if you have sleepiness, you should go to the doctor, get it worked up, that sort of thing. So labeling in various forms I think would be mostly what we would do.

In certain cases you can attempt in labeling to more formally restrict who can prescribe it and this sort of thing, but I don't think we would anticipate that sort of thing here. The drug has been out on the market for a number of years. We obviously want to hear what you think,

but so far we haven't thought that there is a particular safety concern which would usually drive that sort of thing. So a lot of information to the relevant parties.

DR. MIGNOT: And how effective is this information?

DR. KATZ: I'll let Dr. Temple answer that.

DR. TEMPLE: This is under the general heading of risk management, which everybody is busy worrying about now, and the conversation often turns to the risk management tools that you have. Well, the physician labeling. That's one tool. We know that doesn't always work. The next thing you think about is a combination of making sure promotion is appropriate, which we try to do, and perhaps directing information to the patient specifically. If you were to ask me how well we know those things work, I will tell you I don't know the answer to that. But patient labeling is certainly used widely. Many of the sedative hypnotics have labeling that says don't use this too long, be careful, watch out if you're going to drive a car, stuff like that. And you can think of things you could do here that would do that, reminding people that sleep apnea isn't cured by something that takes care of your daytime sleepiness. There are other problems associated with it and you really better see a doctor about it and get the right machinery and stuff like that. So

those things could be considered.

If there's something we're really, really worried about, we sometimes have limited distribution systems. It's not easy to think of doing that without some quite dramatic cause for drugs already on the market without it for a long time. But troublesome drugs like thalidomide and things like that have special distribution systems and other drugs too. That's relatively extreme. It's relatively disruptive and you need a pretty good reason for doing that.

DR. KAWAS: Dr. Krahn?

DR. KRAHN: I guess my concern about Provigil is that patients may really go in to their physicians requesting it and they may desire it to reduce their need to sleep at night. So they may view it as replacement for the normal amount of nighttime sleep. And how are we going to put in place some safeguards to reduce its misuse in that way?

I do think that it's different than a sleeping pill. Many patients want to sleep at night, but it replaces something that's missing and they don't want to sleep more than they should be. Here a person may want to enhance a physiologic state and have, let's say, 20 hours of alertness in place of what is more normal. That's why I think that this is an important issue for Provigil with an

expanded indication.

DR. KATZ: Besides the approaches we've already talked about in terms of labeling and describing in labeling, again to focus back on the professional labeling, there can be language in that instructing the physician that a diagnosis has to be made that this should be only be used in patients who have had a formal diagnosis.

The other thing that has been done in the past are educational campaigns where companies produce documents that can be designed to be sent to the physicians, as well as the patients, explaining in greater detail who this should be used for, what it is capable of doing, what it is not capable of doing, and not in terms of treating the underlying illness, that sort of thing. So, again, it's more avenues of information.

Short of that, I'm not sure. Again, as Dr. Temple said, unless there's a real known significant risk to the treatment, more restricted distributions would be, I think, problematic in this case.

DR. TEMPLE: You can be fairly sure that none of the attempts to encourage proper behavior will be fully effective. Fully might be even over-optimistic or less than fully might be an over-optimistic statement.

But it's not an easy answer. If you read the papers, apparently a lot of people are existing on less

sleep than they need already, which is one of the reasons there are dangerous drivers and things like that. It's not completely obvious whether off-label use that helps them deal with their bad behavior is worse or better than not doing anything. Those are not easy questions. If they're driving next to me, I think I'd prefer they be on it.

(Laughter.)

DR. TEMPLE: So as a general matter, we don't believe that we can control what physicians and patients do fully. If it's a teratogen, we take very excessive, very strong steps to try to make sure nobody gets the wrong drug. If it's other things, we don't do as much, but we try to get it right through labeling and patient labeling and making sure promotion doesn't over-promise and things like that.

DR. MIGNOT: Just to follow up on this question, I think one of my concerns was especially for shift workers that may have sleep apnea additional to their shift work. Sleep apnea is so common that I'm just worried that something like this could occur where a patient would have both disorders. It's a bit difficult to ask us to somehow vote on this I think without knowing what the label will say, in a way, because I think that's really going to be critical that people are really warned that they shouldn't use it as a replacement for CPAP for treatment of

sleep apnea.

DR. TEMPLE: We're listening to that concern. Speaking for Russ, we know that the labeling should be clear on that.

It's not out of the question, you know, that more people who notice that they're sleepy will actually get to their doctors for sleep apnea as a result of better information. There's not a lot of ways to get that information to people, and a commercial sponsor with an interest is one way of getting it. So it could even be good.

DR. KAWAS: Do we have any other questions or comments or queries from the advisory committee? If not, we'll move on to the questions for a vote.

(No response.)

DR. KAWAS: No, okay.

Question number 1, using the International Classification of Sleep Disorders, which actually divides sleep into dyssomnias, parasomnias, sleep disorders, and proposed sleep disorders, the sponsor has defined disorders of sleep and wakefulness associated with excessive sleepiness. Does the committee agree with this designation?

I think the way we're going to do this today is we'll start at one end of the table and let each person

vote. We'll switch the order periodically just to build up the suspense.

(Laughter.)

DR. KAWAS: So, Dr. Azarnoff, would you like to start?

DR. AZARNOFF: I don't believe I have a vote.

DR. KAWAS: Oh, I apologize.

Dr. Ebert.

DR. EBERT: I'm going to take the approach to this one from primarily an academic standpoint and say that I vote yes.

DR. KAWAS: Dr. Mignot?

DR. MIGNOT: Yes.

DR. KAWAS: Dr. Krahn?

DR. KRAHN: Yes.

DR. KAWAS: Dr. van Belle?

DR. van BELLE: I defer to the experts in this. I'm not an expert so I'm not voting either for or against.

DR. KAWAS: Abstain.

DR. van BELLE: I'm abstaining. Thank you.

DR. KAWAS: Okay.

Dr. Wolinsky?

DR. WOLINSKY: Yes.

DR. KAWAS: I vote yes at least in the sense that there's excessive sleepiness and all of those

conditions.

DR. KAWAS: Dr. Kattah?

DR. KATTAH: Yes.

DR. KAWAS: Dr. Neubauer?

DR. NEUBAUER: I vote yes.

DR. KAWAS: So the vote is all yes and 1 abstain.

Second, the sponsor believes that the above group can be divided into three categories based on presumed cause of the excessive sleepiness. The categories are: sleep-wake dysregulation, sleep disruption, and circadian misalignment. Does the committee agree with this classification?

Dr. Neubauer?

DR. NEUBAUER: I'll agree, yes.

DR. KATTAH: Yes.

DR. KAWAS: Yes.

DR. WOLINSKY: Yes.

DR. van BELLE: Abstain again.

DR. KAWAS: Abstain.

DR. KRAHN: Yes.

DR. MIGNOT: Yes.

DR. EBERT: Yes.

DR. KAWAS: The third question, does the committee agree that the disorders studied by the sponsor,

which are narcolepsy, obstructive sleep apnea, and shift work sleep disorder, are representative of the three categories described above?

I guess we'll start with Dr. Ebert.

DR. EBERT: That they're representative of the categories described above, I would say yes.

DR. KAWAS: I'm sorry. I should have said this first. One of the questions in my mind is what do we mean by representative here? Does the agency have any guidance to give us on that? I mean, my inclination right now is to say no, they're not representative. They're the most common, for sure, but there's a big difference between obstructive sleep apnea and periodic leg movements, for example, potentially. So in what way do you want us to discuss the representativeness?

DR. KATZ: Well, again, the next question sort of asks the $64,000 question, or more.

(Laughter.)

DR. KATZ: But what we're really trying to get at is whether or not the approach that the sponsor has proposed and has undertaken is adequate. In other words, if the drug is studied in shift work sleep disorder, can we therefore generalize and say, well, this drug works in disorders of circadian misalignment? That's what we mean by representativeness. So that's what we mean. Again, the

fourth question which asks overall do the data support the claim incorporates that concept, but that's what we mean. If you show it works in one disorder, which they have done, in each of the three categories, does that mean that the drug will work and we can reliably conclude that the drug will work in all disorders in that category.

DR. TEMPLE: This also comes slightly in two flavors also. Sometimes the potential reality of it helps focus.

The indication is written broadly and maybe they could say this works for circadian abnormalities. But the other possibility is that you might see conceivably a specific claim for jet lag which has never been studied. So, on the one hand, there's the sort of general idea which someone might conclude applies to jet lag but not a specific claim, I work in jet lag. And the other is, you get those specific claims even though you haven't specifically studied them.

This comes up a lot of other times. We insist that there be data on both men and women, old and young, black and white, and the labeling all says it seemed to work basically similarly. But if somebody set out and did a campaign, I work in patients over 65, without specific studies of that, that might make us nervous. So it's nuanced and not entirely satisfactory because we do want

broad information. This has a little bit of that.

So as you go through this, you might think about how you feel about that. Even if you think the broad claim is supported, how do you feel about specific conditions under that claim that have not actually been studied. I mean, you might think it's okay. I'm not trying to tell you what to think.

DR. KAWAS: Great. I think actually that helps me somewhat. I hope the committee feels the same way.

On that note, Dr. Ebert, would you like to vote?

DR. EBERT: Given the slight change I think in the term "representative," what I'm hearing now is that we're saying that that disease would infer that it would apply to all conditions within that category, I would like to change my vote to no.

DR. KAWAS: Thank you.

Dr. Mignot?

DR. MIGNOT: I still have a question about this specific issue. It's impossible to really predict all. Obviously, diseases are heterogeneous and I don't think you can ever have something that's all. You could say almost all, but you cannot say all. For example, periodic hypersomnia or certain forms of idiopathic hypersomnia may be described later as having a sub-cause that will not

respond to modafinil. If it was "almost all" -- "representative" is the broader term for the large majority of patients -- I would say yes. But if it's "all" -- completely all -- I don't think that's possible to really answer. I want to know if you mean --

DR. KATZ: Well, what we mean by the question is driven by what the sponsor is proposing. The sponsor is proposing that the drug be approved for excessive sleepiness associated with disorders of sleep and wakefulness. If such a claim is granted, the implication is that it works to treat excessive sleepiness in disorders of sleep and wakefulness which, as they've defined it, includes that whole list of disorders that are subsumed under the three categories they've created. That's all. I mean, it's inclusive. The implication is that because it worked in shift workers, it will work in the six other conditions that are subsumed under circadian misalignment. I don't think there is, for the purposes of labeling as they've proposed it -- the indication as they proposed it, I don't think it's some. I think the intention is for the conclusion to apply to all conditions subsumed under this broader heading.

DR. MIGNOT: I'm sorry to ask this question again, but maybe if you were pooling patients, like if you do a clinical trial and you say they are all disorders of

-- you know, it's a statistical argument really -- all disorders of sleep that have sleepiness and you pool them all and you have 10,000 of them, and then you will see a statistically significant effect, then the answer would be yes because, of course, there will be some patients that will not maybe react to the drug.

DR. KATZ: Well, it depends. You could do a large study and have only 2 patients with restless legs, and you'd be hard-pressed to say, well, it applies to restless legs.

But here, the situation is much more stark. I didn't add up the total number of disorders that are included here under disorders of sleep and wakefulness, but it's a large number. They studied three. And they are asking us to conclude that based on the findings in those three specific conditions, that the drug will be effective in all the others. That's really the whole question, much of what we've been discussing today.

So now we have to decide whether or not we think that's valid. You have unanimously concluded that disorders of sleep and wakefulness associated with excessive sleepiness is a real thing and that the three subcategories that the sponsor has subsumed those disorders under is real, meaning presumably that they share a common pathophysiology or something. Now we have to decide

whether or not we think that those three indications support all the rest.

That doesn't necessarily mean in labeling we would list all of those, but I don't know what we would do in labeling yet, as far as that goes. But the implication will be that this drug works to treat the sleepiness associated with this entire list of disorders. At least that's the way I interpret their proposal.

DR. TEMPLE: There are also potential nuances. We haven't figured out what the labeling should be. But, for example, one could also conceivably use the broad language and then say, the drug was specifically studied in the following conditions and not others. This isn't to say we would ultimately conclude that's the right thing to do, but there's really no limit to how you do those things and not a lot of precedent, I have to tell you, either.

DR. KATZ: Right, but even such an approach where you just list -- I would sort of anticipate that's probably close to what we might do, just say here's the overall claim, here are the conditions it would be studied in. In fact, we would do something very close to that in any event because there's a part of labeling where we describe the trials that served as the basis for the approval. And those are the trials that were done, so those are the trials we would describe. You could put it

in the indication section. Anyway, it would certainly be somewhere in labeling.

Nonetheless, the overall claim, which is what we're talking about here, or indication, presumably applies to the entire universe of disorders in those categories.

DR. MIGNOT: I vote yes.

DR. KAWAS: Dr. Krahn?

DR. KRAHN: No. This discussion has been very helpful, and I realize labeling might help address this issue, but I think that it's hard to highlight three disorders and say that that represents all the other disorders.

DR. KAWAS: Dr. van Belle.

DR. van BELLE: Well, I'm going to say something about this.

First of all, the word "representative" has a very specific statistical meaning; namely, "representative" means randomly selected from a population. Well, clearly that was not the case here.

On the other hand, there was discussion with the FDA about what would constitute representative conditions according to these three categories I think. In fairness to the sponsor, I think we should work from that.

So in statistics, there is another way to sort of get out of the representativeness and to simply talk

about a convenience sample. So to my mind, these three studies represented three convenience samples from each of those three areas. So if you allow me to substitute the word "convenience" sample for representative, then I do think that the sponsor has, indeed, satisfied the condition.

DR. KAWAS: Please.

DR. KATZ: I really don't want the primary issue to get lost in the language. You can call it representative. You can call it anything you want. It's the fundamental concept that really matters, which is again if they show it works in these disorders, can we conclude that it will work in all the other disorders with excessive sleep, with the larger category that they defined. I don't care if we call that representative or not, but that's really the fundamental issue that we're grappling with in this question.

DR. van BELLE: But the analogy by Dr. Temple earlier today about, for example, pain, that not every possible condition for pain is studied and yet approvals are given for conditions of pain. That must be based on studies very similar to this situation here.

DR. TEMPLE: Well, and a history that goes back 60 years too which is a little different.

DR. KATZ: So do we have a vote?

DR. KAWAS: Yes, I need to make sure I understand Dr. van Belle's vote on question number 3.

DR. van BELLE: Yes, in the way that I've defined the representative.

(Laughter.)

DR. KAWAS: Got it.

Dr. Wolinsky.

DR. WOLINSKY: I actually see the fundamental issue as a little bit different than what I'm hearing espoused on that end of the table. First of all, I think that within any one of the three conditions that have been tested, the patients are representative of the response. As best I could tell from the data presented, not every patient got a response.

I also understand from the data that was presented that there was no claim that there was any specific treatment of the underlying disease but just an amelioration of symptoms which were relatively common to a broad variety of diseases that could be specified. I felt that the data presented in the classification system was such that, in fact, these are three conditions, each one representative of an example of that classification system.

If I thought they were treating diseases, I would have to say no, but they are treating symptoms, so I have to say yes.

DR. KAWAS: I think that was a yes.

DR. KATZ: Yes, that's what I wrote down.

(Laughter.)

DR. KAWAS: And my vote is going to be no. Although I agreed with the categories, you can keep categorizing things, and the three categories on presumed cause of the excessive sleepiness was an acceptable division for me, but that didn't mean, to my mind, that we have a common pathophysiology. From that standpoint, I feel strongly that I think the sponsor made some very wise choices in what they chose to study, i.e., they studied the most common disorders in each of those categories.

But at this point I feel that seeing evidence, for example, that this may reduce the excessive sleepiness of obstructive sleep apnea and may be reasonably safe for people with obstructive sleep apnea, it doesn't tell me anything about its efficacy or safety, for example, in central apnea. It doesn't tell me anything about its behavior in other diseases like periodic leg movements. It may work in narcolepsy, but I don't feel that I have enough information to assume that it would work in periodic hypersomnolence. The information from my perspective doesn't give me enough information about efficacy or safety in the other diseases in the category, for the most part.

Dr. Kattah.

DR. TEMPLE: Can I ask something? Is this a matter of the number of models? If there were more models, could you ever be convinced, or is it just that you think really you just can't know until you study it in any setting?

DR. KAWAS: I think in some settings and some places where the diseases are better understood pathophysiologically, it might be numbers. But in this case I think we're grouping a very diverse group of conditions under each of the three categories, and to my mind the pathophysiology of those are likely to differ so substantially that I'd be concerned about what effects it would have in these conditions. Does that answer your question?

DR. TEMPLE: Yes. I think you've reached the conclusion that the treatment here should not be considered a mere symptom, if you like, but something that may have something to do with the pathophysiology of the disease. I think that's the differences that we're seeing. I mean, if you believe it's just a symptom, then you wouldn't worry about having every conceivable disease. If you're not so sure about that, then you really sort have to go one by one. I think that's what the differences are.

DR. KAWAS: That capsulized it well, yes.

DR. KATTAH: I guess as the comments are going

around, the more I hear about it, the more I think that we're looking at sleepiness as a comprehensive term, and in that sense, then the answer will be no because it doesn't encompass common pathophysiology, and it has not established all cases of daytime sleepiness. So in that sense, I will say the answer will be no.

DR. KAWAS: Dr. Neubauer?

DR. NEUBAUER: I vote no. It's really more of a technical issue than a practical one because I think that probably there are final common pathways related to sleepiness that modafinil has a potential to help with. The only thing that troubles me here is the selection. We have narcolepsy on the one hand, which is clearly a disease. We have obstructive sleep apnea hypopnea syndrome, which is a syndrome, and then there is the shift work disorder, which is really nothing that's very well defined at all.

I wouldn't have a problem if it was just shift workers who were sleepy. Now, whether or not to treat them would be another issue, but at least in terms of saying they're representative of these categories, the sleepiness and insomnia that's part of the experience of many shift workers, would be very reasonable here.

But the interpretation that we've heard here is that a special subset of shift workers who have something

else wrong with them, who have some other underlying vulnerability that is only brought forth under the circumstances of their doing the shift work. In fact, if that's the case, then those people with this particular vulnerability actually would belong in a different category which would be the sleep-wake dysregulation, more like the narcolepsy patient, but something that is only brought out under those circumstances. So it's nothing that's intrinsic to shift work itself if that's the population we're told is studied here.

DR. KAWAS: Remind me. Your vote is no.

DR. NEUBAUER: No, correct.

DR. KAWAS: I'm trying to figure out the tabulation here, and it looks to me like 3 yeses and 5 noes, with all kinds of qualifications.

Actually, if I may go back to your question, Dr. Temple. For example, knowing that it works in shift workers, for example, who have a kind of, in their own way, a regular schedule, it doesn't tell me what it will do for a delayed sleep phase person where their sleepiness is always at a different time of day. The disorder has completely different underpinnings even though it fell into the same category, and I think this might have been Dr. Neubauer's point, whether or not they're environmental or disease or intrinsic-induced. You know, you put a bunch of

things in the same category.

Question number 4. Does the committee agree that the sponsor has submitted substantial evidence of effectiveness for the indication for the treatment of excessive sleepiness associated with disorders of sleep and wakefulness?

Would you like to start, Dr. Neubauer? We should start in the middle of the table sometime. Actually I will. How about if I start with Dr. Wolinsky? We need to liven up things here.

DR. WOLINSKY: Well, I assume that this vote should wind up being very similar to the last vote, otherwise my logic fails me. But I will add a little different comment. I think that the clinician, armed with the data that we've seen, approaches patients with this category of symptoms as what I would call and others have called an n of 1 study with a quick vote back as to whether or not there was effectiveness. So I say yes.

DR. KAWAS: Dr. van Belle?

DR. van BELLE: Yes.

DR. KAWAS: Dr. Krahn?

DR. KRAHN: No, again because of the global nature of the indication.

DR. KAWAS: Dr. Mignot?

DR. MIGNOT: Yes.

DR. KAWAS: Dr. Ebert?

DR. EBERT: No. I feel that although I think the drug is effective in treating the symptoms, my concern is that the approach to the symptom will overshadow the need for a diagnosis. Again, as Dr. Krahn mentioned earlier, in many cases this drug may be prescribed by primary care physicians that may feel that they're approaching the symptom and have not done a complete job of approaching the diagnosis.

DR. TEMPLE: That's a somewhat different -- not that it's not a legitimate concern, but it's quite a different concern. So we need to understand what you're saying. Are you saying, oh, yes, it probably does work anytime where a person is sleepy, but I'm worried about using it so broadly? That's sort of an answer of yes, but I don't want to approve it for that, which is not the same as saying, no, I don't believe it, which for example Dr. Kawas has been saying. So it would help us if you distinguished which of those things you're saying.

DR. EBERT: What I'm saying is I'm concerned whether it's from a detailing standpoint or from an approach that if a patient presents with that symptom, that as we mentioned by many people here, perhaps the patient has sleep apnea, and rather than working that patient up and trying to fully use front-line therapy such as CPAP,

that instead we would be approaching it more from a symptom standpoint. It would bypass a full diagnosis.

DR. KATZ: But just to follow up on what Dr. Temple said, should we take from that that you think, though, that the effectiveness -- forget about approvable because I don't think the question actually asks about approvable. We usually don't. We just ask if there's substantial evidence of effectiveness. So do you think the data support the claim? As I say, put out of your mind for the moment that this is related to approval.

DR. EBERT: Okay. Well, again, to me the term indication, as you probably are alluding to, is synonymous with approval. So I understand what you're saying. If we were to take that word out of the question, I still think, again similar to what my vote was in number 3, that there's not enough information to make the broad application to a variety of diagnoses.

DR. KAWAS: So that's a no. Right?

Dr. Kattah?

DR. KATTAH: Yes.

DR. KAWAS: Dr. Neubauer?

DR. NEUBAUER: No. And I say that with some reservations because I think that modafinil does have a lot of potential in a broad range of categories, and it really comes down to what you mean by effectiveness because they

have submitted substantial evidence of clinical improvement, which really might be very important for a lot of people.

However, my real reservation relates to the shift work sleep disorder studied because while the clinical improvement associated with 1 or 2 minutes on the MSLT may be great, how can we say that it is effective for that population when the treated subjects still had an MSLT of 3.8? These are people that we would be worried about being out on the road driving and this is when they've had the medication. So I'm reluctant to say that it is truly effective for that population even though there is a clear clinical improvement.

DR. KATZ: Again, just as a typical matter, the treatments that in general we approve certainly are no cures. There's no obligation that they be cures. The treatments that we ordinarily approve on average have relatively small treatment effects. That doesn't mean you couldn't conclude that in this particular case that would be the wrong thing to do. Of course, you could do that. But just as a general background, we recognize that the treatments that are approved in our division and in most divisions are symptomatic treatments.

It's not unheard of to have similar situations to what you have here which is that patients enter a trial

based on some severity. They're treated. The drug is better than placebo and they still probably could meet the criteria to enter the trial, but nonetheless, they're better than they would have been had they not had the treatment. In general, in that sort of setting, we decide that's good. Of course, a mean effect hides a distribution of effects and some people may have large effects.

So the fact that the symptom hasn't been eradicated is perfectly consistent with how drugs are approved traditionally. But again, in any individual case, you could decide that that's just not good enough.

DR. KAWAS: Are you comfortable with your decision?

DR. NEUBAUER: I am.

DR. KAWAS: Good.

I believe that the sponsor has submitted substantial evidence of the effectiveness for the indication of excessive sleepiness in three situations which are obstructive sleep apnea, shift worker sleep disorder, which is a subset of shift workers, and for narcolepsy, but not for the general treatment of all the groups of disorders that they put into that category. So my vote is no.

So that makes the vote total here, I think, 4 and 4. I'm sure that helped.

(Laughter.)

DR. KAWAS: For our sleep experts, for whatever it's worth, they were also divided between the two votes with one of them on the yes side and two on the no side.

Has the sponsor demonstrated that Provigil can be used safely for this broad indication?

Dr. Kattah?

DR. KATTAH: I think that in narcolepsy -- well, that's not an issue right now -- it has done this and also in the shift work sleep disorder.

In the group of patients with sleep apnea, I'm somewhat concerned. I raised the question about the headache. If you look at the two trials, 303 was 12 weeks and 402, 4 weeks. There was a twofold incidence of headache in the group with sleep apnea, and I wondered if that might relate to increasing intracranial pressure. I know that there is a high incidence of pseudotumor cerebri in sleep apnea, and if we see now an increment in the headache, given the short duration of the trial, it makes me think that there could be perhaps a mechanism whereby changes in blood pressure may be occurring at the same time accounting for this increased incidence of headache.

And my answer will be yes for the shift work sleep disorder, but not in the sleep apnea. I would want to have more information and longer follow-up.

DR. KAWAS: Thank you. I'm not sure how to count that in the tab, but it's a good thing that's Ms. Patel's job I hope.

Dr. Neubauer?

DR. NEUBAUER: Yes.

DR. KAWAS: Dr. Wolinsky?

DR. WOLINSKY: Yes.

DR. KAWAS: Dr. van Belle?

DR. van BELLE: Yes.

DR. KAWAS: Dr. Krahn?

DR. KRAHN: Yes.

DR. KAWAS: Dr. Mignot?

DR. MIGNOT: No. Yes, I still have the same concern I guess. My concern is that it doesn't treat all the symptoms of sleepiness and it really depends on what will be written or how the drug will be prescribed in terms of not efficacious enough maybe in some patients that will have sleep-wake -- you know, that will be a shift worker and take modafinil and thinking that they're perfectly safe, where they are not. I think also we really need to make sure that patients with sleep apnea not untreated take the medication. Maybe some of that can be addressed by the labeling, and I would trust the FDA to look at this issue very carefully. But as it is now, I don't think I can make a yes without looking at what will be done to ensure that

this is not the case.

DR. KAWAS: Dr. Ebert?

DR. EBERT: Yes.

DR. KAWAS: And I think my vote is no. I'm certainly comfortable, however, that the sponsor has demonstrated adequate safety for the indication in the three diseases that they studied. I just can't comfortably generalize that based on what we discussed earlier.

Now, we have two more questions that we were supposed to discuss if we voted yes on questions 1 through 5. I'm not exactly sure --

DR. KATZ: If you didn't vote yes. In other words, the point of these two questions is if you don't think it should be approved for the broad indication, do you think it should be approved for anything? It's already approved for excessive sleepiness associated with narcolepsy. So does the committee think that there's sufficient data to get the individual conditions that actually were studied into labeling?

DR. KAWAS: So would you like to hear from everybody or only the individuals who said no?

DR. KATZ: That's a good question. Everybody, although I suspect we could predict the answer for the ones who said yes, but let's hear from everybody.

DR. KAWAS: Okay, excellent. So the first of

those questions is, has the sponsor provided substantial evidence of effectiveness to support the use of Provigil in the treatment of excessive sleepiness in patients diagnosed with sleep apnea?

Can we start with Dr. Krahn?

DR. KRAHN: Certainly. Yes.

DR. KAWAS: Dr. Mignot?

DR. MIGNOT: Yes. I would add diagnosed and treated because they were treated with CPAP, and I think that's important to mention that.

DR. KAWAS: So for the apnea patients, if they're already on CPAP.

DR. MIGNOT: Yes.

Dr. Ebert.

DR. EBERT: Yes, with a similar statement as an adjunctive therapy to CPAP.

DR. KAWAS: Excellent.

Dr. van Belle.

DR. van BELLE: Yes.

DR. KAWAS: Dr. Wolinsky?

DR. WOLINSKY: Yes.

DR. KAWAS: And I say yes.

Dr. Kattah?

DR. KATTAH: Yes.

DR. KAWAS: And Dr. Neubauer.

DR. NEUBAUER: Yes.

DR. KAWAS: We've got a unanimous yes.

The final question.

DR. KATZ: Before you get to the final question, typically if we were dealing with a new chemical entity that had not been approved for anything, a finding of substantial evidence would require that there be independent replication in the disease in question. So that means usually at least two so-called adequate and well-controlled trials supporting that.

There is one trial in shift work. On the other hand, it occurs in the context of two trials in narcolepsy and two trials in sleep apnea. So I'm just throwing that out as something that people, before they give us their advice, might want to think about.

DR. KAWAS: I think that's a crucial point. Thank you.

Yes, Dr. Hershkowitz.

DR. HERSHKOWITZ: Yes, can I just make one point? With obstructive sleep apnea, the test itself was not specifically designed to be what one would consider a pivotal trial. It wasn't quite designed the way we suggest. It had a single primary endpoint which was a subjective endpoint, and it was a somewhat small study. I know this is related to the past issue that you voted on,

but I just wanted to get it out for the record.

DR. KAWAS: Dr. Katz?

DR. KATZ: Just to follow up on what I had said and I said this finding in a single study in shift work occurs in the context of multiple trials in other presumably related settings, it's not uncommon for us to approve a new indication on the basis of a single trial in the context of multiple other trials on related endpoints, like for example, a drug might be approved initially to treat partial seizures on the basis of multiple adequately controlled trials. If a sponsor wants to get a drug approved for generalized seizures, it might be acceptable for them to do only one trial in generalized seizures, and we sort of borrow strength, to use a term, from the previous data, and we say, well, it's not exactly the same. That's why they had to do another trial, but it's related. So we sort of consider the whole package of evidence.

So I'm just trying to give you a regulatory or a historical context for your decision on the last question. Right, we even have a guidance which talks about when a single trial would be acceptable as substantial evidence. It's this sort of thing.

DR. MIGNOT: Should we revote considering this?

DR. KATZ: Well, no. So far you haven't voted yet on the one that only had one study. I just want to

make sure you know these things before you vote on that last question.

DR. KAWAS: Do you want to reconsider your vote on the previous after this discussion?

DR. MIGNOT: No. Sorry.

DR. KAWAS: There were two sleep apnea studies. We never really discussed the effect in both of those in particular, but there were two sleep studies that were nominally positive, although not set up by typical pivotal trial criteria.

Dr. Azarnoff, did you have some questions or comments you'd like to make?

DR. AZARNOFF: I was just going to repeat what Dr. Katz told you, that single trials are approvable with supporting data.

DR. KAWAS: There is a very clear set of guidelines from the FDA, as I recall, on when a single trial is acceptable. Do you think it would be of some benefit to tell the committee members what those are? My recall of them is not good enough to do that for the group.

DR. TEMPLE: I'm not sure I'm going to remember all of them, but I'll remember some of them. This generally refers to situations where you're looking at a claim for a drug that already has some kind of claim and you bring forth other data. The examples that are given

are where you have data at one dose, you don't usually need two studies at another dose. We might rely on a study of a drug alone and only ask for a single study where it was to be used in combination. If the conditions are closely related, a subject to be considered, you might move to a closely related disease with just a single study. That happens in oncology all the time. Different stages of the disease or severity of the disease, you don't usually need two studies to move from one to the other. It's examples like that.

DR. KAWAS: Thank you.

On that note, Dr. Ebert, would you like to begin?

DR. EBERT: Yes. I'll vote yes. I think that again the emphasis here is on treatment of a symptom not on the amelioration or the elimination of the disease, and given the fact that the drug has had a similar effect on that symptom for the other diseases that have been discussed, I feel comfortable with that indication.

DR. KAWAS: Dr. Mignot?

DR. MIGNOT: Providing that there is some very strong labeling regarding the possibility of having shift work disorder and sleep apnea, for example, which I think is going to be extremely common, I would vote yes.

DR. KAWAS: Dr. Krahn?

DR. KRAHN: Providing that there's very strong labeling that is for shift work sleep disorder rather than shift work, I'll vote yes.

DR. van BELLE: Yes.

DR. KAWAS: Dr. Wolinsky?

DR. WOLINSKY: Yes.

DR. KAWAS: Given that from my perspective the criteria is two independent studies and we only have one, I vote no.

Dr. Kattah?

DR. KATTAH: Yes.

DR. KAWAS: Dr. Neubauer.

DR. NEUBAUER: No, because I think the conceptual issues of exactly what constitutes the shift work sleep disorder, as opposed to those individuals who are doing shift work and experience some sleepiness, and also back to the question of the effectiveness that I discussed earlier with these people still being in a range of very profound sleepiness.

DR. KAWAS: Thank you.

So the tally on this is 6 yeses and 2 noes.

Any other questions, things, discussions, queries you would like us to address?

DR. KATZ: I can't think of anything.

DR. KAWAS: I hereby declare lunch. This

meeting is adjourned.

(Whereupon, at 1:54 p.m., the committee was adjourned.)