FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

Thursday, November 14, 2013

8:00 a.m. to 3:00 p.m.

Sheraton Silver Spring Hotel

Cypress Ballroom

8777 Georgia Avenue

Silver Spring, Maryland

Meeting Roster

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P R O C E E D I N G S

Call to Order

Introduction of Committee

DR. FOUNTAIN: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I'd also like to identify the FDA press contact, Stephen King. If you're present, please stand.

I'd like to begin also by introducing ourselves for the panel. We can go around the room, and maybe we'll start with Dr. Kramer, on my left.

DR. KRAMER: Yes, hi. I'm Lynn Kramer. I'm the industry representative on the committee. I'm a neurologist also.

MS. SITCOV: I'm Cynthia Sitcov. I'm the patient representative on the committee. This is the fifth committee I've served on at the Central and Peripheral Nervous System. It's an honor to serve.

DR. HOFFMANN: I'm Richard Hoffmann, and I'm

a pharmacist and medical writer. And I'm the consumer representative on this committee.

DR. SACK: I'm Robert Sack. I'm professor of psychiatry and sleep disorders medicine from Oregon Health and Sciences University in Portland, Oregon and an invited member of the committee.

DR. VITIELLO: Michael Vitiello, professor of psychiatry and medicine at the University of Washington, also a temporary member.

DR. EASTMAN: I'm Charmane Eastman from Rush University Medical Center in Chicago. And in our lab, we study melatonin pills we give to normal, healthy volunteers to study phase shifting and sleep-promoting effects.

DR. KRYSCIO: I'm Dick Kryscio from the University of Kentucky. I am a professor of statistics and biostatistics and a temporary member of the committee.

DR. BAGIELLA: Emilia Bagiella. I'm a professor of biostatistics at the Mt. Sinai School of Medicine.

DR. FOUNTAIN: I'm Nathan Fountain and a

professor of neurology at the University of Virginia and chair of the committee.

LCDR JOHNSON: Good morning. I'm Glendolynn Johnson. I'm the DFO for the Peripheral and Central Nervous System Advisory Committee.

DR. CLANCY: I'm Robert Clancy. I'm a professor of neurology and pediatrics at the Children's Hospital Philadelphia and the University of Pennsylvania School of Medicine.

DR. ZIVIN: I'm Justin Zivin. I'm professor emeritus of the University of California San Diego. I was in the neurosciences department, and my specialty was stroke research.

DR. MIELKE: I'm Michelle Mielke, associate professor of epidemiology and neurology at the Mayo Clinic.

DR. LUAN: I'm Julia Luan from FDA CDER. I'm a mathematical statistician.

DR. JILLAPALLI: I'm Devanand Jillapalli. I'm a clinical reviewer at the Division of Neurology Products.

DR. FARKAS: Ron Farkas, clinical team

leader, Division of Neurology Products.

DR. BASTINGS: Eric Bastings, acting director, Division of Neurology Products.

DR. UNGER: Morning. I'm Ellis Unger. I'm director of Office of Drug Evaluation I, Office of New Drugs, FDA.

DR. FOUNTAIN: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by me, the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the

meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass it to Lieutenant Commander Glendolynn Johnson, who will read the conflict of interest statement.

Conflict of Interest Statement

LCDR JOHNSON: The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of

interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C., Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts, when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for their potential financial conflicts of interest of their

own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves new drug application 205677 for tasimelteon capsules, proposed trade name Hetlioz, submitted by Vanda Pharmaceuticals. The proposed indication is for the treatment of non-24-hour sleep-wake disorder in blind individuals without light perception.

This is a particular matters meeting during which specific matters related to Vanda's Hetlioz will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose

any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Lynn Kramer is participating in the meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Kramer's role at the meeting is to represent industry in general and not any particular company. Dr. Kramer is employed with Eisai.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the committee of any financial relationship that they may have with the firm at issue. Thank you.

DR. FOUNTAIN: Dr. Kramer, would you like to

say any disclosures?

DR. KRAMER: Yes. I would like to inform the committee that I was a consultant for Vanda on this particular project. I can't remember the year quite. I think it was 2005 or 2006, and it was at the time of their first trial. At the time, it didn't have any indication, so it was healthy volunteers. I think it was a study done at Harvard. I have no other involvement with the company.

DR. FOUNTAIN: Thank you.

We will now proceed with Dr. Bastings's introductory remarks.

FDA Introductory Remarks

DR. BASTINGS: Good morning. I would like to welcome back the committee members today and extend a special welcome to the temporary members who are coming to offer expertise to today's discussion.

I also want to extend a special welcome to the patients and the representatives who will be testifying today in the open hearing session. And

I will now briefly cover with you the main issues that we would like the committee to discuss.

As you know, tasimelteon is a melatonin agonist proposed for the treatment of non-24-hour sleep-wake disorder, or so-called non-24, in totally blind patients. This is a novel indication for which no drugs has ever been approved by the FDA.

Non-24 is a type of circadian rhythm sleep disorder that occurs in totally blind individuals due to loss of the normal input from the eyes above environmental light levels. The disease is characterized by cyclical daytime sleepiness and nighttime insomnia.

In support of the application, the sponsor submitted the results of two placebo-controlled trials, Study 3201 and 3203. As will be discussed by Dr. Jillapalli, medical reviewers for this application, and by Dr. Luan, statistical reviewer, an agreement on the primary endpoint could not be reached with the sponsor during the development program.

The sponsor proposed a primary endpoint of entrainment of the circadian melatonin rhythm as measured by urinary metabolite of melatonin aMT6s.

FDA did not accept a biomarker-based primary endpoint because the FDA felt that the clinical benefit from entrainment in non-24 would occur in a reasonably brief period of time and would be rather immeasurable. In that setting, FDA asked the sponsor to propose a primary endpoint capable of demonstrating a clinical benefit, but the sponsor decided to maintain the biomarker-based primary endpoint.

There were, however, agreements reached with the sponsor on clinical endpoints. Specifically, the FDA agreed that endpoints that focused on sleep on the days when symptoms were worst would have the greatest likelihood of identifying a beneficial effect and would be acceptable.

Specifically, the lower quartile of nighttime total sleep time and the upper quartile of daytime total sleep duration were considered by FDA to represent valid endpoints, but again they

were considered by the sponsor as secondary in their trials.

FDA agrees that both studies were positive based on the applicant's prespecified primary analyses. However, as we just discussed, the analyses were based on a biomarker that FDA had not accepted. Secondary endpoint directly assessing clinical benefits were also mostly positive, but were not ordered to correct for type 1 error due to multiple comparisons.

So the first question to the committee will be to discuss whether non-24 is appropriate as an indication for FDA approval. We would like the committee to discuss whether they find the intended population and diagnostic criteria reasonable, and whether they have any concerns with the way the condition is defined or represented. And we also would like the committee to discuss whether they are satisfied that non-24 is a bona fide sleep disorder with consequence for patients.

Our second question we ask you to discuss is the appropriateness of clinical endpoints and,

specifically, the lower quartile of nighttime total sleep time and the upper quartile of daytime total sleep duration. Again, these endpoints are novel and have never been used before to support approval of new drugs.

First, our first question we ask you to discuss is the evidence of efficacy presented and specifically whether you have any concern with the design, conduct, and analysis of the efficacy trials. And we ask you to vote on whether substantial evidence for efficacy has been presented for drug and for this indication.

Finally, we ask you to discuss and vote whether the safety evidence presented for tasimelteon in non-24 has been adequately addressed.

Finally, as I believe the term of Dr. Fountain as chair of this advisory committee is coming to an end, I would like to express my deep gratitude for the excellent job that Dr. Fountain has done in this function and for the many hours he has spent preparing for and participating in the

advisory committee meetings. So Dr. Fountain, thank you very much for everything.

I now turn the meeting back to you.

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

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting. Likewise, FDA encourages you, at the beginning of your presentations, to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at

the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentations.

Sponsor Presentation - Mihael Polymeropoulos

DR. POLYMEROPOULOS: Thank you. Good morning. I am Mihael Polymeropoulos. I am the founder and chief executive officer of Vanda Pharmaceuticals. I am a physician trained in psychiatry and genetics.

Before we begin today, I would like to sincerely thank all our colleagues, investigators, experts, advisors that helped us develop this program over the last 10 years; the FDA, for numerous discussions, meetings, advised again over the years of development; and of course, the advocacy organizations for the blind here in the United States, in France, in Germany, and of course, all are very dedicated patients who gave their trust and inspiration in the development of this program.

We're here to discuss today our work on

tasimelteon in the treatment of non-24. The proposed trade name is Hetlioz. The indication is treatment of non-24 in the totally blind and the proposed class is that of a novel class of circadian regulator.

Non-24 is a circadian rhythm disorder that is a result of the inability to entrain the master clock of the suprachiasmatic nucleus in the hypothalamus to the 24-hour day. That inability of entrainment, in turn, leads to non-entrainment of a number of hormones, including melatonin from the pineal, cortisol from the adrenal.

The master clock is entrained by light. Each one of us has an endogenous clock that is not 24, but for most of us, longer than 24 hours. Light, sensed through the eyes and received by a specialized group of neurons in the retina -- the intrinsically photosensitive retinal ganglion cells -- transmits this information through the retinohypothalamic tract to the SCN or suprachiasmatic nucleus, where the master clock is resetting every day, the clock, to a 24-hour

period. The SCN in turn entrains hormone secretion under circadian control like melatonin and cortisol.

In the totally blind, the inability to sense light and, therefore, activate this path leads to non-entrainment. And blind people with non-24 have a circadian period of 24 and a half hours. That leads to a dyssynchrony by perpetually delaying by a half-hour its day in relation to the 24-hour world.

The circadian time and system is a complex system that is beginning to be understood. In a simple cartoon here, it shows that the main environmental entrainment, or known in the field as a timekeeper, is the light dark perception. That resets the clock sitting in the suprachiasmatic nucleus, which leads to controlling circadian processes of sleep and wakefulness -- we'll discuss a lot today about that -- cortisol and melatonin, heart rate, core body temperature, and a myriad of peripheral clocks in almost every tissue of the body, controlling cardiovascular, metabolic

homeostasis, the immune system, the cell cycle processes as well.

Non-24 is a rare orphan disorder. However, it is quite prevalent in the totally blind. Approximately 80,000 people in the U.S. are expected to be totally blind with non-24. It is a serious, debilitating, chronic disorder with no available treatment today.

It is characterized by severe, cyclical sleep-wake symptoms and inappropriate timing and consolidation of sleep episodes. This leads to a significant impairment in social and occupational functioning, preventing these patients to be as attentive as they want to be at school, productive at work, and having fruitful relationships. The effects on cardiovascular, metabolic symptoms are only beginning to be understood.

In 2010, the U.S. FDA granted orphan designation for this disorder in the totally blind. In 2011, the European regulatory agency, EMA, followed. In July 2013, the U.S. FDA granted priority review for this rare disorder with an

unmet medical need.

What you don't see in this slide is a reflection of the numerous meetings, consultations, advice with the FDA during this novel development program. And as you heard from Dr. Bastings and you see in the briefing book, these discussions were not always in agreement, but that's what happens when you have a completely new product to develop.

However, our goal all along was to develop the product in the best way possible and do two things, stay true to the science but also stay true to the regulatory concept of providing clinical benefit to patients and demonstrating it.

As Dr. Bastings pointed out, the primary endpoint was entrainment of the master clock. And in consultations, discussions with the FDA, we actually added a second primary endpoint that will discuss a lot about hopefully addressing the clinical benefit in this disorder.

Considerations during the development program was the rarity of the disorder, the

difficulty recruiting, and again we're extremely thankful to the international advocacy organizations for the blind. There is no approved treatment. And some endpoint concepts will be discussed today.

First, entrainment is in the causal pathway of the disease. Both sleep amount and timing have to be key considerations in developing a clinical composite to measure benefit. And finally, the cyclicity of the disorder is a key consideration in calculating endpoints.

The clinical development program consisted of two pivotal studies, the SET Study 26, duration of treatment, measuring as primary endpoints the entrainment and the clinical response composite, and the RESET study, a 19-week study measuring maintenance of entrainment and maintenance of clinical response.

We believe that our results on entrainment and clinical response measures demonstrate a specific and clinically meaningful effect, that the safety database established tasimelteon to be a

safe and well-tolerated agent for chronic use, and finally the overall benefit-risk ratio is positive for the treatment of patients with non-24.

A bit on the agenda today, I will be followed by Dr. Czeisler, who is the chair of the scientific advisory board at Vanda and a professor at Harvard Medical School, who will discuss history and pathophysiology of non-24 disorder.

Dr. Licamele from Vanda will discuss the clinical endpoints, what they are, why we chose them. Dr. Dressman will review all the efficacy data. Dr. Baroldi will discuss clinical pharmacology, Dr. Sliman the safety, and finally, I will come back at the end for a few minutes to discuss some new analysis that the FDA requested during the course of this review.

Dr. Czeisler?

Sponsor Presentation - Charles Czeisler

DR. CZEISLER: Thank you very much, Dr. Polymeropoulos. First, by way of disclosure, I have not been an investigator on the clinical trials evaluating the efficacy and safety of

tasimelteon, as I am a paid consultant to Vanda Pharmaceuticals, and I also have an equity interest in Vanda Pharmaceuticals.

I am going to be discussing the history and pathophysiology of non-24 disorder. The history of this disorder goes back to 1948, when Dr. Remler in Germany first reported circadian rhythm and sleep disorders in a blind population, in a totally blind population.

He studied 75 totally blind people and did a constant posture study in which he actually measured body temperature, and gave meals every hour, and so on in a protocol that is reminiscent of many of the protocols that are used today, very careful evaluation. And he demonstrated that in 43 percent of totally blind people, their body temperature rhythm was completely inverted with a peak during the nighttime and a trough during the daytime. He also demonstrated that their blood pressure, heart rate, and urine rhythms were also abnormal.

He reported that the predominant clinical

symptom by far was sleep disturbance, in 45 percent of the patients, with some individuals only having a sleep disturbance at times, followed by periods of regular sleep.

Then, in 1977, there was a case study by Laughton Miles and others at Stanford, in which he demonstrated a non-24 period of both the sleep-wake cycle and the timing of the body temperature, and cortisol, and other rhythms in a blind person living in society, who was unable to synchronize to the 24-hour day.

Then, two years later, Orth and colleagues did a study, and Sack in 1992, Nakagawa in 1992, and Klein and others in 1993, showing that non-24 hour periods of the circadian rhythms of body temperature and cortisol could exist in blind people who maintained a 24-hour period of their sleep-wake time for social and cultural reasons.

So it would be as if you traveled to Japan, you were trying to sleep at night in Japan. Your sleep might be disturbed. Your waking might be disturbed during the daytime, but you were trying

to live on that time zone. And so what was discovered in these subsequent cases is that most totally blind people attempt to live on the 24-hour day even though their internal circadian rhythms are precessing with a non-24 period.

Subsequently, we showed, in 1995, that a small group of totally blind patients could actually -- their circadian rhythms could be reset by light that they could not see because the eye, just like the ear has two functions -- one is hearing and the other is balance -- the eye also has two functions, one being sight and the other being circadian photo reception.

So we discovered that a very small population of totally blind people who lost their sight could still maintain their circadian photo reception, whereas others, both functions were lost if an eye were more severely damaged. And Gooley, Berson, and Hattar later showed -- because it took us five years to get that initial study published because people found it hard to believe that the eye had this second function.

Then the discoveries by Gooley, Berson, and Hattar that there was a separate system in the eye, separate from the rods and cones, and that some of the ganglion cells in the eyes, about 1 or 2 percent of them, were intrinsically photosensitive, and that those intrinsically photosensitive ganglion cells contained a novel photopigment, melanopsin, which was responsible for mediating circadian entrainment in the small subset of the population that could do so.

To understand non-24 hour disorder, one must realize that there is a circadian clock in the brain. Actually, many of our tissues have a clock. The kidney, the gonads, the eye, the lungs, and so on, the liver, have their own clocks, but they are synchronized together by this master circadian clock in the brain, in the hypothalamus of the brain, that is a collection of about 50,000 neurons on either side of the third ventricle in the anterior region of the hypothalamus.

It acts as, if you will, the conductor of the orchestra of different clocks in the body,

sending out -- and it is the region that is synchronized to the light-dark cycle from the outside world. The suprachiasmatic nucleus generates a self-sustained oscillation with an intrinsic period that, on average, as Dr. Polymeropoulos mentioned, is slightly longer than 24 hours.

These retinal sensors, these intrinsically photosensitive retinal ganglion cells, transmit light information from the retina to this suprachiasmatic nucleus of the hypothalamus via a monosynaptic retinal hypothalamic track.

The periodic light-dark cycle, which normally has an imposed period of 24 hours in normally sighted people and in a minority of these blind people with intact retinal ganglion cells, entrains the suprachiasmatic nucleus to the observed period of 24 hours in normally-sighted individuals.

This master circadian clock controls circadian rhythms of endocrine functions, such as pineal melatonin, adrenal cortisol and thyroid

hormone, sleep-wake patterns via the circadian rhythm in sleepiness, alertness, and in the ability to sleep, and the ability to remain awake.

It controls daily variations in performance rhythms such as cognitive throughput, reaction time, memory, and coordination; cardiovascular rhythms such as blood pressure and heart rate; metabolic rhythms such as insulin secretion and glucose tolerance, lipids, immune system; and renal rhythms.

I'm going to focus on two rhythms, melatonin and cortisol, that have been used as markers. They are such robust oscillations that they have been used as markers of the output of this internal biological clock. Melatonin normally peaks at night and cortisol peaks in the morning. Some people think that blind people would not have circadian oscillations. But actually, in blind people with non-24-hour disorder, both melatonin and cortisol rhythms maintain robust oscillations, but they are simply not synchronized to the 24-hour day.

There's a graphic here from Sack and colleagues showing that melatonin rhythm is peaking during the biological night in these individuals and cresting during the biological morning. They continue to oscillate with a non-24-hour period and are not entrained or synchronized to the 24-hour day.

The process of synchronization to the 24-hour day -- and I have a cartoon from Tom Wehr's article illustrating how the circadian system is connected, how the light-dark cycle influences the circadian system. The light-dark information coming in through the eye is transmitted along that retinal hypothalamic track to the suprachiasmatic nucleus, down the spinal cord to the intermediary lateral cell column of the spinal cord, and up to the superior cervical ganglion, and then to the pineal gland, where it regulates the release of pineal melatonin at night.

In an individual who is receiving that light-dark information, the melatonin rhythm is released every night. And here, I'm showing

consecutive nights for a couple of weeks, every day of the rhythm, peaking at night and being low during the daytime.

In the absence of light input, if you're sighted, but you're living continuously in darkness, the oscillation continues, maintaining the secretion of melatonin with a near-24-hour period.

However, in the absence of either the eyes or the light-dark cycle, then what happens is that the rhythm, as I said, is not synchronized to the 24-hour day. It continues to send -- the SCN continues to send that signal to the pineal gland, but the period is not exactly 24 hours.

So what is being illustrated in this slide is that an individual with a non-24-hour, longer than-24-hour period, then every day the melatonin will be peaking at a later time.

Here's an example of a blind person who does not have non-24 disorder in the upper left-hand panel. And in this case, the excretion of a metabolite of melatonin in the urine is being

assessed at weekly intervals for 48 hours.

What you can see in this slide, in this normally entrained individual who is living in society where the imposed period of the light-dark cycle is 24 hours and the observed period is 24 hours, in week 1, week 2, week 3, and week 4 of these sequential assessments that occur over a month-long interval, the melatonin rhythm in each case, the excretion of this metabolite, is peaking during the nighttime hours during these 48-hour time window segments.

In the next panel on this slide, I am going to show you an individual with non-24 disorder and show how these 48-hour assessments at weekly intervals will not be occurring at the same time of day.

So in this example, you can see, in week 1, week 2, week 3, and then in week 4, that the timing of the rhythm begins peaking in the middle of the daytime. Then it moves to later in the daytime, peaking at around 1800 hours. Then, in week 3, it is peaking even later around midnight or 1:00 in

the morning. And then, in week 4, it actually comes completely around and is now peaking again during the nighttime, and then would continue on and on.

So in this particular individual, who has a 24.7-hour period of the circadian system, you see that it takes about 35 days, because at .7 hours a day, it takes about 35 days to come completely around and go through the 24-hour, to be back where it started.

That is called a circadian beat cycle. So there is the intrinsic period of the oscillator at 24.7 hours. And then, as that precesses around and goes slightly around the clock, that takes 35 days, which is the beat cycle.

Now, here is an illustration of a very recent paper from July of 2013, reviewing non-24 hour disorder in blind patients and looking at the variability and influence of environmental synchronizers. And as you can see, there are a number of different patients illustrated in this diagram. And some of them have been studied for

more than a year.

The vertical axis is the number of days that they have been followed. They have had weekly, or every few weeks, assessments of the phase of the timing of their release of the hormone melatonin into the bloodstream. And you can see in patient number 9, the circadian beat cycle takes 133 days to complete one cycle because the period is very close to 24 hours, being at 24.18 hours, whereas, in patient number 2, the beat cycle is 73 days because the intrinsic period is about 24 and a third of an hour.

So it takes three days to go one hour, and therefore about 72 days to go around the entire 24 hours. And in the case of patient number 10, where the period is very close to 25 hours. It actually takes only 25 days to go around because it's going at almost an hour a day. And so it only takes just over 24 days to go completely around the clock for that particular beat cycle.

Now, how does sleep relate to entrainment? The timing of sleep-wake patterns, as I mentioned,

is driven by the output of the circadian clock, but it is not the only factor. So there is a second factor, which is homeostatic regulation of sleep. And the simplest way I can describe that is that the greater the number of hours that you're awake, the greater is the drive for sleep. The more you sleep, the less is the drive for sleep.

But those are not even the only two factors that influence the timing of sleep, the sleep-wake cycle. So you have the circadian rhythm, which in these patients does not have a period of 24 hours. You have homeostatic regulation of alertness, sleep, and sleep propensity, and wake propensity. But then you have the work schedule.

So if an individual is supposed to be working during the daytime, even though that might be the time of their sleep propensity, they may drink coffee or take other things during the daytime to help them stay awake and try to sleep at night. And their social schedule will also be on a 24-hour schedule as well as cultural expectations. So these are various factors that are influencing

the timing of sleep in these patients.

If we look at the ability to sleep as a function of circadian phase -- and this is the work of Dr. Joe Hull for his doctoral thesis -- you can see that in this diagram where totally blind people are put in bed in the laboratory and attempting to sleep at all different circadian phases, you can see in the lower panel is the timing of the endogenous rhythm of melatonin secretion. In the next panel up is the percent of time that they are lying awake in bed, unable to sleep.

You see that when the melatonin is not being secreted and they're attempting to sleep during their biological daytime, they are awake 35 to 40 percent of the time, whereas when they are attempting to sleep during the time of their biological night, they are sleeping 90 percent of the time.

Then in the upper two panels, you can see what happens to their waking function when they are attempting to wake at all different circadian phases. And when they are attempting to wake

during their biological night, their alertness is degraded and their performance as measured by -- their neurobehavioral performance, as measured by lapses of attention, is at a nadir.

So they have a disturbed sleep-wake cycle. This has a severe impact on social and occupational functioning and an adverse impact on cognitive functioning and learning. There is also increasing evidence that recurrent disruption of circadian rhythms adversely affects cardiovascular and metabolic homeostasis.

By way of illustration, I am going to review a situation that does not occur in blind people, but occurred in a very small group of sighted people that I was asked to investigate by NASA in 2001. And this was because there was a rebellion among the jet propulsion laboratory personnel at Cal Tech during 1997 Mars Pathfinder mission.

When they were on that mission, they found that living on the Mars day taxed the personnel there beyond what the personnel called beyond reasonable limits and prompted a rebellion, which

is why I was asked to come in and investigate. And they actually wanted to turn off the two little rovers that were on Mars and stop the program, which was of great concern to NASA.

We did experimental studies, then, in my laboratory in which we simulated the impact of the Martian day, on-sighted people trying to live on the Martian day, and demonstrated, as you can see in the left-hand panel, some of the individuals were able to maintain synchronization to the Martian day, but that was a small minority, whereas on the right-hand panel, you can see that what most of them experienced was the same kind of disruption of their circadian rhythms as seen in blind people, with the peaks of melatonin occurring during their biological -- during the time that they were trying to stay awake and function.

So they suffered from circadian misalignment, chronic sleep disruption, cognitive impairment, and as Ken Wright and others in the lab showed, an inability to learn when they were being given tasks on a recurring basis.

So normally, sighted people living on the Earth day have an observed period of 24 hours in response to the imposed period of 24 hours. In these individuals who are trying to be subjected to the Martian day, they exhibited, most of them, an average period of 24 hours and nine minutes as they were trying to live on the 24-hour and 39-minute Martian day. And that's what led to symptoms that were very similar to non-24 disorder in the blind.

The blind, in essence, their internal clock is oscillating with a period that's very close to that of the Martian day, but they're trying to live here on Earth.

So there is a need for an effective therapeutic for a non-24-hour disorder in blind people because the patients suffer from recurrent delaying of their internal circadian clock with respect to the 24-hour day. To be effective, a therapeutic must be able to reset the master circadian clock in totally blind patients without light perception.

The gold standard measure of effectiveness

for a treatment of non-24 disorder -- and I have urged the company of this -- for the past 10 years must be entrainment of the circadian system because if a therapeutic could provide symptomatic relief, but did not entrain the circadian system, that would have to be designated as a treatment failure even if it showed symptomatic clinical improvement. And that is why I have been relatively strident in insisting that the primary outcome measure be entrainment and recommending that to the company.

Improvement in sleep-wake timing should occur as a consequence of entraining the master circadian clock, but improvement in sleep-wake timing without entrainment should not be deemed as a success. Thank you very much for your attention.

Sponsor Presentation - Louis Licamele

DR. LICAMELE: Good morning. I am Louis Licamele. And in this presentation today, I will discuss the clinical endpoints for the tasimelteon development program, which were developed in collaboration with both circadian experts as well as through discussions with the FDA. I will

discuss two things, first what these endpoints measure as well as why we selected them.

The first endpoint of entrainment, as introduced by Dr. Czeisler, demonstrates efficacy in resetting the master clock to the 24-hour day. The next class of endpoints is centered around the non-24-hour clinical response scale or N24CRS, which is aimed at measuring improvements in both sleep-wake measures as well as overall functioning.

Before we start discussing the clinical endpoints, let's consider for a second why the obvious sleep outcomes of total nighttime sleep and total daytime sleep are not appropriate for non-24.

Nighttime total sleep time and daytime total sleep duration are not specific endpoints for non-24 for two reasons. First, they're not focused on the periodic misalignment between circadian period and the external 24-hour clock. And second, minimal disruption is expected in both nTST and dTSD when individuals are in phase. Furthermore, this will result in reduced detection power for this rare and orphan disorder. For these reasons,

nTST and dTSD are not appropriate for non-24.

Let me now discuss what are more appropriate measures of effectiveness. I will discuss entrainment in the non-24-hour clinical response scale.

Again, entrainment is a measure of the synchronization of the master clock to the 24-hour day. There are standard methods for measuring entrainment in the field, and there are three key terms I would like to define for this presentation.

Analytes used for circadian period measurement include a first urinary melatonin metabolite or aMT6s and, second, urinary cortisol. Acrophase, which is the peak time of endogenous analyte secretion, was measured over a 48-hour period. This was repeated weekly for at least four weeks. Tau, or the length of an individual's circadian period, was measured by a linear regression across these acrophases. Data from a non-24 patient illustrate the change in acrophase from week to week.

This individual had four acrophase

measurements, each a week apart. During week 1, their acrophase was 1:49 p.m. On week 2, their acrophase was about 5:20 p.m., at week 3 9:30 p.m. And by week 4, the acrophase moved to 3:00 a.m. For each of these acrophase measurements, we also obtained the standard error and the p-value representing the goodness of fit.

To calculate tau, let's take a look at the linear regression in the next slide. The weekly acrophase values move later over time, generating a slope greater than zero, reflecting the fact that this patient is not entrained.

The X axis shows weeks and the Y axis shows the time of acrophase. This non-entrained patient has a tau value of 24.58, about 35 minutes longer than the 24-hour day. Since this endogenous rhythm delays 35 minutes every day, it will take 42 days to cycle back to their starting point. Therefore, this patient's cycle length is 42 days.

Different people have different endogenous taus and therefore, different cycle lengths. In this composite of four different tau values, we see

in the upper left an individual whose tau is 24. They are entrained, and this is the goal of treatment. The non-24 patient in the upper right has a tau of 24.3, corresponding to a cycle length of 80 days. In other words, this patient's cycle would be aligned with the external 24-hour day once every 80 days.

In the bottom left is a non-24 patient with a tau of 24.5. They drift half an hour further out of alignment every day. The higher tau results in a shorter cycle length such that the patient in the lower right of the slide with the highest tau has a cycle length of just 30 days.

Lack of entrainment is associated with cyclical changes in sleep and wake measures. The raster plots derived from these four individuals' sleep diaries reflect the timing of their sleep every day for over 100 days. Nighttime and daytime sleep are double-plotted to assist in individually identifying cyclical patterns. The study days are on the Y axis in hours and the hours of the 24-hour day are on the X axis.

The data is double-plotted in that a 48-hour window is shown on each line. The top line on the Y axis, marked as zero, shows day 1 to the left followed by day 2 to the right. The next line shows day 2 followed by day 3, and then day 3 followed by day 4. And this pattern continues.

Nighttime sleep is represented by the blue horizontal bars, and daytime sleep is represented by the black horizontal bars. The red stars indicate the aMT6s acrophase. And we see in the upper left an entrained person, as indicated by the fact that the red stars are aligned vertically and occurring during the night.

This entrained individual tends to have consistent sleep, mainly occurring at the appropriate time, at night. They suffer from little daytime sleep. The other three individuals have non-24. And while the majority of these patients will try to sleep at night, they experience cyclical patterns of sleep disturbance.

When a patient's circadian rhythms are out of phase with the 24-hour day, they may experience

a very strong circadian drive to sleep during the day regardless of the amount of sleep they had the night before. During other phases, the patient may not report having any daytime sleep.

Given that there's clearly a problem across many different sleep-wake parameters, the ideal clinical outcome for evaluating treatment of non-24 should take into account the cyclical sleep-wake issues of both amount and timing. The non-24 clinical response scale is designed to account for all these factors.

LQ-nTST, or the lower quartile of nighttime total sleep time, measures the average nighttime sleep during the patient's worst 25 percent of nights. UQ-dTSD, or the upper quartile of daytime total sleep duration, measures the average daytime sleep during the worst 25 percent of days. MoST measures the timing and consolidation of sleep. And the CGI-C, or the Clinical Global Impression of Change, is a physician-rated scale of global functioning.

In addition to being a non-24 clinical

response scale component, each measure is also an individual secondary endpoint for these trials as continuous outcomes.

Let's review each one of these components and their characteristics. The LQ-nTST focuses on the worst nights of sleep, defined as the 25 percent of nights during which patients have the shortest total nighttime sleep. The Y axis is the total nighttime sleep in minutes, and the X axis is study days. Data for one patient is shown, and each dot represents one night of sleep. The blue shading captures the quartile days that the patient had the least nighttime sleep.

Here, we see how nighttime total sleep time, plotted on the Y axis, is significantly reduced when patients are out of phase. The data shown is the average across all randomized individuals during the screening portion of the SET study. The X axis shows the progression of being in phase to out of phase and coming back into phase with the 24-hour day. When these individuals are in phase, there's no difference between their nighttime total

sleep and that of their entrained counterparts.

Non-24 is a cyclic disorder. When non-24 patients are 180 degrees out of phase, they experience dramatically less nighttime sleep. As expected, the majority of patients' worst nights occurred during this out-of-phase period, as can be seen by overlaying the distribution of LQ-nTST in red.

The second Y axis on the right corresponds to the percent of LQ-nTST at a given phase. LQ-nTST and phase are highly correlated. LQ-nTST was chosen, as it allows us to measure the specific effect of non-24 in a straightforward and simple manner.

In summary, the important properties of LQ-nTST are that it enriches for the worst night analysis, reflective of the cyclical nature of non-24, it's highly correlated with circadian phase, and it's clinically meaningful, as it's a direct reflection of the amount of nighttime sleep, when patients are suffering the most.

Similarly, the UQ-dTSD measure focuses on

the maximum amount of daytime sleep. The upper quartile of daytime sleep duration, or UQ-dTSD, is shown for a patient. The Y axis is the total daytime sleep duration in minutes, and the X axis is study days.

Even though this patient is able to avoid daytime sleep during 75 percent of their days, during the other 25 percent of days, they suffer from sleeping on average three hours and sometimes as much as six hours during the day.

Here, we see how daytime total sleep duration, plotted on the Y axis, is significantly increased when patients are out of phase. The X axis is the same as before. It shows circadian phase. And again, this is the average across the population of screening.

When in phase, there's no difference between them and their entrained counterparts. It's when these non-24 individuals are 180 degrees out of phase that they suffer from a large amount of daytime sleep. The majority of the patients' worst days occurred during this out-of-phase period, as

can be seen by overlaying the distribution of UQ-dTSD in red.

The second Y axis on the right corresponds to the percent of UQ-dTSD at a given phase. UQ-dTSD and phase are highly correlated. UQ-dTSD allows us to measure the specific effect for non-24 on daytime sleep in a straightforward and simple manner.

In summary, the important properties of UQ-dTSD are that it, again, enriches for the worst day analysis, reflective of the cyclical nature of non-24, it's highly correlated with circadian phase, and it is clinically meaningful, as it is a direct reflection of the patient's ability to reduce daytime sleep.

LQ-nTST and UQ-dTSD measure sleep amount. The next component, MoST, measures sleep timing. The midpoint of sleep timing, or MoST, is the mean weighted average of all sleep occurring in a 24-hour period relative to a patient's desired bedtime.

MoST measures timing and consolidation of

sleep. Potential scores range from minus 12 to plus 12. For an example, a healthy individual who sleeps seven to eight hours at their desired bedtime with no daytime sleep will have a MoST value of 3.5 to 4. The average MoST value will trend towards zero or a negative number as an individual's sleep becomes more fragmented and distributed throughout a 24-hour day.

On the next slide, we can visually get a sense of how MoST operates. In this slide, we have a patient's raster plot on the left and their daily MoST values plotted on the right. The study days are plotted on the Y axis, starting with day zero at the top, and over 120 days are shown.

The raster plot on the left shows you that when an individual is in phase at around day 40, the patient has little daytime sleep. And the majority of their sleep occurs at night during their desired sleep period.

During this time, the MoST value is close to the target of 4, indicated by the orange vertical line on the plot on the right. On approximately

day 80, they begin to have reduced nighttime sleep and an increase in daytime sleep as they drift out of phase.

Focusing on the plot on the right, we see that MoST values become more variable and experience a shift to the left or smaller numbers when this patient is out of phase.

Similar to the analysis we saw before or LQ-nTST and UQ-dTSD, here we show MoST plotted on the Y axis across the circadian cycle. The X axis is the same as before. It shows circadian phase and, again, this is the average across the population at screening.

When in phase, MoST is close to 3.5, which is expected. It's what we expect from healthy individuals. Non-24 patients have lower MoST scores when they are 180 degrees out of phase. The important properties of MoST are that it measures the timing and consolidation of sleep, of all sleep episodes across a 24-hour period. It's highly correlated with circadian phase. And while novel, it's potentially clinically meaningful because it

reflects a patient's ability to consolidate most of their sleep at night.

The final component of the non-24 hour clinical response scale is CGI-C. CGI-C, or the Clinical Global Impression of Change, is a well-understood physician-reported outcome of overall functioning improvement. CGI-C is a 7-point scale, and the next slide shows how it's scored. A score of 4 represents no change. Scores of 3, 2, and 1 show increasing levels of improvement. And scores 5, 6, and 7 show worsening.

The non-24 hour clinical response scale is a composite scale of categorical endpoints for clinical improvement in nighttime sleep, daytime sleep duration, sleep timing, and global functioning. Each assessment on the n24CRS is dichotomized to a specific threshold of improvement so that a patient scores 1 if improved and 0 if not improved.

The threshold for LQ-nTST is an increase of at least 45 minutes in nighttime sleep. Similarly, the threshold for UQ-dTSD is an improvement or

reduction of at least 45 minutes in daytime sleep. The threshold for MoST is an increase or improvement of at least 30 minutes in the average MoST score. And the threshold for CGI-C is a 2 or less, corresponding to much improved or very much improved.

Clinical response is defined as meeting two criteria. First, the patient has to have an entrained master clock, as measured by aMT6s. Second, they must have a score of at least 3 or greater on the non-24-hour clinical response scale. This is reflected in two patient examples.

This patient began tasimelteon treatment at roughly day 130. The screening data are in blue and the post-randomization data is in green. As before, daytime sleep is in black and the red stars represent the timing of peak aMT6s.

With tasimelteon treatment, the patient is entrained, as reflected by the alignment of the red stars. And this patient experiences increases in nighttime sleep, decreased daytime sleep, and more consistent MoST values that are tightly clustered

and stabilized around 4, as shown on the right panel. This patient is a responder who is entrained and achieved N24CRS score of 4 by crossing the threshold of response for each of the subcomponents.

This included improvements of over two hours of LQ-nTST and UQ-dTSD. The clinician reported an overall change in global functioning of very much improved or 1 on the CGI-C.

The results are very different for a non-responder. This non-entrained patient's pattern of erratic sleep continues during placebo treatment, shown in green. They clearly do not have much improvement in nighttime sleep or reduction in daytime sleep. The MoST scores appear centered around the same range and are still highly variable and destabilized, consistent with the cyclical pattern that can visually be observed in the raster plot on the left. Obviously, this patient gets a zero on all the measures of their N24CRS score, resulting in an N24CRS score of zero. This patient is not entrained, and they are not considered a

clinical responder.

The lack of entrainment was correlated with the lack of clinical response. Looking back at the population at screening, there is also a strong correlation between entrainment and clinical response on these same sleep-wake parameters.

The clinical measurements of LQ-nTST, UQ-dTSD, and MoST are highly predictive of entrainment status, as can be seen in this analysis of entrained individuals versus non-24 hour patients during the screening portion of the SET study.

These measures are highly specific to non-24. Non-24 patients experience an hour less nighttime sleep per night, as measured by LQ-nTST, and similarly, an hour more daytime sleep per day, as measured by UQ-dTSD, compared to entrained individuals.

You can see that entrained individuals do in fact have an average MoST score of 3.5 hours, which is what we expect for healthy individuals. The non-entrained have an average MoST score of roughly

2.8 hours. The differences are all statistically significant, providing further evidence of the reliability and specificity of these measures. Taken together, these prespecified endpoints provide a clear measurement of the effects of a circadian regulator.

In summary, entrainment is a binary endpoint measuring the resetting of the master clock, based on urinary analyte levels. Clinical response, also a binary outcome, requires entrainment plus a score of 3 or greater on the N24CRS. LQ-nTST, UQ-dTSD, MoST, and CGI-C are all continuous measures.

Here briefly are some key references in regards to methods. And I would now like to introduce Dr. Marlene Dressman, the vice president and the non-24 hour clinical program head.

Sponsor Presentation - Marlene Dressman

DR. DRESSMAN: Good morning. Thank you, Dr. Licamele. The tasimelteon clinical program demonstrated the safety and efficacy of 20 milligrams of tasimelteon for the treatment of non-24 hour disorder in the totally blind.

Tasimelteon safety and efficacy profile is based on a complete clinical development program consisting of 22 clinical trials of 1,652 patients and healthy volunteers, including over 1300 individuals that were treated with tasimelteon. Dr. Sliman will talk more about the numbers of patients and their exposures in the safety discussion.

The tasimelteon clinical program included 14 clinical pharmacology and pharmacokinetic studies, a phase 2 circadian phase-shifting study, 2101, which provided the basis for studying non-24 in phase 3.

The phase 3 program for the treatment of non-24 in the totally blind comprises two phase 3 studies, SET and RESET, and two ongoing safety studies in the non-24 population, 3202 and 3204. The program is the largest comprehensive trial of non-24 patients ever conducted in the world, with over 180 patients treated across multiple sites and three countries. The phase 3 program assessed the safety and efficacy of the 20-milligram dose of

tasimelteon.

There are three lines of evidence that were discussed in the briefing book that support the 20-milligram dose selection. These three lines of evidence all support 20 milligrams as the minimum dose demonstrating efficacy. This is the only dose studied in a phase 3 non-24 studies due to the rarity of the disorder.

The two pivotal efficacy and safety studies in non-24 with totally blind patients were SET and RESET. SET was a 26-week study that assessed the efficacy of entrainment and clinical response. RESET was a 19-week study designed to show the maintenance of the effects on entrainment and clinical response.

Due to the challenges of recruiting patients in this rare orphan disorder, we allowed patients that participated in the SET study to enroll directly into the RESET study. This provided a unique opportunity to examine patients under different treatment conditions.

SET was a randomized, double-mast, parallel,

placebo-controlled multi-center trial in totally blind patients. Eighty-four patients between the ages of 23 and 74 years with non-24 were randomized. For inclusion in the randomization arm, patients had to have non-entrained circadian rhythm with a tau greater than or equal to 24.25 and a 95 percent confidence interval of 24.1 to 24.9. Patients also had to report a complaint on the sleep-wake complaint questionnaire.

Patients that had a tau greater than 24.0 but that did not meet the inclusion criteria for the tau values for the randomized arm were given the opportunity to participate in the open label arm.

The study was conducted in 33 sites, 27 in the U.S., and 6 in Germany. Seventy-six patients enrolled in the U.S. sites and 8 in Germany. The first patient was screened on August 25th in 2010, and the database was locked on December 12th, 2012. The SET study consisted of two parts, screening and the double-masked phase. Screening lasted on average three months and the double-masked phase

was six months in duration.

An attempt was made to initiate dosing in the double-masked phase when patients were in phase. There were three types of efficacy data that were collected. circadian period or tau, represented by the dark blue boxes, was estimated during screening, the double-masked phase, and during month 7 for a subset of patients that continued on into the RESET study.

In the double-masked phase, tau is measured very early, beginning at week 2. Sleep wake diaries, represented by the green horizontal bar, were collected throughout the entire study. Patient diaries were collected via an interactive voice recording system. Patients were required to call in the morning no later than one hour after their scheduled awakening and then again no later than 15 minutes after their daily dosing.

During these calls, patients were asked prerecorded questions about their nighttime and daytime sleep. Physician assessments of global functioning, or CGI-C, were assessed at months 2,

4, and 6, and safety assessments were conducted every month.

It is also important to add that after completion of the tasimelteon arm of the double-masked phase, 17 patients continued on into the run-in phase of RESET and collected tau data during month 7.

The prespecified primary objectives were entrainment of circadian rhythms and clinical response. Entrainment was defined as a tau less than 24.1 with a 95 percent confidence interval that included 24.0. Clinical response required a combination of entrainment and a score of 3 or greater on the non-24 clinical response scale.

The prespecified secondary objectives asked two types of questions. The first was whether other endocrine hormones regulated by the master body clock were entrained, as measured by cortisol at month 1. And the second type of question assessed the magnitude of the clinical response, as measured by the individual components of the N24CRS scale.

Values of LQ-nTST, UQ-dTSD, and MoST were averaged from sleep diary data collected throughout the entire study. Screening values were used in the model as covariates. CGI-C was the average score for months 4 and 6.

Three hundred ninety-one subjects were screened and 136 were treated either in the double-masked phase or in the open label arm. Eighty-four patients were randomized 1 to 1 to receive either placebo or tasimelteon, 20 milligrams, one hour before their scheduled bedtime at the same time every night.

Seventy out of the 84 patients in the double-masked phase completed the study, noted here at the bottom left as completers. Included in these 70 patients are 8 patients, 4 on placebo and 4 on tasimelteon, who had adequate data collected for the primary and secondary endpoints during the double-masked phase, but who were discontinued by Vanda when the study was closed.

The reasons for discontinuations for all of the rest of the patients were balanced between

treatment arms. All patients in the double-masked phase were totally blind and their cause of blindness had etiology representative of those known to cause complete loss of light perception.

The most prevalent cause of blindness was retinopathy of prematurity, which occurred in 33 percent of the patients. Retinoblastoma was the cause of blindness in 13 percent of the patients; 15 percent had ocular trauma, 10 percent glaucoma, and 9 percent had congenital glaucoma.

The tasimelteon and placebo arms were well matched for age, gender, race, and BMI. During the three-month screening period, we measured circadian periods and collected sleep data. Patients had an average circadian period of 24.5 hours, which translates to a circadian cycle length of approximately 50 days.

Non-24 patients were only sleeping 3.25 hours per night during their worst 25 percent of nights. That's only 3.25 hours. And they were sleeping an average of 2.5 hours during their daytime every day, during their worst days. The

midpoint of sleep was 2.61 in placebo and 2.82 in tasimelteon-treated patients.

There were two prespecified statistical assessment populations, the ITT and analysis population. The ITT population with N=78 consisted of all randomized patients with a tau calculated post-randomization, and this population was the one used for the entrainment endpoints.

The analysis population consisted of 72 patients, who were all in the ITT population and had at least 70 percent of one circadian cycle of nighttime total sleep time data during each of screening and treatment.

The primary clinical response endpoints and the secondary clinical endpoints were assessed in the analysis population to assure that there was adequate sleep-wake data available for each patient in this cyclical disorder. The ITT star population consisted of all randomized subjects. The ITT star was used in an FDA-requested post hoc sensitivity analysis that confirmed the results of the primary analysis.

Both of the predefined primary endpoints were statistically significant and favored tasimelteon in the SET study. Entrainment was measured early, in month 1, and 20 percent were entrained on tasimelteon, compared to 2.6 percent on placebo. Significance was tested with a Barnard's two-sided unconditional exact test and yielded a p-value of 0.017.

To remind you, clinical response meant that patients had to be entrained either at month 7 or month 1 and have a score of at least 3 on the non-24 clinical response scale. Twenty-four percent of tasimelteon patients showed a clinical response compared to zero on placebo, with a p-value of 0.0028.

Multiple sensitivity analyses were conducted to assess the robustness of the clinical response. All of the sensitivity analyses support the conclusions of the primary analyses. The results favored tasimelteon and were statistically significant, regardless of the timing of the assessment, of entrainment, or the number of

components in the N24CRS that were positive.

The first sensitivity analysis in this table is based only on entrainment data from month 1 and it remained significant. The next three analyses used different criteria for the cutoff on the N24CRS scale of 2 or 3. The clinical response rate for these cutoffs ranged between 29 and 58 percent and are all statistically significant.

All of the primary endpoint and sensitivity analyses are represented in these forest plots. Each point estimate is to the right of zero, favoring tasimelteon. Now, let's take a look at the entrainment rate overall.

As an exploratory analysis, we looked at what happened if circadian period was assessed at a time point later than month 1. This was feasible because 17 SET patients treated with tasimelteon subsequently then enrolled into RESET.

These 17 patients had their circadian period assessed on two occasions, the first being month 1 in SET and then again at month 7 during RESET. Ten of the 17 patients, or 59 percent, were entrained

at month 7 on tasimelteon compared to 20 percent at month 1. Nonetheless, statistical significance was achieved in the SET study, regardless of the timing of assessment.

Now that we know that tasimelteon entrains the melatonin circadian rhythms, we asked whether tasimelteon entrains other hormones controlled by the master body clock.

Entrainment of cortisol was also achieved by tasimelteon for a significant difference from placebo. The results were consistent with the entrainment results for melatonin with a p-value of 0.03 in favor of tasimelteon. Entrainment of the timing of melatonin and cortisol secretion, which are synthesized by different glands, is evidence that tasimelteon entrains the master body clock.

In addition to cortisol, we examined the magnitude of the effect of the individual components of the non-24 clinical response scale. Each of the individual components favored tasimelteon with p-values below 0.05. The tasimelteon treatment arm had an improvement in

nighttime sleep of 57 minutes per night in the worst nights, compared to 17 minutes in placebo, as measured by LQ-nTST.

Similarly, daytime sleep improved by 47 minutes per day for the worst days, compared to 18 minutes on placebo, as measured by UQ-dTSD. Midpoint of sleep timing improved by 35 minutes, compared to 14 in placebo. And importantly, tasimelteon-treated patients experienced positive changes in global functioning while placebo patients had little or no improvement.

The results in the analysis population are consistent across different ITT analysis populations. While the prespecified analysis population is the most appropriate population for assessing clinical measures for this cyclical disorder, we conducted post hoc sensitivity analyses in the protocol-specified ITT population and the ITT star populations.

nTST and dTSD were also included in the analyses. dTSD is significant for both ITT and ITT star; nTST is significant in ITT and has a p-value

equal to 0.06 for the ITT star. Results for the prespecified secondary endpoints are all significant and consistent in the ITT and ITT star populations, with the per-protocol analyses just presented.

This forest plot illustrates that, regardless of the analysis populations, the secondary endpoints all favor tasimelteon.

Additional secondary clinical endpoints were assessed. These consisted of different combinations of the already presented clinical and entrainment endpoints. A categorical measure requiring a 90-minute improvement in both LQ-nTST and UQ-dTSD numerically favored tasimelteon. And the post hoc sensitivity analysis of 45-minute improvements in both was also significant.

Categorical endpoints of entrainment plus a clinical measure of either LQ-nTST or entrainment plus UQ-dTSD, entrainment plus MoST, or entrainment plus CGI-I all favor the efficacy of tasimelteon with p-values less than .05.

Here is a graphical representation of these

additional secondary endpoints. All of the endpoints favor tasimelteon.

To understand the magnitude of the clinical benefits in entrained patients, we examined LQ-nTST, UQ-dTSD, MoST, and CGI-C in this entrained population. Compared to placebo, tasimelteon-treated patients that entrained benefitted from 82 more minutes of sleep per night for LQ-nTST. They had 74 minutes less of daytime sleep per day, plotted here as a positive value; entrained inpatients that experienced improvement of 52 minutes in the timing of their sleep and they had an improvement of 1.2 points on the CGI-C scale compared to placebo.

The benefits of tasimelteon treatment are also apparent in looking at the raster plots of individual patients. Examination of the totality of the sleep, wake, and entrainment data across the SET study provides a powerful visual aid for assessing efficacy.

Here, data for two patients are illustrated on raster plots. The upper blue portion represent

the screening phase and the lower green represents the double-masked phase. Both patients have not entrained circadian rhythms during screening. This is illustrated by the red stars, which move from left to right, and these represent the six sulfadoxine acrophase delaying daily.

The patients' nighttime sleep patterns, the blue horizontal lines during screening, are cyclical for sleep onset, wake time, and amount, especially in patient 1. They each experience excessive daytime sleeping, represented by the black horizontal lines.

Both patients were treated with tasimelteon during the double-masked phase and both experienced entrainment, as evidenced by the red stars, occurring at the same time each night in a vertical line. They also experienced stabilization of their sleep-wake patterns, as demonstrated by a reduction of the black lines during the day. Both patients are sleeping more at night, less during the day, and their circadian rhythms are entrained.

Now, I would like to take a minute to

present the historical perspective of the SET trial. The challenges in designing the SET study stem from the novelty of the indication in a rare orphan disorder. There is no regulatory precedence for appropriate efficacy endpoints for a circadian rhythm disorder.

nTST assessed at weeks 3, 4, 5, and 6 post-randomization was the primary endpoint in the original protocol. After discussions with the FDA, it was mutually agreed that nTST is not specific for a circadian rhythm disorder like non-24. The primary endpoint was therefore modified in May of 2012 to entrainment.

Entrainment is specific and definitional of the disorder. And it is the most appropriate measure of an efficacious treatment for non-24. After further discussions with the agency, the N24CRS clinical response assessment was included to address the need for a clinical primary endpoint.

In summary, the SET study demonstrated tasimelteon is a specific and effective treatment for non-24-hour disorder in the totally blind.

Tasimelteon entrains the master body clock, as evidenced by entrainment of melatonin and cortisol circadian rhythms. And tasimelteon showed clinically meaningful benefits, as reflected in the clinical response measures, both in terms of the timing and amount of sleep, as well as improvement in global functioning.

The second pivotal study was RESET. RESET had a randomized withdrawal design that confirmed the efficacy of tasimelteon and demonstrated the benefit and need for continued tasimelteon administration over time.

The study was conducted in 18 U.S. sites. These sites randomized 20 totally blind patients between the ages of 27 and 68. All of these patients had non-24 and entrained during the open-label run-in phase with 20 milligrams of tasimelteon. They were then randomized to continue tasimelteon or withdraw to placebo.

The first patient first visit was September 15th, 2011, and database lock was January 16th, 2013.

The screening phase was 11 weeks long, and the randomized withdraw phase was eight weeks. During screening, tau was assessed during week 6 through 9, then again during the randomized withdraw phase during weeks 3 through 6.

Patients began category sleep diaries on week 6 and continued throughout the remainder of the study. Sleep diaries were collected in the same manner as the SET study. Safety assessments were conducted approximately every month throughout the entire study.

While SET demonstrated tasimelteon's efficacy in entrainment and clinical response, the focus of RESET was on the maintenance of these benefits. RESET included both measures of entrainment, plus all of the sleep-wake endpoints used in SET. It also assessed nighttime total sleep time, total daytime sleep duration, a categorical endpoint of entrainment plus nTST, and time to relapse of total nighttime sleep.

Forty-eight subjects that met the RESET screening criteria had data for tau calculation

during the run-in phase. Twenty-four of the 48 subjects were entrained. Twenty entered the randomized withdrawal phase, 10 of which were randomized to placebo and 10 continued receiving 20 milligrams of tasimelteon.

All subjects completed the study and are included in the ITT population used for all analyses. There were no significant differences between placebo or tasimelteon for age, gender, race, or BMI. The baseline characteristics for patients in the run-in phase were balanced between treatment arms.

Now, let's examine what happens during the randomized withdraw phase. Tasimelteon succeeded on the primary endpoint of maintenance of entrainment in the RESET study. Only 20 percent of patients who were randomized to receive placebo continued to be entrained. In contrast, 90 percent of patients on tasimelteon continued to be entrained. This was statistically significant, with a p-value of 0.0026.

This is definitive evidence that tasimelteon

entrains the master body clock and that continued daily dosing is needed to maintain entrainment. The value of continued treatment with tasimelteon is apparent in the individual taus of each of the patients in RESET.

Tau measurements for each RESET patient are plotted here. The blue line represents tau during the run-in phase, when patients were entrained, and the red line represents tau during the randomized withdrawal phase.

On the left are the 10 patients who continued to receive tasimelteon and on the right are the 10 who received placebo. The orange box data represents patients that maintained entrainment. Nine of these were on tasimelteon, and only 2 were on placebo.

Now, let's examine what happened to the secondary endpoints. Cortisol data, like melatonin, demonstrated daily tasimelteon treatment is necessary to maintain entrainment. Like melatonin, only 20 percent of patients on placebo remained entrained for cortisol. In comparison,

80 percent of patients on tasimelteon maintained entrainment.

The difference between treatment arms was significant. While entrainment is the most relevant endpoint for measuring efficacy, we also examined clinical evidence of maintenance of circadian response.

Withdrawing from tasimelteon treatment results in a decrease of more than an hour of nighttime sleep in the worst nights of sleep and an increase of almost an hour in the worst days of sleep. These results are statistically significant.

nTST and dTSD showed numerical differences between treatment arms of 32 minutes less of nighttime sleep for placebo and 21 minutes more of daytime sleep in placebo on average. Statistical significance was not achieved because of a small sample size. There was not a statistical difference between treatment arms for the categorical endpoints of non-entrained and a 30-minute decrement in nTST.

We also looked at the data in a very interesting way. We examined circadian time to relapse for nTST. We arbitrarily prespecified the time to relapse as the loss of an average of 45 minutes per night of sleep within one week.

What we see in the highlighted Kaplan-Meier curve is that fewer tasimelteon-treated patients relapse in orange and that placebo-treated patients in gray relapsed earlier. On the X axis is circadian days and on the Y axis is the percent of patients that relapsed.

All patients completed the eight-week randomized withdraw phase, and the black hashed censored marks represent the last observation a person had for the study in circadian days. Post hoc exploratory analyses of 30, 60, and 75 minutes' time to relapse were all so significant for tasimelteon. The most important point is that the majority of the placebo patients relapse, and they do it quickly.

RESET showed that continued tasimelteon treatment is required to maintain entrainment of

the master body clock, as evidenced by melatonin and cortisol data, and that tasimelteon maintains clinically meaningful benefit in measures of nighttime sleep, daytime sleep, and timing of sleep.

Raster plots of 2 patients that participated in SET and RESET illustrate these results. Both patients were treated with 20 milligrams of tasimelteon during SET. Patient 3 participated in the randomized arm and patient 4 in the open label arm. They continued on 20 milligrams of tasimelteon during the run-in phase of RESET, and then were randomized to withdrawal on placebo.

During the SET randomization phase, patient 3 was not entrained when measured at month 1. It appears she may have initiated dosing while out of phase. At about day 190, she comes back into phase, and it appears as if her daytime sleeping dramatically dissipates, likely because she has entrained circadian rhythms.

She is in fact entrained when assessed during the run-in phase of RESET, as evidenced by

the stars aligning vertically around day 420. Then, when tasimelteon is discontinued and she's treated with placebo, her excessive daytime sleep immediately returns and she's no longer entrained, with her aMT6s acrophase delaying daily at the bottom of her raster plot.

Patient 4 participated in the open label arm of SET and therefore did not have tau assessed. However, she does appear to improve with a dramatic decrease in her daytime sleep and a stabilization of her wake times.

Entrainment is confirmed when her circadian rhythms are re-assessed during the RESET run-in phase around day 390. When her tasimelteon is withdrawn and she is dosed with placebo, her clinical symptoms immediately return and she has lots of daytime sleep.

Looking across both studies, the results are consistent for primary and secondary endpoints. These studies demonstrate that tasimelteon is a circadian regulator that entrains the master body clock as shown by melatonin and cortisol.

Entrainment results in significant and clinically meaningful improvements of circadian measures of LQ-nTST, UQ-dTSD, and MoST. These results demonstrate specific efficacy for this circadian rhythm disorder.

The efficacy of tasimelteon has been demonstrated in both pivotal studies. In summary, tasimelteon entrains the master body clock. Patients may require more than one month of treatment to become entrained. Patients should be treated for at least one full circadian cycle, typically 40 to 80 days, for an adequate trial of treatment. Tasimelteon improved clinical outcomes of nighttime sleep, daytime sleep, timing of sleep, and global functioning. Continued tasimelteon treatment is required to maintain benefit.

Thank you for your attention. Now, Dr. Paolo Baroldi, Vanda's chief medical officer, will present the clinical pharmacokinetics of tasimelteon.

Sponsor Presentation - Paolo Baroldi

DR. BAROLDI: Thank you, Marlene.

Good morning. A broad characterization of tasimelteon pharmacokinetic and metabolic profile has been performed to support the correct use of this product. I will very briefly present some of the key metabolic and pharmacokinetic features of tasimelteon, its receptor-binding profile, as well as of that of its metabolites, and finally, some extrinsic factors affecting the pharmacokinetics and pharmacodynamics of tasimelteon.

Tasimelteon is rapidly absorbed and extensively metabolized primarily by oxidation. CYP1A2 is the major isoenzyme involved in the hepatic metabolism of tasimelteon, while CYP3A4 is the major isoenzyme involving its intestinal metabolism.

1A1, 2C9, 2D6 also metabolize tasimelteon to a lesser extent. Lucor (ph) invasion is the major phase 2 metabolic route. And because multiple isoenzymes are involved in the metabolism of tasimelteon, the risk of drug-drug interactions is reduced.

To summarize, these are the traditional PK

parameters of tasimelteon. The time to reach the plasma peak concentrations, its Tmax, is approximately half an hour. The mean terminal half-life of the parent compound is one hour and 20 minutes. And that of the major metabolites is approximately the same, with the exception of the major metabolite M3, which is around 3.7 hours.

The protein binding of tasimelteon is moderate, the elimination of course mostly in the urine, and tasimelteon is linear over a dose range of 1 to 300 milligrams.

These data show the balanced affinity of tasimelteon as a dual melatonin receptor agonist for MT1 and MT2 receptors, with a slight preference for the MT2 receptor. Its metabolites have significantly less affinity for MT2 or MT1 receptors.

Tasimelteon and its major metabolites did not show any significant affinity for a panel of more than 160 commonly screened receptors, including receptors of narrow transmittal systems like dopamine, norepinephrine, serotonin, gaba,

acetylcholine, opioids, MDMA, and cannabinoids.

The identified potential interactions with some extrinsic factors affecting the key metabolic routes of tasimelteon have been tested clinically. Drug-drug interaction studies suggest minimal effect on tasimelteon kinetics.

The results shown in these slides can be summarized as follows. Tasimelteon should be administered with caution in combination with fluvoxamine or other strong CYP1A2 inhibitors. For people who smoke more than 10 cigarettes per day, and patients who take rifampin or other 384 potent inducers, conditions under which the plasma exposures of tasimelteon are reduced, we recommend that based on clinical judgment, a dose adjustment may be considered.

The co-administration of tasimelteon with high doses of alcohol shows no additive effect of tasimelteon on pharmacodynamic alcohol effects.

In summary, the pharmacokinetic characteristic of tasimelteon make it an ideal pharmacological agent for the treatment of non-24

in totally blind individuals. The very short half-life of tasimelteon and its metabolites, with no accumulation in the system, clinically translates into an idea versatile input to the target receptors and an intermittent treatment even under chronic administration conditions. This might also play a role in the benign safety profile of tasimelteon.

Now, Dr. Sliman will describe this safety profile. Thank you for your attention.

Sponsor Presentation - Joseph Sliman

DR. SLIMAN: Thank you, Dr. Baroldi. The safety of tasimelteon was evaluated during clinical development across multiple subject populations and indications, providing an expanded safety database beyond its orphan indication. In all populations studied, tasimelteon is well tolerated and has a consistent and favorable safety profile.

Tasimelteon was well tolerated among non-24 patients in our pivotal phase 3 studies, as well as among patients in the other phase 2 and phase 3 studies of insomnia. Tasimelteon has been well

demonstrated to be well tolerated in doses up to 300 milligrams and at doses of 20 milligrams per day for more than 12 months of cumulative daily therapy.

There were no deaths during the course of clinical development and there were few serious adverse events among placebo-controlled subjects, none of which were attributed to study drug. There were no clinically relevant changes, trends, or clinical events identified in laboratory, ECG parameters, or adverse events reported. And there was no evidence of next-day effects, no evidence of increased risk of suicidality or withdrawal, and no evidence of endocrine safety signals associated with tasimelteon.

In the integrated safety database, the study group 1 safety population is defined as all subjects exposed to any dose of tasimelteon, regardless of duration of treatment. This consisted of 1,346 individuals. Study group 1 was then divided into five pools for safety analyses. The primary safety analysis consisted of 52

tasimelteon-treated, placebo-controlled subjects in the SET and RESET studies, while the expanded safety analysis included 429 tasimelteon-treated placebo-controlled subjects from all phase 2 and phase 3 efficacy studies, which included the insomnia studies 004 and 3104 as well as the SET study.

Now, among the 1,346 individuals who received at least one dose of tasimelteon, 149 individuals were dosed for at least 12 weeks, 111 individuals for more than six months, and 44 individuals for at least 12 months of cumulative daily therapy as of the submission date of the document.

Given the expected size of the indicated orphan population, which is totally blind adults with non-24, the number of patients exposed and the duration of exposure is adequate for safety assessments. And as of the safety update at 120 days, the number of individuals exposed for at least 12 months of cumulative daily therapy has increased to 93.

In the expanded safety analysis, the rates of treatment-emergent adverse events in placebo-controlled efficacy studies was 39.4 percent for placebo subjects and 49.9 percent for tasimelteon-treated subjects.

Again, there were no deaths reported during any clinical study during the course of clinical development, and the rates of serious adverse events were very similar between treatment groups at 1.5 and 1.6 percent respectively.

The discontinuation rates due to adverse event were also similar between treatment groups, 3.0 percent in placebo-treated subjects and 3.3 percent among tasimelteon-treated subjects. The most common of these adverse events occurred at low rates in both arms, and the majority of these events were both infrequent and mild to moderate in severity.

Using a criteria of at least 3 percent rate of incidence in tasimelteon-treated subjects and at least a rate twice that found in placebo subjects to identify events of interest, only somnolence met

criteria for clinical relevance in the expanded safety analysis. However, there was no evidence of excess somnolence in tasimelteon-treated non-24 subjects in the primary safety analysis, as somnolence was primarily reported in Study 004, which studied elderly individuals, that is, greater than or equal to 65 years of age, with primary insomnia.

Next-day effects were assessed using various methodologies throughout the clinical development program. And there were no clinically relevant differences or safety signals identified using the visual analog scale, digit symbol substitution test, Karolinska Sleepiness Scale, or the Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire.

Aggregation of adverse event terms that could be considered consistent with clinical next-day effects then confirmed the absence of a safety signal related to next-day effects.

Now, tasimelteon is a circadian regulator. Endocrine parameters were examined during the SET study. And in doing so, there were no clinically

relevant differences observed between tasimelteon-treated and placebo-treated patients for any endocrine clinical or laboratory parameter.

So in summary, tasimelteon was well tolerated among non-24 patients and patients in all phase 2 and phase 3 studies of insomnia. There were no deaths during the course of clinical development and very few serious adverse events among placebo-controlled subjects, none of which were attributable to study drug.

Vivid and unusual dreams were observed and they are an expected result of tasimelteon's mechanism of action, but these do not constitute a safety signal. There was no safety signal or excess rates or severity of any type of adverse event in non-24 patients taking daily tasimelteon therapy for more than one year.

Overall, reported adverse events and serious adverse events among tasimelteon-treated patients was similar to the rates identified in placebo-treated patients. Tasimelteon has a favorable safety and tolerability profile for the treatment

of non-24 hour disorder. Thank you.

Dr. Polymeropoulos?

DR. POLYMEROPOULOS: Before we conclude our presentation, I wanted to address an analysis that the FDA requested during the review period, which we call a phase analysis.

The analysis asked to measure the change in total sleep time between in-phase and out-of-phase. And just to remind you, in this diagram, the X axis are study days. The Y axis is nighttime sleep total sleep time. And what you see is that an effort was made during the SET study to initiate treatment while in phase. And when in phase or zero degrees, you're expected to sleep the most. When you are out of phase, 180 degrees, you are expected to sleep the least.

So the FDA suggested, if you were to take the first 0 to 20 percent of the cycle and compare the sleep with that of the 50 to 70 percent, one could calculate the difference. And therefore, you should be able to demonstrate what is the goal of treatment, which is minimize the difference between

in-phase and out-of-phase.

As you can see, for this individual here, a difference of the 0 to 20 minus the 50 to 70 will give you the positive number, lots of sleep in phase, less sleep out of phase.

Now, there is a caveat. As we are measuring tau in order to predict phase after randomization, you remember this was done during the screening phase. And therefore, by day 29 we have a good estimate of what the tau measurement is. However, when you project it out to day 66, which is in this case the first day of randomization, of course you can believe that it is close to in phase, but in fact, the dotted lines of the confidence interval, the 95 percent CI, suggest, actually, this person could be anywhere on the 24-hour clock.

When we looked at the data and did for an individual that was randomized out of phase, shown in the scatter plot on the top, the left is the nighttime sleep. The right is the daytime sleep. Blue are the nights during screening and green during randomization. The little dotted line

suggests the day of randomization.

You can see, this individual is actually randomized when out of phase, and when they're sleeping the most, which is also shown in the daytime sleep to the right and in the raster plot at the bottom. About 16 percent of the patients randomized in the SET study, we believe were randomized when out of phase.

So how do we do the analysis when we're not sure exactly what the phase is? The concept is as follows. The blue wavy line is the individual that is randomized in phase, and the brown red line is an individual randomized out of phase. That's 16 percent of people.

So one can simply take the absolute value of change between 0 to 20 and 50 to 70. And therefore, we measure directly the change and not worrying about the sign. As in this case, for individual A, the difference between in and out-of-phase would be a positive number. For the individual B, it would be a negative number.

Actually, for individual B, you may think

they improved a lot. Actually, they didn't improve at all, as reflected by the absolute change. So we applied this absolute change to the data and here are the results.

The table on the top shows the absolute difference between in-phase and out-of-phase, comparing placebo and tasimelteon in the first cycle after randomization, the second cycle after randomization, and then cycle 1 and 2 together.

As you can see, all the results are significant and consistent with the significant effect of a difference between drug and placebo. Tasimelteon-treated patients during cycle 1 had a .9 hours' improvement versus their placebo counterparts. The same results are seen at the bottom, when we examine daytime sleep for cycle 1, cycle 2, and both cycles together.

So in conclusion, with this analysis of cyclicity, along with the entrainment data that were reviewed and the various analyses of clinical measurements, we conclude that tasimelteon is an effective agent for non-24, and coupled with the

safety profile that demonstrates it's well-tolerated, we believe it can add benefit to the treatment of patients with non-24.

Thank you very much, Dr. Chairman.

Clarifying Questions

DR. FOUNTAIN: Thank you.

Are there any clarifying questions for the sponsor? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. And these are the clarifying questions about the presentations. Dr. Hoffmann?

DR. HOFFMANN: Richard Hoffmann. I really found this presentation to be very interesting, and it shows us how complex sleep really is. I just have a couple of questions. In comparison to melatonin itself, is the main difference, the most significant difference between tasimelteon and melatonin its half-life? Or are there other differences in affinity for the melatonin receptors or its metabolism? That's my first question.

The second question, I guess, is kind of

theoretical, but in this complex neuronal pathway between the retina and its photoreceptors going to the pineal gland and its secretion of melatonin, have the neural transmitters in that pathway been identified? Thank you.

DR. POLYMEROPOULOS: Thank you very much. The first question was how tasimelteon differs from melatonin, which is the endogenous hormone. Of course, I cannot comment on melatonin because we have not compared tasimelteon to melatonin.

What we have attempted to do is develop tasimelteon as a pharmaceutical agent with predictable pharmacokinetics and also demonstrate the pharmacodynamics so it can be a useful agent with consistency for patients with non-24.

To address your second question on neurotransmitters, indeed, there is a tremendous amount of work over the last 10, 20 years in understanding the molecular basis of the molecular clock. And the key members of that clock, which are transcription regulators, especially BMAL1 and PER, have been well characterized and also the

steps of phosphorylation that maybe are very responsible in controlling the speed of tau.

So it is not believed that there is some other gross neurotransmitters, with the exception of melanopsin, that Dr. Czeisler said in the IPR disease, but rather, an intricate system of molecular machinery that addresses the clock on the membrane in the cytoplasm in the nucleus.

DR. HOFFMANN: So no neural transmitters are involved?

DR. POLYMEROPOULOS: No new neural transmitters. Of course, all the common neurotransmitters do play a significant role in the different synapses, but when it comes to the molecular clock, it is actually new molecules.

DR. HOFFMANN: Thank you.

DR. FOUNTAIN: Dr. Bagiella?

DR. BAGIELLA: You mentioned that 16 percent of the patients were out of phase at the time of randomization. Can you tell us whether they were balanced in the groups? You had approximately 8 percent in each group.

DR. POLYMEROPOULOS: I am sorry. I did not hear the last part of your question.

DR. BAGIELLA: So I'm asking whether or not the 16 percent of the patients that were out of phase at the time of randomization were equally distributed in the two groups.

DR. POLYMEROPOULOS: Thank you. Yes, they were. And also to add to that, this is actually of interest because in clinical practice, you would expect that patients will arrive at different phases.

Indeed, in the RESET study, where we invited 48 patients to come in, the timing of their tau estimation and treatment was regardless of phase. So these 48 patients came in. They had six weeks of tasimelteon treatment, and then some estimate of the tau. Twenty-four out of these 48, or 50 percent, entrained in the subsequent weeks. We'd suggest that patients most likely will entrain regardless of phase, and this is consistent with literature that has been already discussed and published. And an adequate treatment is the most

important part of this whole story.

So if you are starting in phase, maybe you can get entrained very quickly, as we show as early as week 2, but if you're out of phase, you may have to wait for about half a cycle until you're captured, and now you're entrained.

DR. FOUNTAIN: I have a question related to that, to follow up on that. Why measure tau so early, then, if you'd expect it to be entrained later in some of the other groups, that is, if you're further out of phase? Because several people made a point that you purposely measured tau early, but it would seem, during the course of treatment, because you're going to treat them for the whole duration of the treatment period, why not measure it later?

DR. POLYMEROPOULOS: Absolutely. If we could have done anything different in this program, we'd have measured entrainment most probably early and a little later. The reason, though, for this choice was that we did not have a large program to model ourselves after. And we were worried that

this very cumbersome measurement, we allowed so much burden to patients, and we'll experience discontinuations, and therefore put the primary endpoint in peril.

So it was a compromise of do it late enough to accommodate exactly what you discussed about circadian phase, but also do it early so you don't lose any patients. Well, it turns out that the compliance of our patient population was tremendous. In fact, as you saw, many of them continued on through additional studies. And I cannot say enough of their bravery to do these extremely cumbersome collections of total 48-hour urines week in/week out at screening, randomization, the RESET study, and then again. And the appreciation is tremendous for this blind population doing these very, very complex studies.

DR. FOUNTAIN: Thank you. Dr. Clancy?

DR. CLANCY: So I also found this to be a fascinating study, but the way I understand it, if we start with a non-sighted person who has the non-24, they can start off in sync with the rest of

the world. Their clock is matched because their timing is different. Eventually, they'll become out of sync.

Now, when they are in sync, their problems are not too bad. They sleep pretty well during the night. They don't sleep that much during the day. My question is, if we go to the part where they're hurting the most, so the lowest quartiles -- so we were told by Dr. Dressman that in the worst quartiles at baseline, for either the placebos or study drug, that they were sleeping 3.2 hours a night. That's not a lot of sleep. And yet, the criteria that Dr. Louis Licamele gave us for success was an extra 45 minutes of sleep. So at that phase in their cycle, they may go from 3.2 hours to 4 hours. That's still pretty dreadful.

My question is, where did that 45 minutes come from? How was that chosen? Why wasn't something more generous picked? Because that would have made a more meaningful statement of a normalcy for this population.

DR. POLYMEROPOULOS: Well, I want to do a couple of things. One is address directly why 45 was chosen and also put in the context of the individual patients. Those patients that are entrained, what actually is the benefit to them?

So the 45 minutes was a proposal that we made to the FDA of something of a magnitude that was never seen before with any soporific agents. To remind you, soporific agents generally have a 15-, 20-minute improvement on average. And therefore, the 45 minutes seem to be a very robust measure.

The 3.25 is an observation of the entire screening period with all the patients together. And you remember, not everybody responds. We believe that about 50 percent of the patients eventually get entrained. And in terms of the very large responses, Dr. Dressman discussed 28 to 57 percent, depending on criteria. But it is important to review what happens in the entrained people.

If I could have the slide up, please? On

the upper-left panel, you see the lower quartile improvement among people who are entrained. And indeed here, in those 13 patients that met the entrainment criteria, you see that there are 97 minutes or an hour and a half improvement. So the 45 minutes was, of course, a cutoff. But if a higher cutoff was chosen of 60 minutes or even 75 minutes, the results would have continued to be similar.

DR. CLANCY: But it was an arbitrary time?

DR. POLYMEROPOULOS: Absolutely.

DR. FOUNTAIN: Dr. Zivin?

DR. ZIVIN: Does this drug have narcoleptic properties? I have two questions. That's the first one.

DR. POLYMEROPOULOS: The drug does not have any narcoleptic properties.

DR. ZIVIN: Doesn't?

DR. POLYMEROPOULOS: Does not.

DR. ZIVIN: Okay. The second question, then, is, why is it necessary to have a drug like this when a narcoleptic plus an alarm clock should

be able to get people back into phase with the rest of society?

DR. POLYMEROPOULOS: I don't think I can address this question, but what I can tell you is the pain and suffering that I have heard from blind patients. And actually, we have had a number of unsolicited letters that came in to me and my colleagues, describing the loss of opportunity for this highly disabled population over 40, 50, 60 years of time that prevents them from enjoying the common things that you and I enjoy: school, jobs, relationships.

Therefore, a solution that is not tested, a suggestion of, "Get another drug," or, "Get an alarm clock," really does not match the pain and suffering. What we are trying to do is we're trying to address this unmet medical need for patients who had all these other tools available to them, but nonetheless, they are suffering continuously, and we are very sympathetic to that.

DR. ZIVIN: Now, I can understand where people would have a problem if they got out of

phase with society, but it doesn't seem to me that anything more sophisticated than an alarm clock would keep them in phase.

DR. POLYMEROPOULOS: Maybe I should actually ask Dr. Czeisler to address this question. He is an expert in this and would be able to discuss more.

DR. CZEISLER: Thank you, Dr. Polymeropoulos. These patients have been, in fact, brought into laboratories with an attempt to have them -- and the very first patient that was studied by Laughton Miles and colleagues at Stanford University, who was unable to synchronize to the 24-hour day, was brought into the laboratory and subjected to exactly what you suggest, an alarm clock, brought out of bed, people keeping the individual awake during the daytime and sleeping at nighttime.

Unfortunately, in these patients without light input to the circadian clock, which is the primary synchronizer of this internal biological clock, even if they wake up and are kept awake

during the daytime forcefully, it is not sufficient to entrain their circadian rhythms.

In that particular case, as is reported in the science by Miles and colleagues, the patient, after about 10 days of being forced to be awake during the daytime, withdrew participation and discontinued in the laboratory because he could not tolerate it. It was so disabling for him to try to fight this internal clock.

There are inter-individual differences in the sensitivity to trying to function when your internal clock is misaligned with the timing of the 24-hour day. Some people are particularly sensitive. But it has been shown that the typical hypnotic agent such as the benzodiazepines is unsuccessful in entraining circadian rhythms. It can't help when you're traveling across time zones in resetting your internal clock, for example. It only provides symptomatic relief.

So this is why I strongly advised the company that providing symptomatic relief of simply enhancing nighttime sleep time without going

through the arduous process of demonstrating entrainment, which requires six months of study of these participants, the demonstration of entrainment was key because if you didn't entrain the circadian clock, then the treatment program would not be successful.

DR. FOUNTAIN: Could I take advantage of your presence there to ask you a related question, Dr. Czeisler? Would you like to comment on the previous question about why not just use melatonin?

DR. CZEISLER: Pardon me?

DR. FOUNTAIN: Would you like to comment on the previous question of why not just use melatonin?

DR. CZEISLER: I didn't hear that previous question.

DR. FOUNTAIN: Why not use melatonin instead of designing a new drug?

DR. CZEISLER: Melatonin has been shown to be effective in pioneering studies that were carried out by both Dr. Robert Sack and Dr. Steven Lockley, who did a series of patients and evaluated

melatonin in a sample.

Melatonin has never gone through a registration trial in which it is evaluated systematically in which the safety and efficacy of melatonin in a large population such as this have been evaluated. But certainly, the efficacy of melatonin was inspirational to this melatonin agonist and to its evaluation.

Dr. Polymeropoulos?

DR. FOUNTAIN: Thank you. Dr. Vitiello?

DR. VITIELLO: Thank you. I have a couple of clarifying questions and then one other comment. While we're on the topic of entrainment, the numbers vary, but could you say your best estimate is about 50 percent of people entrain? Is that fair?

DR. POLYMEROPOULOS: Yes. A comment there, we think that it is most probably 50 percent or better, and there are a couple of things that we also have observed. One is, as it was suggested before, people with longer tau, 24.75 and longer, seem not to have very good results. It's in about

10 percent of the patients. And also, patients, about 10 percent, that take beta blockers and suppress the endogenous melatonin, they also seem to be less likely to entrain. So if you were to take those people out of the equation, the 10 percent with long taus, 10 percent with beta blockers, the entrainment rate is going to be 70, 75 percent.

DR. VITIELLO: So you actually answered my next question, which was, why do you get roughly 50, but that helps. Dr. Dressman mentioned the alignment of cortisol as well as melatonin. Can I assume that those are in the same people? That was not stated.

DR. POLYMEROPOULOS: Yes. The 14 people for whom we have melatonin entrainment, we went and looked back at each one of them. And all 14 were consistent with entrainment. The reason I use consistent carefully is because you already know that cortisol data are not as clean as --

DR. VITIELLO: Yes.

DR. POLYMEROPOULOS: -- melatonin data for

cosinor fit. And therefore, we were not just looking that they were absolutely entrained with the criteria used for the melatonin, but each one of them had data that were not inconsistent with entrainment.

DR. VITIELLO: So the cortisol data was looked at within the entrained subsample.

DR. POLYMEROPOULOS: Correct. And therefore, 100 percent of the entrained melatonin people are expected to have been, 100 of them, cortisol entrained as well.

DR. VITIELLO: Got it. Thank you. And then I had one other comment, which was, one of the conclusions in the efficacy trial was, global functioning improved. That's based on a clinician-rated "how are they doing in the trial" treatment.

Now, maybe it's because I'm a psychologist, I'm sensitive to that, but you might be a little more cautious about stating things like global function, which to me would have to do with cognitive functioning during the day and things like that. That's a rating scale of treatment

efficacy, perceived physician treatment efficacy, not global functioning.

I offer that as a comment.

DR. POLYMEROPOULOS: That is a very point. First of all, the CGI is clinician rated. It is a global impression scale that, as rated, it looks not only at how was their sleep, but it looks at the other things. How is their life? So that is the connotation of functioning that's been used.

But in the study in France, in 3202, we also looked at the patient global impression scale. So it gives you now not just the data on the patient. And I would like to ask Dr. Dressman if she can come up and present those data.

DR. VITIELLO: That is very helpful. And in terms of description of the measure, then, the CGI -- is it CGI? The clinician rating.

DR. POLYMEROPOULOS: The clinician is the CGI-C, yes.

DR. VITIELLO: Yes, CGI-C. Excuse me. It might be useful to include it. This is also a global impression of how the patient is doing

overall, not just within the context of study outcomes, because that's how it reads and that's how it was presented.

DR. POLYMEROPOULOS: Yes. So two things, I will ask Dr. Dressman to show us the patient global impression scale and how does that correlate with the CGI. And also, I would like, after that, to ask Dr. Lankford, who is one of the investigators and rated patients for the CGI, to tell us exactly how he delivered that scale.

DR. VITIELLO: Thank you.

DR. DRESSMAN: Study 3202 is an open label tasimelteon study in France. May I have the slide up, please? And in this study, patients and physicians reported global functioning scales. So the patients had a nighttime sleep PGI-C, a similar scale as the CGI-C, and then a daytime sleep PGI-C.

While this is open label, it is consistent with the magnitude of the change that we saw in the SET study in that the mean CGI-C was 2.26, which is an improvement -- a lower number is an improvement -- from 4 being no change at all.

PGI-C was 2.37 for nighttime sleep, and the mean daytime sleep was 2.76. So the patient-reported outcomes were consistent with the Clinician Global Impression of Change.

DR. LANKFORD: I'm Alan Lankford. I am the director of the Sleep Disorder Center of Georgia in Atlanta. I was investigator for Vanda on these trials. I have received honoraria for consulting services from Vanda, and in addition, I have no financial interest in Vanda, nor do I have any interest in the outcome of this meeting.

I would like to get some clarification if I may on the exact nature of the question in regard to the CGI-C.

The overall functioning of the patient was taken into consideration when we did those ratings. We were looking at efficacy in a blinded fashion, but we were looking at efficacy. But in addition, we were looking for information from the patient on how they were functioning in their activities of daily living. In addition, if they were gainfully employed, for example, what was happening in that

context. What was happening in terms of relationships they may have been involved in.

So we were looking and gaining information from those patients in that regard, in a broader, more global sense.

DR. FOUNTAIN: Thank you. Ms. Sitcov?

MS. SITCOV: Cynthia Sitcov. I represent the MS community. I've been living with MS. I've been diagnosed for over 40 years. And my question is this. There are many, many people in the MS community who suffer from sleep disorders, yet they're entrained. I mean, they don't have, to my knowledge, an issue with a 24-hour clock, circadian rhythm issues. There are many of us who suffer from restless leg syndrome. It's not uncommon. I personally have a severe case of restless leg syndrome.

If this drug is approved, do you see it as being able to have a wide birth in terms of being able to be used for conditions beside non-24?

DR. POLYMEROPOULOS: Unfortunately not. And the reason is, we have started a very specific

circadian disorder of absence of entrainment due to lack of light. So I can tell you a little bit about our future plans. And it is to understand more why people with faster clocks, like 24.75, do not entrain and try to develop schema doses for that. That's number one.

Number two is to study in the pediatric population. They're a lot of blind children, especially those that started age 1 or 2 with retinoblastoma, that suffer from this. We only have studied adults.

Number 3, we want to look at a very debilitating disorder, Smith-Magenis syndrome. This is a chromosomal abnormality on chromosome 17 that presents with a cardinal feature of sleep issues, and it's due to a deletion of a gene RAI1 on chromosome 17, causing tremendous suffering for these kids, young adults, and their families as well.

So we know that there are a lot of needs of understanding better the molecular basis of sleep disorders in the context of other disorders.

Unfortunately, tasimelteon may not be the solution for this, but we are committed to continue to study on this narrow road of circadian indications.

MS. SITCOV: Thank you.

DR. FOUNTAIN: Dr. Sack?

DR. SACK: I'm wondering if there's any indication of a phase response curve for the effects of this drug.

DR. POLYMEROPOULOS: We have not done the PRC, the full phase response curve, that yourself and others have studied for melatonin. What we do understand, however, is that the PRC most probably will be similar to that of the endogenous melatonin substance. And we can only surmise that, from those patients, that we're starting treatment out of phase and, therefore, we know something about their cycle speed and when they came in phase. So that window of four or five hours for phase events may apply.

We do not, however, know much about the phase delay portions of this.

DR. SACK: Kind of a follow-up question,

then, if you were to treat somebody who had a tau of less than 24 hours -- since, say, in a clinical context, we may not know that; we don't have markers in the clinical world -- what would be the outcome of a nightly treatment with this drug?

DR. POLYMEROPOULOS: We have not studied that. You'll recall the inclusion criteria were people with a tau greater than 24. And yes. There is a small number of patients -- in fact, out of the couple of hundred patients for whom we estimate it out, 2 or 3 of them appear to have a tau of about 23.9.

I cannot answer the question of what would happen because we didn't study it. If I was to take an educated guess from the work of others, it is likely that nightly administration will eventually be successful in entrainment. But that's a hypothesis. We have not studied that.

DR. FOUNTAIN: Dr. Eastman?

DR. EASTMAN: Charmane Eastman. So this is actually related to whether there's a PRC for tasimelteon, but it's a simple question. Why did

you pick one hour before bedtime for the drug administration?

DR. POLYMEROPOULOS: We are aware of debate in the literature of what is the right time of administering. We had to balance two things. One is just the PRC, just the time that we'll be able to cause a consistent phase event, but also balance something very important for the world out there.

The timing that you take an agent doesn't just have circadian effects. We know that a melatonin agonist will have soporific properties as well. And therefore, administering five hours before bedtime can be problematic for some people because they want to go about their lives without feeling sleepy.

So while it may be true, like work that you have done and others, to show a four- or five-hour prior to bedtime may be perfect for the phase event portion, it may not be the best when people are trying to manage their lives in the next four or five hours, and there may be an added soporific effect. So it was a compromise we had to do.

DR. FOUNTAIN: Dr. Clancy?

DR. CLANCY: I just wanted to put a pitch for considering the study of children with autism, and there are a lot of them. And probably the second most common complaint that the family has is that the child doesn't know day from night. They just don't get the kind of clues. They are sighted, but when Mom and Dad are up half through the night, trying to calm their kid down, that's a major disturbance in their quality of life.

DR. POLYMEROPOULOS: We are aware of that. And in fact, the Smith-Magenis syndrome that I mentioned does have behavioral and acting-out behaviors, primarily reminiscent of some of the autistic spectrum disorders. When it comes to autism, there have been publications of a reduced amount of endogenous melatonin. But unfortunately, I don't know much more than that. And whether a melatonin agonist will be effective or not will have to be shown.

DR. FOUNTAIN: Thank you. I have a question. And that is, I think the data you've

shown, the discussion Dr. Czeisler shows, that you're entraining the rhythm, and simple hypnotics or sedatives don't fix things. But on the other hand, things that affect sleep could have an effect on the outcome of the study.

So were there any controls for sleep hygiene, or habits, or things like that?

DR. POLYMEROPOULOS: Yes. I would like to ask Dr. Dressman if she can discuss any additional medication that were not allowed or allowed and also some instructions of how the patients were supposed to sleep during the study.

Dr. Dressman?

DR. KRYSCIO: I just have one simple question. And how did you choose the age range of the patients in your study?

DR. FOUNTAIN: Why don't we answer this question first, and then we'll come to that one.

DR. DRESSMAN: So part of the inclusion/exclusion criteria was such that people who were on sedatives or anything that would interfere with sleep or cause drowsiness was

excluded. That was not allowed during the study. And then with regard to sleep hygiene, patients were asked to choose a specific bedtime and a specific wake time so that we could measure the amount of time awake and distinguish between nighttime sleep and daytime sleep.

They were instructed -- if you recall, they called in twice a day, and they had to take their drug one hour before bedtime. And then they were instructed to prepare for bed, so do whatever, wash their face, quiet down, get ready for bed. And then they were instructed to get in bed.

Now, given the disorder, not everyone would fall asleep. We did not require that they stay in bed or that they sleep, but we asked that they try to go to sleep and that they not have any requirements to get up early the next day. They had to be able to wake up at their defined wake time if allowed.

So they couldn't have conflicting work schedules that would not allow them to sleep that nine-hour period. So they were required to have a

nine-hour period that they could sleep.

Then the inclusion criteria on the age was, they just had to be over 18 years of age to participate in the study and less than 75 years of age.

DR. FOUNTAIN: Dr. Vitiello?

DR. VITIELLO: Just a clarifying question. If drugs that impacted sleep were an exclusion, didn't you mention that beta blockers were part of -- so beta blockers do affect sleep, but you let people with beta blockers in? I just want to be clear about that.

DR. POLYMEROPOULOS: While it is true that beta blockers can have an effect and do so, none of them have been approved.

DR. VITIELLO: These were prescriptive sedative agents --

DR. POLYMEROPOULOS: Right. Exactly.

DR. VITIELLO: -- is what --

DR. POLYMEROPOULOS: None of them have been approved for insomnia.

DR. VITIELLO: Yes.

DR. POLYMEROPOULOS: So all we could do is make sure that we're not on sedative hypnotics that can confound the effect.

DR. VITIELLO: Because when I hear drugs that impact sleep, any CNS drug that impacts sleep can be a problem, so I just wanted to be clear of your exclusion criteria.

DR. POLYMEROPOULOS: Right. And the important thing also to note is that we are trying to do our trials in a way that is informative for real-world circumstances. And another very interesting little thing here is that 20 to 30 percent of our patients had major depression. They were taking SSRIs, successfully treated, stable, and they were allowed in the study. So it was not that we excluded everybody from their common ailments and treatments. All we required is that they have stable treatment of their major depression.

DR. FOUNTAIN: Thank you. Dr. Sack?

DR. SACK: In regard to the beta blockers, I guess I have to challenge a little bit the idea of

taking out those patients. I don't know of any data about, at least that affects melatonin, exogenous melatonin having an interference from beta blockers.

In fact, theoretically, one might expect possibly even an improvement in effect because if you consider the situation where the endogenous melatonin is competing with the exogenous melatonergic drug, you would like to decrease the competition of the endogenous melatonin effect on the clock. So I have difficulty with that particular --

DR. POLYMEROPOULOS: Thank you. Actually, we fully agree with you. And in fact, we did allow patients with beta blockers in the study for the very reason that we would like to understand how it works.

There was a surprising observation. It's just an observation. It has not been confirmed. But actually, it suggests a negative association between low levels of endogenous melatonin and entrainment. Whether the endogenous levels are

caused by a beta blocker or you have normally lower levels -- some people have lower levels than others -- it appears that this actually reduces the entrainment rate. This is an early finding. We've not published it. It's part of the common technical dossier, but it could be an intriguing thing to follow up in the future.

DR. FOUNTAIN: Dr. Vitiello?

DR. VITIELLO: Yes. I did not suggest removing them or not using them. I just wanted to be clear about the exclusion criteria you used. I completely agree with having them in. It's just, I wanted to be clear about what you meant, then, by saying you excluded people for drugs that impacted sleep.

DR. POLYMEROPOULOS: Understood. I only meant, in the analysis, if we look at subpopulation analysis. Yes.

DR. FOUNTAIN: If there are no more clarifying questions -- all right. We are head on the agenda by just a little bit, but I think now would be a good time to take a break. So we'll

take a 15-minute break.

Panel members, please remember that there should be no discussion of the meeting topic during the break among yourselves or with any member of the audience. And it is 10:35, so we'll resume at 10:50.

(Whereupon, a recess was taken.)

DR. FOUNTAIN: If everyone would be seated, we will resume. And we can now proceed with the FDA presentation.

FDA Presentation - Devanand Jillapalli

DR. JILLAPALLI: I am Devanand Jillapalli, and I'm a medical officer in the Division of Neurology Products. My presentation is divided into two parts. In the first part, I will discuss a few introductory slides followed by regulatory history, in which I will discuss the areas of disagreement and agreement between the agency and the applicant. Then Dr. Julia Luan will present the agency's statistical analysis of the clinical endpoints.

After Dr. Luan's presentation, I will come

back to present the second part of my talk on the efficacy and safety of tasimelteon.

Clinical benefit, which is necessary for approval, is demonstrated by endpoints that are clinically meaningful. These clinical endpoints are those that directly assess for long life, improved physical condition, or reduced pain, which is often referred to as how a patient feels, functions, or survives. By the way, there is a typographical error. The high court decision was in 1979, not 1977.

Established surrogate endpoints can be used instead of clinical outcomes. Established surrogate endpoints are those for which there has been a consistent demonstration of beneficial quantitative relationship between the surrogate and the desired clinical outcome over many trials and over many drugs.

For serious and life-threatening conditions, accelerated approval can take place under Subpart H if an effect on a surrogate endpoint is reasonably likely to predict clinical benefit. Please note

that the accelerated approval is conditional, based on reasonably likely prediction of the clinical benefit. Final approval is based on verification or demonstration of that clinical benefit.

As previously mentioned, surrogate endpoints do not directly assess clinical benefit. They may be used to describe a disease, and an effect on the surrogate endpoint may be correlated, sometimes highly correlated, with effects on clinical endpoint. They are, in some situations, used in clinical trials to predict clinical benefit, for example in life-threatening diseases under Subpart H. But surrogate endpoints do not directly assess clinical benefit.

On the other hand, clinical endpoints directly measure clinical benefit. A primary clinical endpoint can demonstrate clinical benefit and define the success of a trial. This benefit can then be described in labeling to allow patients and healthcare providers to assess benefit versus risk.

This slide highlights some of the dates when

regulatory infractions took place between the agency and the applicant. An interaction occurred December the 10th, 2012, that was inadvertently left out of the agency's briefing book. There was no agreement between the agency and the applicant on the primary endpoint as you've heard.

This slide highlights the disagreement on the primary endpoint. The applicant initially proposed night total sleep time as the primary endpoint. The agency did not agree with this endpoint, as it is an endpoint that is often used in insomnia trials, where it is used to capture a soporific or a sleep-promoting effect.

Night total sleep time did not appear to be adequate to capture the effect of tasimelteon on the periodicity or the cyclicity of nighttime symptoms in the non-24 hour disorder.

The applicant later proposed entrainment of circadian melatonin rhythm, as measured by urinary metabolite of melatonin, but there was no agreement because this endpoint does not directly measure clinical benefit. The applicant also proposed the

step-down primary endpoint that you have heard about. The agency also disagreed because that endpoint was a composite endpoint containing entrainment.

The agency asked for clinical primary endpoint to directly assess clinical benefit for two reasons. Clinical benefit in non-24 hour disorder could occur in a reasonable time frame. Clinical endpoints could readily measure benefit on nighttime and daytime sleep.

There was an agreement between the applicant and the agency during early drug development that nighttime sleep and daytime naps were the two most important direct measures of clinical benefit.

The applicant proposed a lower quartile of night total sleep time as a clinical endpoint because of correlation of this endpoint with the most symptomatic phase of the circadian cycle when there is maximum misalignment, and also since the lower quartile of night total sleep time data had less variability than the entire night total sleep time. The applicant also proposed the upper

quartile of daytime total sleep duration as a clinical endpoint for similar reasons.

The agency agreed to both the lower quartile of night total sleep time and the upper quartile of day total sleep duration as clinically meaningful endpoints. However, these endpoints, while included as secondary endpoints, were not ordered in the trial to control for inflation of type 1 error.

Dr. Julia Luan will now present the agency's analysis of clinical endpoints.

FDA Presentation - Julia Luan

DR. LUAN: Good morning, everyone. I'm Julia Luan from FDA CDER. I'm the statistical reviewer for this NDA. Today, I will present the efficacy analysis of tasimelteon.

Here is an outline of my presentation. I will begin with background. Since the sponsor and Dr. Jillapalli have already presented the background information for this NDA, and Dr. Jillapalli will present more background information, I will only give a summary of

important events related to statistical analysis. After that, I will present my efficacy analysis in a summary.

This slide gives a summary of important events that occurred in Study 3201. In the original protocol, the primary endpoint proposed by the sponsor was night total sleep time, and the sample size was 160 patients, based on the postulated mean treatment difference of 39 minutes and a standard deviation of 66 minutes.

In Amendment 6, the sample size was changed from 160 to 100 patients based on the new postulated mean treatment difference of 30 minutes and a standard deviation of 45 minutes.

In Amendment 9, the primary endpoint was changed to entrainment and the sample size was reduced to 84 patients. At the time of Amendment 9, which was May 21st, 2012, 95 percent of the patients were randomized, and 56 percent of the patients completed the study.

The last amendment, Amendment 11, was dated December 11, 2012 and the data were unblinded the

next day. It's not clear to the agency how much these changes might have impacted the trial results.

Please note that there is no agreement between the sponsor and the agency regarding primary endpoint analysis population and analysis method. The agency decided the efficacy evaluation for this indication should be based on clinical endpoints. The agency has conveyed this decision to the sponsor during the IND review process. In addition, I'd like to point out my analysis is a post hoc analysis without multiplicity adjustment.

This slide is a summary of statistical issues, sponsor's position, and agency's position. For Study 3201, the sponsor used entrainment as the primary endpoint and the clinical response rate as the step-down primary endpoint. The agency decided the efficacy evaluation for this NDA should be based on the clinical endpoints listed in this table.

The agency also disagrees with the analysis populations used by the sponsor for Study 3201.

For this study, 84 patients were randomized. The ITT population defined by the sponsor included 78 patients because 6 patients were excluded from the randomized population due to no tau calculated post-randomization. This sponsor ITT population was used to analyze the primary endpoint.

The analysis population defined by the sponsor included 72 patients because 6 more patients were excluded from sponsor ITT population due to less than 70 percent of one circadian cycle of night total sleep time daytime reported at baseline and post-baseline. This sponsor's analysis population was used to analyze the step-down primary endpoint and efficacy endpoints.

In summary, 12 patients were excluded from 84 randomized patients. However, out of 84 patients who took study medication and had at least one baseline and post-baseline assessment, based on the ITT principle, all 84 patients should be included in the ITT population. This ITT population is a randomized population. Sponsor's ITT and analysis population was selected after

randomization and there are non-randomized subsets.

In terms of analysis method, sponsor used ANCOVA to analyze the clinical endpoints. However, due to sample size, non-normal distribution of the data, and some heterogeneity in variance, I think permutation ANCOVA would be more appropriate.

In addition, in ANCOVA analysis for Study 3201, study site was included as a factor in the analysis model, but the clinical study report shows that the randomization was now stratified by study site. Normally, if the randomization was not stratified by study site, in order to comply with the trial design, site is not necessarily included as a factor in the analysis model.

Therefore, I think permutation ANCOVA without site would be more appropriate than ANCOVA with site.

For Study 3203, since 20 patients were randomized and they all completed the study, the analysis population is not an issue. The issues related to primary endpoint and analysis method were similar to Study 3201. But I'd like to point

out, for Study 3203, the randomization was not stratified by site, and site was not included as a factor in sponsor's ANCOVA analysis.

I'm going to present the following four analyses. First, we will take a look at histograms of each clinical endpoint in each study. I will go over these histograms fairly quickly.

I'd like to point out the clinical endpoints are likely correlated with each other. Then I will show the description of the trial for patients excluded from the randomized population by the sponsor for Study 3201 and explain why I think these 12 patients should be included in efficacy analysis. After that, I will present the results of ANCOVA analysis and permutation in ANCOVA analysis based on ITT population.

This is the histogram for lower quartile night total sleep time for Study 3201. The upper panel is for placebo. The lower panel is for treatment. It seems that there is a shift in the distribution in favor of the treatment group. For lower quartile night total sleep time, larger value

indicates longer nighttime sleep and the positive change from baseline means improvement.

This is the histogram for lower quartile night total sleep time for Study 3203. This is for upper quartile daytime total sleep duration for Study 3201. For this endpoint, smaller values indicate shorter daytime sleep and a positive change from baseline means improvement. It seems that the treatment group is doing better than the placebo group.

This is for upper quartile daytime total sleep duration for Study 3203. This is for clinician global impression of change for Study 3201. It's a seven-point rating scale; 1 means very much improved; 7 means very much worse. It appears that the treatment group has a better outcome. CGI-C was not an endpoint for Study 3203.

This is for night total sleep time for Study 3201. From the histogram, it seems it's not clear which treatment group is doing better.

This is for night total sleep time for Study 3203. The last clinical endpoint is daytime

total sleep duration. This is for Study 3201. It appears that the treatment group is doing better than the placebo. This is for daytime total sleep duration for Study 3203.

In summary, for some of the clinical endpoints, it appears that the treatment group has a better outcome. In addition, we can see that, for most of the clinical endpoints, the distribution of the data is not normal.

As I mentioned previously, in sponsor's efficacy analysis for clinical endpoints, 12 patients were excluded from the efficacy analysis due to insufficient data. This table presents the information for these 12 patients. It gives cycle length percent of one circadian cycle of night total sleep time daytime reported at baseline and post-baseline.

Among the 12 patients, 10 patients had more than 50 percent of one circadian cycle data at baseline and 6 patients had more than 50 percent of one circadian cycle data at post-baseline. It seems that the data are not extremely sparse for

these 12 patients, and I think they should be included in the efficacy analysis.

This table presents the results of ANCOVA analysis for Study 3201. In sponsor's ANCOVA analysis for Study 3201, study site was included as a factor in the analysis model. However, since the randomization was not stratified by site, it's not necessary to include a site as a factor in the model.

Based on the results of ANCOVA analysis without site, we can see that the nominal p-values are all significant or marginally significant except for night total sleep time.

This table presents the results of ANCOVA analysis for Study 3203. For this study, 20 patients were randomized, and they all completed the study, so the analysis population is not an issue. The results from sponsor's analysis and my analysis are the same. The nominal p-values are significant or marginally significant except for night total sleep time.

This slide shows the results of a

permutation ANCOVA without or with site as a factor in the model. I think permutation ANCOVA without site is more appropriate for this study.

Based on the results of a permutation ANCOVA without site, the nominal p-values were significant or marginally significant except for night total sleep time. In addition, we noticed that the p-values from permutation ANCOVA without site are very similar to ANCOVA without site.

This slide shows the results of a permutation ANCOVA for Study 3203. The nominal p-values were significant except for night total sleep time. And the p-values from permutation ANCOVA and ANCOVA are fairly close.

Here is my summary. The two studies appear to suggest that tasimelteon 20-milligram may be beneficial for non-24-hour disorder in totally blind individuals, based on all the clinical endpoints except for night total sleep time, which was the original primary endpoint. And last, I'd like to thank my colleagues for a very helpful discussion and the suggestions. That's all from

me. Thank you.

FDA Presentation - Devanand Jillapalli

DR. JILLAPALLI: Thank you, Dr. Luan.

I'll begin the second part of my presentation. There are two main efficacy issues that I'd like to discuss. First is the lack of agreement on primary endpoint and the issues that arise from it. Second is whether there is an effect of tasimelteon on the periodic nature of nighttime and daytime symptoms of non-24-hour disorder.

Periodicity of nighttime and daytime symptoms is a key feature of the non-24-hour disorder. That is, an ordinary sleep-promoting effect would not be adequate to establish the efficacy in non-24-hour disorder.

Efficacy 1, lack of agreement on primary endpoint. And because there was lack of agreement on primary endpoint, there was also no agreement on the analysis population or the statistical analysis of the primary endpoint.

Study 3201 and Study 3203 were both

positive, based on the applicant's prespecified primary statistical analyses. These analyses were not agreed to by the agency as I previously mentioned.

Question. Was clinical benefit shown? Because that is the basis of approval. The applicant's prespecified primary endpoint of entrainment rate in Study 3201 or non-entrainment rate in Study 3203 was positive. Entrainment does not directly measure clinical benefit. The key question is, did patients receive any benefit?

The applicant's prespecified step-down primary endpoint in Study 3201 was the responder analysis based on a combination of entrainment rate and non-24 clinical response scale score of greater than or equal to 3. That is, subjects had to be entrained as assessed by the urinary melatonin and via responder by achieving a non-24 clinical response scale score of greater than or equal to 3.

The non-24 clinical response scale, as you've heard, is composed of four components: the lower quartile of night total sleep time, the upper

quartile of day total sleep duration, the midpoint of sleep timing, and the CGI-C.

Clinical meaningfulness of MoST is uncertain. For example, if you can imagine two patients, all factors being identical, each of them took one nap during the daytime of the same duration. One patient took the nap at 12:00 noon and the other took at 4:00 p.m. MoST will assign a poorer score to the patient that took the nap at 12:00 noon than the person that took the nap at 4:00 p.m.

It is not clear what the timing of that nap meant to each patient. Nevertheless, MoST calculation is based on night total sleep time and daytime naps, and therefore, may be of some value, although questions remain about the potential correlation between MoST and the other components, and the question about redundancy.

The applicant's prespecified step-down primary endpoint analysis, a responder analysis based on a combination of entrainment rate and non-24 clinical response scale, was positive in

Study 3201.

Question. Did the step-down primary endpoint show clinical benefit? The non-24 clinical response scale is a composite endpoint. In order to answer this question, we need to know the fraction of contribution to the positive effect on the step-down primary by its individual components that directly assess clinical benefit.

The individual components of the step-down primary endpoint, lower quartile of night total sleep time, the upper quartile of daytime total sleep duration, and CGI-C directly assess clinical benefit, and therefore, strongly suggest clinical benefit for this step-down primary endpoint. However, there are caveats.

As I mentioned before, we did not agree to the step-down primary endpoint because of the presence of entrainment response as well. The presence of that component, which did not directly assess clinical benefit, and to some extent, MoST, limits the conclusion that we can draw from the clinical benefit that the step-down primary

endpoint provided.

The second caveat is, a total of 12 patients were excluded from the applicant's analysis of the step-down primary endpoint. Eight subjects were excluded from the placebo group versus 4 from the tasimelteon group. These subjects were excluded based on entrainment status and not having at least 70 percent of one-cycle data during baseline and post-randomization, which are not relevant to the evaluation of these clinical endpoints.

All subjects in the study took at least one dose of study medication and had at least one baseline and post-randomization assessment for almost all clinical endpoints. Therefore, all subjects should be included in the analysis.

These caveats limit the conclusion that the step-down primary endpoint show a clinical benefit. However, there is a strong suggestion of benefit because the important components of the non-24 clinical response scale included those endpoints that we had agreed were clinically meaningful.

So we now need to look at the secondary

clinical endpoints such as the lower quartile night total sleep time, upper quartile daytime total sleep duration, and CGI-C. And we also just included in the analysis to establish clinical benefit. Since these secondary clinical endpoints were not ordered, it raises the potential for inflation of type 1 error.

This is a table summarizing the clinical secondary endpoints and their corresponding p-values in Study 3201 and Study 3203, conducted by the agency. These secondary endpoints were not ordered in the trial, as I previously mentioned. All subjects were included in the analysis except for CGI-C, where 13 patients did not have data. Lower quartile of night total sleep time, upper quartile of daytime total sleep duration, CGI-C, and dTSD were statistically significantly positive, favoring tasimelteon in both Study 3201 and Study 3203.

CGI-C was also statistically significantly positive, favoring tasimelteon in Study 3201. However, this endpoint was not assessed in

Study 3203.

Night total sleep time did not achieve statistical significance in either Study 3201 or study 3203. This was an endpoint on which there was disagreement during the development program. Since this endpoint is often used in insomnia trials, where it is used to capture soporific or sleep-promoting effect, the agency felt it was not adequate to capture the effect on the cyclicity of symptoms in non-24-hour disorder.

So if the night total sleep time was excluded from the list of these clinical endpoints, since the remaining endpoints are all positive, it would not order how you rank, but order the remaining endpoints. They're all positive, so there wouldn't be any inflation of type 1 error. However, if the night total sleep time was ranked -- and again, depending on where on the hierarchy of the night total sleep time, there is a potential for inflation of type 1 error.

The inflation of type 1 error was considered by the clinical team. As noted in the previous

slide, with the exception of night total sleep time, for which there was no agreement, the most important separate clinical endpoints were all positive and would not matter how they were ordered.

However, the best reassurance that comes from is independent substantiation, which greatly reduces the potential that the clinical benefit that we saw was a chance finding or whether there was undetected bias.

The conclusion of the clinical team, clinical benefit for tasimelteon has been independently substantiated in two clinical studies.

In the next few slides, I will discuss the effect of tasimelteon on the periodic nature of nighttime and daytime symptoms of the non-24-hour disorder.

As you have heard, symptoms in non-24-hour disorder are periodic in nature. An effect on the periodic nature is important to support the clinical benefit in non-24-hour disorder. In

ordinary sleep-promoting, a soporific effect would not be adequate.

Lower quartile of night total sleep time was chosen as an endpoint because it was thought to reflect the worst nights when patients were most symptomatic. These worst nights are expected to occur periodically and therefore more specific to non-24-hour disorder.

Another approach to evaluate the effect on the cyclicity of symptoms is to look at the entire sleep diary for an effect on the stabilization of the periodic nature of nighttime and daytime symptoms. During the randomization phase of Study 3201, nighttime and daytime sleep data was collected for six months or two circadian cycles, whichever was less.

In the applicant's presentation today, you've heard a description of the methodology that was used to calculate the absolute difference between in-phase, which is the asymptomatic time, and out-of-phase, which is the most symptomatic time, in the circadian cycle.

This slide summarizes the results of the absolute value of the difference for in-phase and out-of-phase in patients with greater than or equal to 70 percent of one cycle during post-randomization.

The table above summarizes the night total sleep duration. And as you can see, the mean values for tasimelteon is lower than placebo and was statistically significant, favoring tasimelteon in cycle 1, cycle 2, and the combination of cycle 1 and 2. Similarly, total sleep duration during the day had a similar effect with statistically significant benefit in favor of tasimelteon compared to placebo.

Statistically significant effect favoring tasimelteon on the absolute value of the difference between in-phase and out-of-phase for cycle 1 and cycle 2 post-randomization indicates an effect of tasimelteon on the periodic nature of non-24-hour disorder.

In conclusion, the clinical benefit for tasimelteon has been independent substantiated in

two adequate and well-controlled clinical studies. There is substantial evidence of effectiveness for tasimelteon in the treatment of non-24-hour disorder.

In the next few slides, I will discuss the safety of tasimelteon. This slide summarizes the safety of tasimelteon. There were no major safety issues identified with regard to serious adverse events, adverse events leading to early withdrawal from trial, potential for drug-induced liver injury, metabolic endocrine laboratory parameters, potential for adverse effect in cardiac repolarization, adverse effect on vital signs, potential for suicide, and adverse effects due to abrupt withdrawal.

This table is a summary of the common treatment-emergent adverse events in subjects with non-24-hour disorder. These adverse events were selected if they were experienced by at least 3 subjects in the tasimelteon group and with a greater than or equal to twofold higher frequency than in the placebo group, and are ranked by

frequency in the tasimelteon group.

There was an excess of subjects with headaches in the tasimelteon group compared to the placebo group. Significant excess of headaches was not seen in insomnia population or healthy volunteers.

So it's not clear if these excess headaches in non-24-hour disorder subjects is unique to this population. There were more subjects with alanine aminotransferase increase in tasimelteon group than in the placebo group, 5 versus 2; 9.6 percent versus 3.9.

There was also an excess of subjects with nightmare and abnormal dreams in the tasimelteon group, in the non-24-hour disorder. Such excess results were seen in subjects with insomnia and is thought to be related to the tasimelteon mechanism of action we just heard in the applicant's presentation. The absolute numbers of the remaining treatment-emergent events are actually quite small, limiting any meaningful inferences.

The overall conclusion, the clinical benefit

of tasimelteon outweighs these risks in subjects with non-24-hour disorder. Thank you.

Clarifying Questions

DR. FOUNTAIN: Are there any clarifying questions for the FDA? Dr. Hoffmann?

DR. HOFFMANN: Richard Hoffmann. I just have one small question. The only other melatonin agonist that's been approved for melteon (ph), the FDA required a medication guide for that particular drug. Is there any consideration or need for a medication guide for patients and for this drug if it's approved? Thank you.

DR. UNGER: We are still thinking about that.

DR. FOUNTAIN: Dr. Zivin?

DR. ZIVIN: I am still having trouble understanding why the FDA and the sponsor couldn't get together on an endpoint for the trial.

DR. JILLAPALLI: I can answer that from the FDA perspective. We were really interested in an endpoint that demonstrated clinical benefit, that is capable of demonstrating clinical benefit,

because that's the basis for approval. And that was the reason for the disagreement.

DR. FOUNTAIN: Dr. Bastings?

DR. BASTINGS: Yes. It's not unusual that sponsors decide to use an endpoint different from the one the FDA is recommending and they do that at their own risk. At the end of the day, we have to look at the study results and decide whether substantial evidence of benefit was provided. But it is not unusual that sponsors would pick a different endpoint.

DR. FOUNTAIN: To follow up on that, often, biomarkers are indirectly related to clinical effects. And so it's obvious here's a biomarker for most clinicians, anyway. I think it'd be pretty well integrated into the way to think about clinical symptoms.

So if the sponsor had done a study before the efficacy trials to show an accepted correlation between circadian rhythm and the composite score, so the non-24 composite index, then would it have been -- in that methodology in general, the

circumstance, would accept a biomarker in place of or in addition to the others?

DR. BASTINGS: No. We would actually ask for more. The way you evaluate a surrogate endpoint is that you have to show consistently in several studies that if you give a drug that improves the biomarker, at the same time, you're improving the clinical benefit.

So basically, it would have been impossible to validate it without doing the study like the one they did, plus other studies with different classes of drugs, where you show consistent in that if you improve the biomarker, at the same time, people will experience a clinical benefit.

DR. FOUNTAIN: Dr. Kryscio?

DR. KRYSCIO: Dick Kryscio. I was going to ask Julia a question. There are several measures of sleep: hours, either lower quartile or upper quartile, total daytime, nighttime. Did you get the correlation among those

DR. LUAN: That is a very good question. And we know that the lower quartile night total

sleep time and upper quartile daytime total sleep time, and other sleep-wake measures, we know they're correlated with each other, but how much they are correlated and the quantification was not evaluated.

DR. FOUNTAIN: Please, sir, on your microphone.

DR. ZIVIN: I would like to know from the sponsor why they decided not to go along with what the FDA's request was for an endpoint.

DR. FOUNTAIN: Dr. Polymeropoulos?

DR. POLYMEROPOULOS: We would prefer to do everything in complete agreement with the regulators, but sometimes it's difficult. I think Dr. Bastings's discussion is very important, that we cannot just say that a marker is correlated with a clinical benefit without having shown this, which constitutes the beginning of the validation process.

The difficulty is that this is a rare orphan indication. It may be there is no other chance to find these 84 great people that came in the study.

These studies cannot be repeated. So you have to deal with very small sample size availability. Now, why not get agreement on what the FDA was offering on the LQ and the UQ and do that?

Two things, all the experts we talked to in review of the literature suggested you must show entrainment because it is actually not a biomarker and it is not a surrogate. It is definitional for the disease, resetting the clock. And surrogate is actually the nighttime or daytime sleep that shows some variability, albeit important to show clinical benefit.

We felt that it was a reasonable compromise to do two things, to have entrainment as a primary endpoint in the causal pathway, but also attempt to develop a scale, the non-24 CRS, and allow this to be as a clinical endpoint.

I understand Dr. Jillapalli's position that composite on the step-down primary required entrainment as a gating. But regardless whether entrainment is used or not, the non-24 CRS scale on itself is positive.

The way we think about non-24 CRS is no different than the HAM-D17 in depression or the PANSS scale in schizophrenia. And it's not perfect, but it could form the toolbox of the next developer to come along.

Our concern is that, just picking the daytime sleep or a measurement of that to the nighttime sleep, it leaves us with only a partial description of what happens in these patients clinically.

DR. FOUNTAIN: Did you want to address that, Dr. Unger?

DR. UNGER: Yes. I'll just mention, I mean, here I think patients care how they feel and function. And for these individuals, I think it's not that difficult to figure out if they feel better, or they function better, or, in this case, they sleep better, whereas I don't think they care very much about a chemical in their urine.

So we use surrogates where it's not practicable to actually measure the endpoint of interest, but here, the agency felt pretty strongly

that it was possible to measure the endpoint of interest. So that's what you want to go for.

The surrogate is helpful in understanding mechanistically that the drug does what it's purported to do. And that's useful. I mean, it would be like a drug for angina for patients with coronary disease. If we give morphine, then it would prevent angina. But it's nice to know that the drug actually affects ischemia.

So there you have it. If you can use that as a marker, you understand the mechanism. It supports the efficacy of the drug. And here, that marker would support the efficacy of the drug. But the efficacy is something a patient -- you know, how they feel or function.

DR. FARKAS: I agree completely, but I think this was pointed out before, that when we base approval on the biomarker, that's contingent upon showing clinical benefit later. And so, in a sense, everything's been done in this development program, the biomarker.

Kind of getting back to Dr. Fountain's

question, the biomarker was positive. The study continued, in some sense, and we have two studies, and the clinical endpoint is positive. So that's always the goal. Even under accelerated approval, it's finding out what the clinical benefit is.

DR. FOUNTAIN: Dr. Clancy?

DR. CLANCY: So I have a general biological question for anyone who knows the answer. So when we saw the pictures of the chemical structure of this compound, it was fairly large and complicated. And it made me wonder how this got to the pineal gland. How did it get through the blood brain barrier? And do we know the mechanism? And could that explain, to some extent, why there were some individuals who responded while others really did not?

DR. FOUNTAIN: Dr. Polymeropoulos or maybe Dr. Czeisler?

DR. POLYMEROPOULOS: Just a point on the molecule, actually, it's not that complicated. It looks like a neurotransmitter. Actually, it looks pretty much like a derivation of serotonin. The

molecular weight is about 300. And the properties of it allow you actually to penetrate well into the brain and distribute well, so nothing unusual about that.

DR. FOUNTAIN: Dr. Sack?

DR. SACK: If I understand correctly, the major clinical markers improved in the treated group, of which only at least 4 were entrained initially, perhaps more than that later. Are we to conclude that there's some benefit for this drug apart from its entrainment effect?

DR. FOUNTAIN: I guess it depends on who you're directing that at. Maybe another way to ask that would be, what's the evidence besides entrainment that it's having an effect?

DR. SACK: I was thinking that most of the subjects were not entrained or at least only half of them. And yet, all of the subjects were included in the clinical benefit analysis statistically.

So I guess I'm wondering, does that mean that there was some benefit to subjects in terms of

their sleep and daytime alertness even though they weren't entrained?

DR. JILLAPALLI: The benefit on the clinical endpoints were obviously mean group averages, which means that there were some that had a much greater benefit and some had lesser benefit. But we did not specifically look, at least the agency, to see in the entrained patients, how much benefit they had compared to those -- in terms of the clinical endpoints, compared to the non-entrained patients, again, in terms of the clinical endpoints. We did not do that analysis.

DR. FOUNTAIN: Dr. Polymeropoulos, I guess another way to ask that would be, is there a very tight correlation between entrainment and the outcome of those specific measures? It seems to me like total sleep to daytime, total sleep duration, would seem like it's logically the longest or the best correlation.

DR. POLYMEROPOULOS: We actually have done what we call the mediation analysis. By asking the question, if we now put entrainment in the model as

a factor and, therefore, entrained and not-entrained look the same, what is the remaining effect?

Let me see if we have that slide. If we can put that slide up, I will ask Dr. Licamele to come and discuss this.

DR. LICAMELE: Thank you. So as we see in the first column here, we have the analysis across both LQ-nTST, UQ-dTSD, and MoST. The first column shows the treatment effect as it was modeled in the study.

As Dr. Polymeropoulos mentioned, if we actually add entrainment to the model to see how much it's explaining, we see that entrainment effect is what is driving the analysis in the last column. Everything is very highly significant.

DR. POLYMEROPOULOS: Just to conclude that, the difference that are a few entrained people, in fact 20 percent, 8, in the primary endpoint, that would not reconcile well with all these clinical responders. What it is, is that entrainment was defined with very tight criteria to make sure we

don't have false positives. And therefore, inspection of the data would allow you to see a few more entrained people.

So that is the difference that you see in the numbers. But when you do the definitive statistical analysis, put entrainment in the model, we do not believe the drug does anything else on the sleep unless there is entrainment.

DR. FOUNTAIN: Dr. Bastings?

DR. BASTINGS: My view is that it's nice to have entrainment, but what I really care about is whether people experience a benefit. And the way you show that is by looking at nighttime sleep time and daytime sleep duration. And to me, whether they have entrainment or not demonstrated with the biomarker is not terribly important. What I really want is for people to feel better.

DR. FOUNTAIN: Dr. Vitiello?

DR. VITIELLO: I want to emphasize Dr. Farkas' point. This way, we can have our cake and eat it, too. I think that the disagreement that occurred was actually very healthy, because

what we've learned is more than we would have if we had gone with either approach. I'd want to commend the FDA, though, about not going with the original proposed nighttime total sleep time because that would have been a ghastly measure, as we saw in the outcomes.

It turns out that we see that there is a mechanistic aspect to this that also correlates very tightly with the clinical outcomes. And you don't always see that, as has been mentioned.

So I think that this is a good thing. I see the glass as much more than half full.

DR. FOUNTAIN: Dr. Sack?

DR. SACK: I have been trying to imagine this drug in approval, and then in the clinic, and with the clinician faced with patients who are totally blind, and with a decision as to whether or not to have them take this drug, which they may take for the rest of their lives.

So we would not have a biomarker at this point because there's no FDA-approved assay for melatonin or sulfadoxine melantonin.

So the clinician is then going to have to try to decide, is this person free-running? That is, do they have non-24? Are they one of the blind people who maybe a third of which are actually entrained?

Or does this patient have a tau of less than 24 hours? Or do they have a tau of greater than 24.7? I think, actually, that this field is going to limp along until a biomarker is available to clinicians to make some of these discriminations. Otherwise, we run the risk of having patients take a presumably substantially expensive drug for many months with no hope for improvements since, first of all, they may have been entrained in the first place, or it may not be likely to entrain them because they don't fit the criteria that are described in this protocol, which is a fairly refined group of totally blind people with a tau of 24.1 to 24.7.

So I think that there is a place for the biomarker in the future. In fact, I have some difficulties knowing how this drug would be used

without biomarker availability.

DR. FOUNTAIN: Dr. Farkas?

DR. FARKAS: So I should make the distinction that you're on much stronger footing. The FDA understands that there's much stronger footing in using a biomarker to select patients who you think will benefit, to give the drug to. So we agree with the point you made.

The issue is often -- or the concern is really that when you use a biomarker after you've given the drug, that there is all sorts of other effects that you don't understand. There's other parts of the disease. There's other effects of the drug. So it's really a different use, a much, much riskier use of the biomarker.

So again, just to make the distinction, we hear what you're saying. We understand that it's important to select patients who can benefit from a drug, and it's important to understand that the FDA views the use of biomarkers differently depending on whether it's used to select patients or to understand benefit.

DR. FOUNTAIN: Dr. Eastman?

DR. EASTMAN: I think entrainment is a much more important endpoint than any measure of sleep because, if somebody is free-running, a non-24 hour, that means, periodically, they have circadian misalignment. And it's not just sleep that's affected, but other things like eating at the wrong circadian phase can be unhealthy. Even if they manage to sleep well at the wrong phase because they're flexible sleepers or what we call phase tolerant, they're probably going to suffer from some kind of performance deficit. Not everything will be fixed if sleep -- sleep isn't the only important thing.

DR. FOUNTAIN: Dr. Unger, respond to that?

DR. FARKAS: I think I would pick up on the everything part of it, everything being fixed. And I guess that, in some sense, if we look at the data that we have for these patients for sleep, it isn't really clear that everything is fixed in the patients who are entrained.

It's a little hard to know. Again, I don't

want to imply that the clinical endpoint was perfect, either. But it still seems like sleep at night still isn't completely normal and that sleep during the daytime still takes place.

So again, we're not really sure what's going on, but it looks like things aren't completely fixed. And so then, when taking a look at the biomarker and saying, "The biomarker is fixed," do we really know that the patient is fixed and that they're all better? And I think the answer is, well, they might be. And it's something really interesting to look at, but they might not be because there's other things going on. There's other things going on in the disease, even things like dose. I mean, the drug is not exactly replicating the endogenous rhythm of melatonin.

The drug is perhaps causing other effects. So these other benefits are certainly something that can be looked for, but, really, we're often wrong if we assume that they're there.

DR. FOUNTAIN: Dr. Bastings?

DR. BASTINGS: Yes. To extend off what

Dr. Farkas just explained, if you think there are additional benefits to entrainment than just improving sleep, then the way to validate that would be to use clinical endpoints that measure these benefits. And you show that, when you improve a biomarker at the same time, you improve these other clinical benefits.

That's the way you would establish that you have something more than just improving sleep.

DR. FOUNTAIN: We'll have more opportunity for discussion after lunch. And maybe that's something that might be more fully flushed out.

Dr. Mielke, did you have another question, clarifying question?

DR. MIELKE: Sure. If you don't mind, quick. The discussion about biomarkers and clinical endpoints I think is really helpful and especially in pushing the program forward. But I think -- I mean, based on what you've said, too, it looks like -- in my reading of this -- that the drug is clinically effective, and it has an effect on the biomarker.

So I guess, what is your question for the afternoon that you want us to focus on? Or what are you questioning us on?

DR. FARKAS: I think that a large part of the reason that we're here is that this is a new indication and we have used new clinical endpoints, too.

So you seem to be saying, from the way you phrased the question, that it seems like a reasonable indication -- I shouldn't put words into your mouth -- and that the clinical endpoints seemed reasonable. But we haven't talked about this in public with experts before. So that's a large part of what we'd like to talk about this afternoon.

Regarding the biomarker, I think you'll see from the questions that we as the FDA have expressed our viewpoint of that, and we're more interested this afternoon, again, in talking about the way the disease is defined, the population. Some of the issues came up before, like, are we selecting the right people to treat. And again,

are we measuring the right clinical measures?

DR. FOUNTAIN: Thank you. So that's a nice segue to end the morning session on. We will now break for lunch. We'll reconvene in this room at 12:45, at which time we will begin the open public hearing session. Please take any personal belongings you may want with you at this time.

Panel members, please remember that there should be no discussion of the meeting topic during lunch amongst yourselves or with any other member of the audience. Thank you.

(Whereupon, at 11:55 a.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(12:47 p.m.)

Open Public Hearing

DR. FOUNTAIN: Good afternoon. Welcome back. We'll begin the afternoon session of the meeting.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the public open hearing session of the advisory committee meeting, FDA believes it is 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 statement, to advise the committee of any financial relationship that you may have with a sponsor, its products, and 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.

But if you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and commitments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson, that is, by me. Thank you for your cooperation.

Each speaker will have five minutes. And

30 seconds before the five minutes is up, a yellow light will blink. I'm sorry. So to clarify that, the beep will come both 30 seconds before the five minutes are up and then at the end. So you'll know when you have 30 seconds left to speak.

We won't cut you off at five minutes, but I would like everyone to try to respect that time frame so everyone can have their allotted amount of time.

Will speaker number 1 step up to the podium and introduce yourself? And please state your name and any organization you're representing for the record. Thank you.

MS. ERB: Good afternoon, everyone. My name is Suzanne Erb. I am a non-24-hour sleep-wake disorder patient. I am currently taking tasimelteon and have been participating in this study for as long as it's been studied, around 2011. My travel and lodging have been paid for by Vanda Pharmaceuticals. However, I would like to inform this august committee that, even if Vanda had not paid my way, I would have felt that I would

have wanted to participate in this hearing today.

I can't say enough good things about tasimelteon. Prior to taking tasimelteon, my days were characterized by sleepiness and my nights were characterized by wakefulness. I remember always wondering when important events in my life would come up, whether or not I would be awake and alert for them.

When I took my master's comps, I had such a difficult time because I had trouble staying awake, but miraculously, I passed them. The same has been true throughout my occupational life. I'm amazed what I've been able to accomplish despite having non-24-hour sleep-wake disorder.

I believe that I may have known that I had it ever since I was a little child. I remember constantly being told by my parents that I was turning my days into nights and vice versa, and that I was a bad, bad girl. I also felt this all through my life, and I never knew what was wrong. I thought it was me. I thought there was something wrong with me. I remember going to countless

doctors and being told that if I were to have a normal sleep-wake schedule, if I took sleeping pills or other medication, that I would have a normal day and nighttime life.

That never happened. It never happened. And ever since I've taken tasimelteon, I have noticed a huge difference in my life. I don't have to worry anymore about whether or not I get a good night's sleep. I may not always get a perfect night's sleep, but I would say that, in the grand scheme of things, I do sleep well.

The anxiety that I used to have every night is no longer there. I think my health, overall health, is extremely good now. I no longer get migraine headaches. And I don't know if I can attribute that to sleeping better, but I no longer get migraine headaches. I no longer am anxious. I have been able to stay awake all day long and accomplish so much more than I ever did before.

I would also like to say that I did try melatonin at one point, but I wasn't sure exactly how much to take or when to take it. And it really

wasn't effective for me. But I would like to say that tasimelteon has made it possible for me to live a normal functioning life. And I would also like to say thank you to everyone who's participated in this work. But I would wonder what would happen if this drug does not get approved and if I no longer have it available to me, I don't know how I would manage. My whole life would change and I'd be back to where I was.

Thank you so much for giving me this opportunity to testify today.

DR. FOUNTAIN: Thank you.

Will speaker number 2 step up to the podium and introduce yourself? And please state your name and any organization you're representing for the record.

MR. RICCOBIONO: Good afternoon. I'm Mark Riccobiono. I'm executive director of the National Federation of the Blind, and I'm speaking on behalf of the Federation today. Vanda Pharmaceuticals did pay for my travel to this meeting and has been a partner with the National Federation of the Blind

in order to understand better the blind population. I appreciate the opportunity to present today.

It's a pleasure to speak on behalf of the National Federation of the Blind, this country's oldest and largest organization of blind people. At the National Federation of the Blind, we believe that blindness is not a characteristic that defines our future.

Every day, we work together to break down societal barriers because we improve the world when we have access to the information, skills, and relationships that allow us to participate fully and pursue our dreams.

Due to our representation of blind people from all 50 states, the District of Columbia, and Puerto Rico, we speak on behalf of this nation's largest group of totally blind individuals impacted by non-24-hour disorder.

The experience of blind people is that we face significant difficulty in education, employment, and in the community due to the negative perceptions that exist about the

capabilities of blind people. In short, the average person falsely believes that blindness equals inferiority, a lack of capacity, a great need for significant help, unable to compete, and difficulty in understanding normal social patterns.

What people know about blindness is influenced by classic literature, where blind people are tragic figures or amazing superhumans, or comedy skits where the portrayal of the blind as bumbling fools is used to create unusually funny circumstances. Unfortunately, many blind people internalize these same negative views because they grow up in a society that misunderstands blindness as a physical condition that must permanently limit an individual's value in the world.

Imagine now, a totally blind young woman, Sally, who is trying to compete in society. Although she's received some training in how to live independently as a blind person, she is influenced by the negative messages throughout society about the blind, completely unknown to her.

She suffers from non-24-hour disorder.

Sally struggles with sleeplessness, feeling rundown, and periodic depression. After struggling to maintain employment and healthy relationships, she begins to falsely believe that her problems are a result of the inability of the blind to participate fully. And her family and friends internalize these damaging views as well.

Without the availability of a technology to overcome non-24 and without proper educational information, Sally and thousands like her are left to conclude that the symptoms of this rare condition are actually a reflection of the lack of capacity by the blind and not resulting from an invisible secondary medical condition that can be mitigated.

We believe there is a great need for tasimelteon, that it will significantly improve the quality of life for the individuals impacted by non-24, and that society will be better off directly and indirectly from the full participation of these individuals.

On behalf of the National Federation of the

Blind, and especially our totally blind members who knowingly and unknowingly are adversely affected by non-24, we urge the advisory committee to give the proposed technology serious and speedy consideration. Thank you very much.

DR. FOUNTAIN: Thank you.

Will speaker number 3 please step to the podium and introduce yourself? And please state your name and any organization you're representing for the record.

MR. MEYER: I'm Randy Meyer. I'm representing myself here today and Vanda Pharmaceuticals did pay for my travel here.

Picture yourself taking a nap. No problem. Right? Now picture yourself waking up in a gymnasium. Stranger yet, you're enrolled in the heavyweight division at an NCAA wrestling tournament and your name has just been called on deck for mat 3.

Strange dream? Wild fantasy? No, my reality living with non-24 hour disorder. Here's what happened. I went to bed at 9:30 so I'd be

well rested for my 6:30 alarm clock. A couple girls stop by and talking to my roommates, got a little loud, and I was a little distracted. But 15 minutes later, they left, and I was right on the edge of sleep. So I thought, "No problem. I'll just fall right asleep." That's what should happen. Right?

No. That simple distraction was enough to keep me awake until 4:30 in the morning. The alarm clock rang at 6:30. Sleeping in wasn't an option. The bus left at 7:00. So I got up, went to the bus, got there, started my first match at 9:00. The adrenaline was enough to put me through that one. I was all pumped and won that match. But then things really hit home. I'm like, "Boy, you're not going to be competitive in four more matches on two hours' sleep. Not going to happen."

So I decided to do something kind of odd at an NCAA wrestling tournament. I laid down on the side of the gym and went to sleep, took a nap, woke up in time to hear my name called for on deck of mat 3, went and won that match. Took another nap.

There is challenges being blind, but they're easily overcome. I'll tell you right now, a non-24-hour disorder is my true handicap. The technology and stuff that's out there for blindness is getting better and better. And there's no -- being blind than today, and tomorrow, it will even be better.

But there needs to be something for this non-24. First, through my life, no one really believed me. First through sixth grade, I was going away to a school, so I wasn't with my normal family and, of course, I wasn't falling asleep until after midnight on most evenings.

Then you get to school and you try to explain to them. And the teacher just went, "Well, you've just got to get to bed early." No adults would believe you. You were just a seven-, eight-year-old kid. They just figured you were homesick and just trying to come up with excuses on why you shouldn't go to school that day.

So then I progressed on to high school, and I've always been a guy who asked a lot of

questions, so I started to ask some questions. And I said, "Well, what is this all about?" And I started to learn about circadian rhythms, light-dark cycle. I wondered, "How does a blind person fit into that light-dark cycle box?"

I started to share my theories with friends, and they just kind of laughed at me. And I thought, "Hey, I'm already blind. I don't need something else to separate me from these teenagers." So I just moved on.

I fell asleep in some classes, got good grades, so some teachers overlooked it. Other teachers didn't. Then I went to college, and professors didn't really care if you were sleeping in their classes. They didn't care if you showed up. That was on you.

Then I got into the workforce and I started doing financial planning. I did that for 20 years. One reason I picked that is that I could have a little control over my schedule. I could work a 12-hour day and possibly a four-hour day depending on my sleep patterns.

A lot of my clients would be surprised to find out their plans were prepared at midnight and 3:00 in the morning, when I was awake.

I've been elected mayor of my hometown and there the challenge is, if you fall asleep in meetings, people aren't going to look at you as a leader. There's an old saying. If you're leading and no one is following, you're just taking a walk.

I want to be viewed as a strong, confident leader, someone who's not just taking a walk, but someone who is being followed and respected. So my challenge is to manage my schedule around my non-24. If I have a bad night's sleep, I know either one of two things. Sometimes, you can suck it up and make it through the day, but a lot of times, you just have to learn to plan breaks in your day just in case, just in case. You don't know.

Last night, good example. What time did all of you fall asleep at? I was 2:00 or 2:30, up by 5:30. Now I'm talking to all of you. That's the reality of living with this. You don't know when

it's going to happen. It seems to go in about a week-and-a-half, two-week cycle. Last week was beautiful. I was sleeping on time. It was great. This week, I'm like, "Boy, just in time for this presentation, it's going to be an off cycle." And that's exactly what happened.

As I said, I manage my schedule the best I can, but this has definitely prevented me from taking 8:00 to 5:00 jobs because you can't explain this non-24-hour thing to a boss. You're already blind. They're already wrapping their arms around that. You can't explain why you're tired that morning or why you dozed off in that meeting.

So I just learn to go be self-employed. This also affects my family relationships. When your wife's talking to you and you just doze off, or she's reading you something you wanted read, you doze off.

Oh, yeah. That wrestling match in college? Four matches later and three naps later, I won the tournament. Thank you for your time.

DR. FOUNTAIN: Thank you very much.

Will speaker number 4 please step to the podium? Please state your name and any organization you're representing for the record.

MS. LEADER: Good afternoon. My name is Patricia Leader, and I am immediate past president of AER, which is the Association for Education and Rehabilitation of the Blind and Visually Impaired. My travel and lodging was sponsored by Vanda, the sponsor today, for presenting my testimony.

I have educated students who are blind for the past 36 years. I teach my students. However, I support them and their families with counseling, advice, and guidance. In this role, I have frequently been approached by families to discuss and request assistance for their student's sleep issues.

Over the years, I thought the problem stemmed from students who were allowed to stay up too late at night, take afternoon, after-school naps, and were not held to a reasonable schedule at home.

Regularly, students would doze during class,

exhibit lack of focus or inattention to lessons. I have often observed my students who miss school, were unable to complete their assignments, and could not assimilate the concepts.

In consultation with their families, I recommended adherence to a rigid after-school schedule, including no naps, a pre-bedtime routine, and a regular bedtime. Also, changes in diet or times for eating meals have been attempted.

Parents responded by instituting a routine, but reported that they could not keep their students awake in the afternoon, preventing them from being able to retire at night. Families are frequently awakened during normal sleep hours by their children who can't sleep, also find it confusing at other times when their child is able to follow a regular sleep schedule.

Parents describe situations where the students would awaken in the middle of their sleep cycle, unable to return to sleep. The students would wander around the home, a safety issue, play with toys, listen to music, or seek attention from

the parent. This is disruptive to the entire family, who are unable to sleep.

As a result of this disorder, I have seen a high rate of student absenteeism. At various times, I have needed to find a place for a student to sleep during the day at school when they could not maintain a state of alertness in class and literally couldn't stay awake for a class lecture.

I would notice students nodding off in the mainstream classroom as well as during individual one-to-one instruction with me. On the advice of one university professor, we used a device placed on the ear of a student, which would emit a buzzing noise when their head nodded, commonly used for drivers who want to stay awake.

One parent's solution was to teach her child to remain quiet to allow other family members to sleep. Another non-working parent would stay awake to attend to her sleepless child to afford her spouse the opportunity to get a good night's rest as he prepared for the challenges of his daily work schedule.

It's clear that this disorder causes pain and suffering throughout the families and affects achievement and self-esteem for the student. I'm embarrassed to admit that I became aware of the non-24 hour -- I along with my colleagues blamed parents for not enforcing a regimented routine at home and students for not caring about attending in class, staying awake, or being prepared for the rigor of lecture.

As my awareness of non-24 hour increased through review of literature and discussions with my AER colleagues and other professionals in the field of blindness, I recognize that this is a bona fide medical problem.

I now understand that non-24 hour devastates families and students and disrupts their lives. This is a debilitating medical condition facing people who are blind and those who care about them.

The solutions they have attempted, schedules and routines, changes in diet, other strategies, and even taking supplements such as melatonin or sleep medications have been futile. They have

produced no positive results. My awareness of non-24 hour has led me to engage in conversations with parents to educate them about the reality of this disorder and share hope in the possibility of a solution in the near future.

Parents are desperate for a therapy for this unmet medical need to allow them to create a balance in their lives. Students deserve to have the ability to attend school daily, focus in class, master concepts, and progress along with their peers.

Families, students, and teachers like me who become a part of their students' lives are seeking assistance for this critical problem. Vanda's proposed pharmaceutical, tasimelteon, is a solution needed now for people who are blind and suffer from non-24 hour to allow them to create order, and normalcy, and productivity in their lives.

I applaud Vanda for their work in this area and for proposing this desperately needed solution in the field. Thank you for your time and consideration of this concern.

DR. FOUNTAIN: Thank you. Will speaker number 5 please step to the podium? And state your name and any organization that you're representing.

MR. MENDEZ: Good morning. My name is Jack Mendez, and Vanda did sponsor my travel here. I do suffer from non-24 disorder. I am a patient. And my experience, I've had non-24 for as long as I can remember. We had a couple people talk about their experience in the early years.

I can remember, at three years old, being awake at night, and my family tells this story about how I was sitting on the surface of the table, the dining room table, sifting together coffee grounds, and creamer, and sugar all by myself, getting into stuff, kind of mixing stuff together and getting into a real mess.

That kind of early experience sets the stage for other events that have happened in my life. Later on, while in school, I'd fall asleep. This is in kindergarten, elementary, trying to learn ABCs, and my instructor says, "Hey, you're falling asleep here. Wake up." And I was prescribed

sleeping pills. I was prescribed medication for ADD because they thought I might have that.

None of those things helped. I was told by doctors, "You want to sleep, then go to bed at 9:00 every night and wake up at 5:00 in the morning, whatever, get your eight hours. Don't drink coffee. Change your diet," all these common, helpful sleep health recommendations.

I have tried for years and none of it worked, none of those things. Sure, some things helped. You get a little exercise, you feel a little more energy, that sort of thing. But regardless, my experience is that you -- if I went to bed at, say, 11:00 that night, I'm still going to wake up at 2:00 in the morning. I'm still going to wake up at 3:00. If I went to bed at 9:00 or 1:30, I'm still waking up at the same time.

The whole series of emotional anxiety that happens when you're awake at night, because if you have work responsibilities, you're thinking, "Oh, my gosh, I'm going to be awake until 6:30. I've got five more hours to be awake." And then I have

to get up, go to work, perform as expected, and then come home. And I'm married now, so I have responsibilities there and be awake for things. And really, that continues to be a struggle for me.

I do drink coffee during the day. I do do things that might be counter to what is known as good sleep health practice. But at the end of the day, I have to work. I have to do things to be productive in society. And sometimes, that means that I will sleep on weekends for a long time, six, eight hours during the day, plus the sleep that I get at night. Sometimes, that means I do forego events there.

So there were questions about, only an hour of sleep, how beneficial is that. Well, I'll tell you what. If I can get another hour of sleep, on average that's five hours a week more. That would really, really be beneficial for me. So thank you very much.

DR. FOUNTAIN: Thank you.

Will speaker number 6 please step to the podium? And please state your name and any

organization you might be affiliated with.

MR. AUGUSTO: Hello. My name is Carl Augusto, and I'm president and CEO of the American Foundation for the Blind, and Vanda paid for my travel and lodging here.

The American Foundation for the Blind is a leading national nonprofit, which envisions a world in which people who are blind or visually impaired have a quality of access and opportunity and that will achieve to their maximum potential.

The foundation's mission is to remove barriers, create solutions, and expand opportunities for people with vision loss. And there are many myths and stereotypes about the totally blind population. But evidence shows, with the proper training and acquisition of skills, blind people can and do live and work with dignity and success alongside their sighted peers.

Perhaps the biggest challenge facing the blind population today is gaining employment in line with their skills and interests. According to a 2011 American Communities survey, which is

administered by the Census Bureau, 36 percent of blind people between the ages of 21 and 64 are employed, compared to 75 percent of the general population. There are many reasons for this, but a leading reason is, employers can't imagine someone without sight doing the jobs in their company.

Perhaps the group within the blindness population that is facing the biggest challenge are those who are experiencing non-24. An estimated 50 to 70 percent of totally blind people have non-24. This population faces additional challenges not only in the workplace but throughout life as you're hearing this afternoon.

I have known three employees at the American Foundation for the Blind over the years who had non-24. Two had no diagnosis was until very, very recently. All three tried different strategies, pills, including melatonin, coffee, different sleep patterns. Nothing worked.

You heard the word "debilitating." It is truly a debilitating disability. All three of these employees have said the same thing.

Blindness is easy. My disability is non-24. They have been humiliated during active time when they fell asleep, embarrassed, demoralized. One that that he had a severe emotional disability.

I have heard stories from other totally blind people who have chosen not to seek employment because they felt that they couldn't keep a job because of non-24 and who were having difficulty leading normal lives.

Ladies and gentlemen, what a waste of human potential. If there is a safe and effective solution for non-24, I'm confident that more totally blind people will seek employment, converting them from being people who are tax burdens to taxpayers. And beyond employment, we should all look for the day when all blind and visually impaired people can lead their normal lives in the community.

Tasimelteon has a tremendous potential for transforming, yes, revolutionizing the way blind and totally blind people function on a daily basis. Thank you very much.

DR. FOUNTAIN: Thank you.

Will speaker number 7 step up to the podium and introduce yourself? And please state your name and any organization you might be affiliated with.

MS. DORMAN: Good afternoon. My name is Diane Dorman, and I am vice president for public policy for the National Organization for Rare Disorders. I have no personal or financial relationship with Vanda.

I'm here today not on behalf of the company before you today, but on behalf of the patients and their families affected by non-24 as well as the men, women, and children in the United States suffering with one of the 7,000 known rare diseases, that, in the aggregate, affect more than 30 million people in the United States.

NORD, a 501(c)(3) organization, is a unique federation of voluntary health organizations dedicated to helping people with rare orphan diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders to programs

of education, advocacy, research, and service.

NORD's mission is to ensure that all people with rare diseases have access to diagnostics and therapies that extend and improve their lives, and that the United States maintain a regulatory environment that encourages the development and timely approval of safe and effective diagnostics and treatments for patients with rare diseases.

Rare disease research and the development of orphan therapies to treat them are unique in many ways. Patient populations are generally very small and geographically dispersed across the world. There are few researchers and biopharmaceutical companies willing to take on the financial risk associated with this vital and often life-saving work.

Today, there are just over 400 orphan drugs and biologics that treat only a few hundred rare diseases. Given that there are thousands more rare diseases that need specific treatment, it is easy to understand that there are many people who can only hope that, one day, someone will take on the

significant risk to develop a therapy for their condition.

Subpart E maintains that the agency has in place procedures to expedite the development, evaluation, and marketing of new therapies that are intended to treat persons with life-threatening and severely debilitating conditions, especially where no satisfactory alternative therapy exists. Subpart E goes on to say that certain drugs demand flexibility and considers it appropriate to exercise the broadest definition of flexibility when applying those standards.

On behalf of all rare disease patients and their families, as you continue to deliberate, NORD asks only that this advisory committee stand by that commitment and apply a greater degree of flexibility, keeping in mind that there are few treatment options for thousands of rare diseases.

Orphan products are highly specialized for very small patient populations and patients affected by non-24 may be willing to accept more risk and less certainty of benefit in exchange for

access to a therapy treating unmet medical need.

NORD's hope is that information patients have shared with you today may contribute toward your decision making and assessing the benefit/risk equation of a therapy treating a life-threatening unmet medical need. We know that patients at various stages of their condition are willing to take on a greater degree of risk, given the quality of life challenges they face every day. Thank you.

DR. FOUNTAIN: Thank you. Will speaker number 8 step to the podium?

(No response.)

DR. FOUNTAIN: All right. Will speaker number 9 please step to the podium? Please state your name and any organization you might be affiliated with.

DR. ALMASHAT: Thank you. My name is Sammy Almashat. I'm a physician with Public Citizen Health Research Group. I have no conflicts of interest and thank you for the opportunity to speak at this important hearing.

Unfortunately, the tasimelteon development

program raises more questions than answers regarding four specific points: end-of-trial replacement of the prespecified primary endpoint, a highly unusual aspect of pre-approval clinical trials, and raising the question of the validity of post hoc endpoints.

What exactly was the rationale for the final primary composite clinical endpoint? Most importantly, what precedent would approval today set for future approvals of other drugs, including drugs for this debilitating condition? And finally, the potential for misdiagnosis in blind patients, which was raised earlier this morning, and off-label use in sighted patients?

As a medical reviewer points out, among the many characteristics of an adequate and well-controlled trial is that the results reflect a clear prior hypothesis documented in the protocol to reduce the risk of false-positive findings.

Here is an overview of the changes made to the trial protocol since it began in July 2010, including the change suggested almost two years

after the trial began, and after data had been collected on early LA24 subjects analyzed today.

The request to FDA to completely replace the original primary endpoint was made after data had been collected on most subjects included in the final analyses presented today and made in response to recruitment difficulties that required the introduction of a post hoc unvalidated surrogate primary endpoint in fewer subjects.

The proposed urinary surrogate marker for circadian entrainment was correctly rejected by the FDA, unless evaluated with clinically relevant endpoints. However, no agreement was ultimately reached between the agency and the sponsor regarding the primary efficacy endpoint, analysis populations, and analysis methods for either pivotal study, which again is very unusual.

The final primary endpoint chosen by the sponsor was entrainment as measured in urinary surrogate markers plus three -- and it's unclear why three of the following four clinical endpoints was chosen as a threshold. As we saw this morning,

the lower quartile of nighttime total sleep, the upper quartile of daytime total sleep, but also the following two endpoints, the midpoint of sleep timing and the CGI-C; it's unclear to us why these were included in a composite endpoint.

The medical reviewer suggested that MoST is of unknown clinical meaningfulness and CGI-C is not an optimal endpoint, since it relies on clinician's judgments and not patients' self-reports of how they're doing.

Regarding the other two components of the clinical endpoint, there was a prior agreement between the agency and the applicant that nighttime sleep and daytime naps were the two most important direct measures of clinical benefit.

In circadian rhythm disorders such as non-24, therapeutic success would presumably include an improvement in both nighttime and daytime sleep patterns. However, the proportion of subjects showing fewer worst nights and worst days, the two remaining components of the composite endpoint, was not significantly different between

the treatment groups. In particular, when the threshold was set at 90 minutes of improvement in both outcomes, differences were even less evident.

The statistical reviewer concluded the review of the data as follows. According to this reviewer's post hoc exploratory analyses, without multiplicity adjustment, the two studies appear to suggest that tasimelteon, 20 milligrams, may be beneficial in this disorder. However, the results of these two studies should be interpreted with great caution, since they are based on post hoc exploratory analysis without multiplicity adjustment. And thus, it is unknown whether or how much of an overall type 1 error is properly controlled.

Again, the questions raised by changes made so late in a clinical trial include what indication, if any, did the sponsor have with the original primary endpoint would ultimately fail to reach statistical significance.

Importantly, why was this particular combination of four clinical endpoints chosen? And

on what basis was a positive outcome on three of the four clinical components deemed a suitable threshold for clinical response? Finally, why were MoST and CGI-C included in the final outcome, despite the medical reviewer's concerns over the validity of these measures?

Finally, in conclusion, in addition to the concerns over the clinical endpoint and the potential for misdiagnosis that was raised earlier, most importantly, the approval of tasimelteon, given the magnitude of post hoc changes timed so close to the end of data collection, would set an ominous precedent for future new drug development programs.

If this drug is approved today, how will the FDA, in particular, ensure that such an arbitrary and late-in-the-game change in clinical trials is not done either for future drugs in general or for drugs for this particular condition? Thank you.

DR. FOUNTAIN: Thank you.

Would speaker number 10 please step to the podium and state your name and any organization you

might be representing?

DR. ZAMPIERI: Good afternoon. I'm Tom Zampieri. I'm director of government relations for the Blind Veterans Association, and we've been in existence for 68 years. I have no financial reimbursement for travel here today. And BVA doesn't have any government contracts or grants.

I just wanted to speak regarding blinded service members and veterans who have been coming back from the wars in Iraq and Afghanistan. I've had a lot of experience in visiting them. I was an Army physician assistant for 22 years. And for 15 of those years, I was an Army air medical flight surgeon PA, so I had experience in dealing with problems with jet lag and those kinds of conditions that we deal with in the military.

Anyway, the wars in Iraq and Afghanistan, obviously, from those individuals in the room that have read reports, often include polytrauma patients with traumatic brain injuries, amputations, a lot of other injuries associated with a blast.

For those veterans who have had no light perception, one of the things, interestingly, that we came across frequently is the complaint of this non-24-hour sleep disorder. Oftentimes, these injured service members are treated with multiple medications because of the other conditions. They have problems with pain control. Oftentimes, the traumatic brain injuries also have cognitive disorders and all sorts of things.

The complaints that they have about not being able to stay awake during the daytime and having impossible problems sleeping at night, oftentimes they are given medications that, as the other witnesses described, don't address the underlying condition and problem. So getting the circadian cycle back is an effective way to address this.

Masking the symptoms with treating these individuals with a variety of other things only contributes to the problems of polypharmacy and those other issues that physicians that I know at Walter Reed and at other military treatment

facilities struggle with.

It's not unusual for these patients to be on an average of anywhere from 8 to 14 different medications as it is. And then you start to add sedatives or other things to try to "help them sleep" and you just created another problem.

I just appreciate the opportunity to be able to speak today. There have been some studies, small, but looking at the population with traumatic brain injuries, ironically, that suffer from migraines and pain problems. And one of the things that jumped out at this research article that was published was, out of 126 service members with TBIs that they looked at, in the symptoms that they questioned them about, 80 of them complained of sleep problems. And so it's kind of interesting that, sometimes, you find other things when you're looking at one other type of problem.

Anyway, we also have found that individuals from previous wars, Vietnam and Korean War veterans, and even a few of the surviving World War II veterans that I have talked to, that have no

light perception, went through their entire lives with this problem. And again, they were often treated with a variety of other things that didn't work.

So hopefully, considering where this goes, we'll ask that you consider that while this is not a widespread problem for Americans at large, for this population, especially for our injured service members and veterans who have been blinded in combat, this medication may prove to be a way to treat this problem.

So I appreciate the opportunity again here today to speak and thank you very much.

DR. FOUNTAIN: Thank you.

Will speaker number 11 step to the podium and please state your name and any organization you might be representing?

DR. TUREK: Yes. My name is Fred Turek, and I'm a professor in the Department of Neurobiology and the Department of Neurology at Northwestern University, where I also direct the Center for Sleep and Circadian Biology. I've been a

consultant for Vanda. I served on their advisory board, and they paid for my expenses here. I've also received grants from a number of pharmaceutical companies that are interested in finding drugs that can phase-shift the circadian clock.

My research has also been supported by the Department of Transportation, DARPA, NASA, private foundations, and for 35 years the NIH. Listening to what I heard today, I wanted to make this point. For 35 years they've been funding my work, in the beginning, trying to understand what's the biological basis of this clock. But for the last 10 or 15 years, how is disruption of this clock affecting the health and well-being of Americans in our populations?

Since the 1970s, I've been studying how the master circadian clock and the suprachiasmatic nucleus is entrained to the 24-hour day. And I can tell you, it's hard to entrain that clock to non-photic signals. And I've looked at what are the effects in the absence of a light-dark cycle?

I've carried out research on how the SCN controls the expression of a multitude of circadian rhythms when the clock is entrained and when it's not entrained. And when the clock is not entrained in my mice, or my hamsters, or my birds, it's not really a problem. They free-run with a period of 23, 25 hours. But if you're trying to live in a society that's 24 hours, I don't make them do that. As I've heard today, in a dramatic fashion, it can obviously have upsetting effects on one's life.

Now, we've known for, really, probably a century, that disrupting the sleep-wake cycle, circadian cycle, can have effects on safety, performance. That's why there are rules in the trucking industry, the train industry as to hours of service and that. But it's really only been in the last 10 to 15 years. And I even would say even within the last couple of years for some parts of the NIH, that we begin to recognize the importance of disrupted circadian rhythms for diverse illnesses, from diabetes to obesity, to cardiovascular disease, to depression, and some

links to Alzheimer's disease, just to name a few.

Now, because these personal and social lives, as well as their health, are affected of these blind individuals who do not have light perception, I believe that the totally blind should be treated so that they can get entrained to the 24-hour day and not be in a periodic state of jet lag or a periodic state of what shift workers go through when they're trying to sleep at the wrong time of day.

Let me end by saying, in 1976, I was a junior high student. That's not true. But in 1976, I published a paper in Science. It was the first demonstration that melatonin could alter the circadian clock, avert a risk.

Since the early 1980s, I carried out studies that were designed to identify compounds that could phase shift or synchronize the mammalian circadian clock, including a number of melatonergic drugs for other drug companies.

In addition, since the molecular clock is similar in animals as diverse as flies, mice, and

humans, I spent a good part of my professional career doing research on the effects of abnormal circadian rhythms on animal models, looking at various changes in their neural behavior and physical health, with the goal of developing new therapeutic approaches that could phase shift and synchronize the human circadian clock system to maximize safety, performance, productivity, and as I've been trying, link to health.

Now, given the importance of circadian organization across the animal kingdom, I'm really excited about the possibility of having the first circadian clock regulator on the market, and I can't emphasize that enough. There are no circadian clock regulators on the market because it's only recently that we've begun to recognize that disrupting circadian rhythms is adverse for health and well-being.

Now, if you consider that normal circadian organization is a biomarker for health, I would actually say it's a necessity for health. I think you can link quite easily that circadian

disorganization is bad and circadian organization itself is a positive clinical outcome. I've heard the interest in the clinical outcome mentioned a number of times here, and I think one can expect that drugs that can normalize circadian rhythmicity will be found to have positive clinical outcomes for those individuals who are suffering from non-24-hour clock.

I'd also like to just end by thanking you for giving me the opportunity to speak to you because it's kind of exciting for us people who have been studying circadian rhythms from, "Where is that clock located? What is it doing? How is it important?" to see that the FDA in general is beginning to look at drugs that will affect the circadian clock system and, in particular, for this subset of populations who clearly need this drug. Thank you.

DR. FOUNTAIN: Thank you.

Will speaker number 12 please step to the podium and please state your name and any organization that you're representing?

MS. BRUNSON: Good afternoon. My name is Melanie Brunson. I am here both as a person who has personally experienced the firsthand ways in which one's life can be disrupted by non-24-hour disorder and as a representative of the American Council of the Blind.

Vanda Pharmaceuticals asked me to come today and provided my transportation from across the way in Virginia to this hotel. But I want you to know that even if I hadn't been asked, I would have been here today.

For as long as I can remember, I have experienced periods lasting from about 10 days to a couple of months where, night after night, a full night's sleep eludes me, no matter what I do. During the days following those nights, I am incredibly tired. I have a hard time remembering things, even the most basic things like the end of a sentence. I find concentration and, in fact, most daily activities to be a challenge.

I believe my performance at work has suffered. It's really tough to pay attention to

the details of managing tasks and managing people when the only thing you really want to do is figure out how you can manage to take a nap. Getting appropriate exercise is a chore, and even things I enjoy doing are hard to do at those times because I don't even feel like thinking, let alone being active.

Relief has been almost elusive as sleep. It took me five or six years of trial and error experimentation with traditional sleep aids and other remedies, homeopathic and otherwise, before I found a treatment that works most of the time.

I use a microgram dose of melatonin that I have to take three hours before bedtime in order for it to be effective. And this causes me a number of concerns. First of all, this dose is not readily available over the counter, so I have to buy it online.

Second, because of what it is and where I have to get it, I never know that I'm getting what I need. And that may contribute to the fact that, even after starting that treatment, it isn't

foolproof. I still experience periods of disrupted sleep and, sometimes, sleep that doesn't come at all. Fortunately, they're not as long or as frequent now as they used to be, but they still happen.

Getting up at the same time with the aide of an alarm clock doesn't seem to make any difference because even during fairly good times, my deepest sleep seems to occur early in the morning, right before the alarm is supposed to go off. So when the alarm goes off, the only thing it does is let me know that it's the beginning of another day, when I'm going to feel horrible and frustrated.

This is not a good situation. So I am very hopeful that you will begin the process of making another option available to me and to many other people that I know.

As I indicated a while ago, I am the representative of the American Council of the Blind. I happen to be employed as their executive director. And over the years, since I have been aware of non-24-hour disorder, which I found out

about 10 years ago, I have talked to many other of our members who experience the same kinds of things that I have experienced and that you have heard about from other speakers here.

Because they tell me very similar stories to those you've heard today, we have partnered with Vanda to educate our community about non-24 disorder and to let people know that it's not their fault and that they're not crazy, that there really is a major problem.

But for many people, melatonin like I take isn't an option. We need more treatment options because of the major issue this represents to us. Melatonin has side effects for many people. I urge you to give us another option that will let us experience quality sleep at night so we can have full and quality lives during the day.

Thank you very much for the opportunity to come and share with you today. This is a day I have waited for, for a long time. And I will be anxiously awaiting, as many of our thousands of members around the country will, the decision that

you make. Thank you.

Questions to Committee and Discussion

DR. FOUNTAIN: Thank you.

The open public hearing portion of this meeting has now concluded, and we'll no longer take comments from the audience. The committee will now turn its attention to address the task at hand, that is, the careful consideration of the data before the committee as well as the public comments.

So we'll turn our attention to the questions, and there are some discussion points before we vote on the matter. And we talked about many of these things earlier, but now is the time to refine it and to express any kind of concerns. And we can also ask additional questions of the sponsor or the FDA.

So the first question is about efficacy. No drugs are currently FDA approved for non-24-hour sleep-wake disorder, non-24 as we referred to it. Please discuss the appropriateness of non-24 as an indication for FDA approval of drug therapies.

The first part of the discussion is in relation to specifically the question, are the intended population diagnostic criteria reasonable? Dr. Sack?

DR. SACK: Well, I guess if this drug were to be approved, I would like two understandings, just exactly what the diagnostic criteria would be and a labeling situation. Inasmuch as a biomarker would not be available to the usual clinician, what would be the diagnostic criteria?

DR. BASTINGS: Typically, generically, the indication section of labels do not include diagnostic criteria. In this case, the population was enriched based on the biomarker. If there can be a situation where you believe that the drug can only be used in people who have been identified using a biomarker, in that case there is a mechanism to validate that biomarker and to exhibiting to that population. But generally, it's perfectly fine to enrich a trial based on the specific criterion and then extend indication through broader population. So typically, the

indication would say "indicated for non-24 patients," without any specific criteria included in the label.

DR. FOUNTAIN: Do you want to respond to that, Dr. Polymeropoulos?

DR. POLYMEROPOULOS: Yes. Thank you. It is very important to discuss briefly what is the plan. How would physicians recognize the disorder and recognize the effects?

We do not propose to change the diagnostic criteria existing. And maybe we can view the DSM V criteria, which are already established. And if I could have the DSM V slide up, please.

The definition diagnosis for 307.45 is for a pattern of sleep-wake cycles that is not synchronized to the 24-hour day with a consistent daily drift of sleep onset and wake times. Now, the diagnostic criteria require a persistent or recurrent pattern of sleep disruption that's primarily due to an alteration of the circadian system or to misalignment between the endogenous circadian rhythm and the sleep-wake schedule

required by an individual's physical, environmental, social, or professional schedule.

The second is that sleep disruption leads to excessive sleepiness, or insomnia, or both. And number 3, the sleep disturbance causes clinically significant distress. Impairment is also occupational or other important areas of function, as we heard.

But simply on the physician's office, what will typically happen is, a totally blind person with no light perception will present with a chronic sleep complaint. And history and diaries, as suggested by ICSD criteria, the diagnostic manual, would suggest that would suffice to make the diagnosis for more than 90 percent of these patients.

Now, what happens after they take, let's say, the therapeutic tasimelteon, how do they know it worked? Well, it's very apparent. If the sleep complaint does not go away after a full circadian cycle of treatment, then there is treatment failure.

DR. FOUNTAIN: Dr. Bagiella?

DR. BAGIELLA: So I have a related question, which is, given those criteria that you used to diagnose the disease or the disorder, rather, how sensitive they are, how many false positives you can identify? And what would the drug do to a patient who is not a non-24?

DR. POLYMEROPOULOS: Thank you.

Dr. Dressman discussed the inclusion criteria. You're referring to the specific tau measurements, who was included in the study with a tau greater than 24, in fact greater than 24.25.

So for all these people, we know the answer. These are the data in front of us. For the people that are greater than 24 and less than 24.25, these patients actually went in the open label study. And we have this data. We analyzed the data. We presented some of the effects of the drug, but of course, it's beyond today's discussion of a placebo control. But the answer is, the results in the patients that did not meet the 24.25, but have non-24 appear to be similar to the main studies.

Now, for patients that don't have non-24, we don't recommend it, and it's actually easy to keep the drug only in the hands of blind people, given first of all the recognized condition of blindness and, two, the closed distribution system we have.

But we do know something about the safety of the drug in populations that don't have non-24, since we conducted studies in patients with chronic insomnia, and the results are part of the common technical dossier.

If I could have the slide up, please? This is the plan for the tasimelteon, Hetlioz special distribution plan, where no scripts are written directly to go to an open pharmacy and, therefore, any concerns of any off-label use are mitigated.

But moreover, it is very important to note that we are committed to continue to collect data for this population of patients. We have established a network, a steering committee, to make sure we collect both efficacy and safety data on a continuous basis.

I want to take the opportunity after this

emotional public hearing to actually say that we are extremely proud to have worked with the blind community and actually being able to create the first brain label in the United States for any drug. And I wanted to share this picture with you.

If I could have the slide up, please?

This is a proposed picture under PDUFA V. There's a new regulation that eventually, hopefully, all drugs in the United States will have identifiers for blind people. Hetlioz, hopefully, will be the first one.

DR. FOUNTAIN: Thank you. Is it an FDA requirement to have a specialty pharmacy?

DR. BASTINGS: No. There is not an FDA requirement. As you know, in some situations where there is a serious risk to patients, there may be what we call a restricted distribution in which only people who are certified to prescribe the product and who meet certain monitoring that may be required may be able to obtain the drug. In this setting, we don't see a specialty pharmacy as necessary to have a safe use of your product.

DR. FOUNTAIN: Dr. Zivin?

DR. ZIVIN: I would like to know what the sponsor knows about what would happen if a patient took a deliberate or accidental severe overdose.

DR. POLYMEROPOULOS: No patient has taken an overdose to our knowledge. Therefore, we don't have a direct experience. But we do have experience with a dose of the drug up to 300 milligrams, so that is 15 times the recommended dose. And that was given in a controlled cardiac safety study with no adverse events.

DR. FOUNTAIN: Dr. Clancy?

DR. CLANCY: Right. The target population is sort of generally described as a group of people who have no light perception. The most common etiology that was offered was in retinopathy or prematurity. But that's still a very heterogeneous group. There are children that have just small islands of light perception.

So I guess my question is, does it have to be, like, absolute total blackness; if they grimace to bright light; if they have a smirk on their face

when the mom takes them outside? Does that take them out of the criteria? So how exactly is the patient selected from that point of view?

DR. POLYMEROPOULOS: Certainly. So the characterization was with total blindness and an encouragement of a discussion that there is no light perception. Now, the anatomical basis for that distinction is as follows. We understand that, if you have rods and cones, you will be able to transmit sufficient light through the retinohypothalamic tract to inform the SCN.

We also know from animal experiments that if you have a very small number, even of remaining IPR disease, light could be transmitted to the receptor clock, maybe not all the time. Now, how does that translate in the clinic?

In many discussions with blind people, we have come to understand an important distinction. And the advice is, just stick to total blindness because when you start talking about light perception, perception is subjective. And what we've heard is that many blind people do not

actually fully know whether they have a light perception or not. Some of them characterize that if I get out in the heat or the sunlight, I am not sure whether it is the heat or the air that makes me have light perception. But for the purposes of the anatomical basis of the disease, it is a complete absence of light.

Now, many of our patients, those who have retinopathy prematurity with retinoblastoma and others have a enucleation. I am not sure I can get the data real quick, but -- actually, here it is.

If I could have a slide up, please? So here are the causes of actually blindness as anophthalmia. Tasimelteon people without -- with two eyes, 19; 3, one eye; no eyes, 20. So 20 out of 42; placebo 11 out of 42; overall randomized 31 out of 84. So certainly, for those people that are enucleated or have prosthesis, there is no light perception. For the others, I would say it requires total blindness, but we need to be careful not to discuss light perception because that is very subjective.

DR. CLANCY: Thank you.

DR. FOUNTAIN: Dr. Bastings?

DR. BASTINGS: Yes. If you could bring the question back, I would like to clarify our questionnaire. I realize it is a little bit confusing. I think the intention of the question is to ask whether -- if we approve the drug with an indication that says it's indicated for non-24-hour sleep-wake disorder, whether a prescriber, according to existing diagnostic criteria, would be able to correctly identify the patients that are candidates for the treatment. I think that's what we intended to ask in that question.

DR. KRYSCIO: Dick Kryscio. I would like to know, is this drug going to be available to children, of course, who are totally blind?

DR. BASTINGS: No. The initial approval is in adult patients. And in this case, since it's an orphan condition, the FDA cannot require pediatric studies to be conducted according to the law because it's an orphan indication. But the sponsor may elect to have a pediatric program. Right. It

could be used off label, of course.

DR. FOUNTAIN: If I could ask one question, then Dr. Sack. So that goes a bit back to the specialty pharmacy because it's all kind of tied in together. If you have to fulfill a specific diagnostic criteria, then go through a specialty pharmacy, I think that would limit the drug and discourage its use. So is there a reason for the specialty pharmacy?

DR. POLYMEROPOULOS: No. It's actually for access. We recognize that one of the greatest issues that blind patients face for access in healthcare is actually getting there. It is being able to identify the right place and get their prescription filled the first time, pick it up, see the doctor that is familiar with it. So we're trying to create a system that facilitates access to the drug.

But just to go back to the patient again, I want to emphasize that the work that we've done, we asked a simple question, "Do you want to participate in our studies? Are you totally blind?

And do you have a sleep complaint?" And then we took all-comers of that and looked at their entrainment status. Seventy percent had non-24.

So just the simple report by a patient, "I am totally blind and I have a sleep complaint," not even the diaries or the history of cyclicity, when you layer that at the physician's office, I think the diagnosis becomes a lot more straightforward.

DR. FOUNTAIN: Dr. Sack?

DR. SACK: Just a comment on that a little bit, I have been in the situation of evaluating the subjects and patients. And sometimes, we guess that they had a free-running rhythm and were wrong. And sometimes, we guess that they didn't and were wrong. So there are opportunities for error. I think another point to bring out is that, in the slide that you showed earlier from Dr. Emens, there is something called relative coordination that hasn't been discussed. But that's where people are free-running for periods of time. And then they may entrain or come close to entrainment for periods of time. And then they may escape into a

free run. And so there are these complications.

As far as treatment outcomes, relative coordination could be a treatment outcome as well; that is, you showed data where subjects were either entrained or not, sort of either/or, but I suspect that there are also cases in which people would be having phase shifts that would be incomplete enough to entrain them, but would still change their rhythms and their sleep schedule.

So there are complications. And I think for -- I'd not say that these are not reasonable diagnostic criteria, but it's not always a slam dunk.

DR. POLYMEROPOULOS: Yes. And we fully agree with that comment and, at the end of the day, we need to make sure we're treating the right thing and we follow up the right thing. But the diagnostic criteria, of course, we didn't make them. We're following them. Can they be improved? I'm sure they can be improved. And we're aware of the efforts of the community to actually look at improving diagnostic criteria.

Just a final characterization, if a physician today wanted to measure the urinary cortisol, let's say that was a physician that had exhausted the 90 percent of the diagnostic criteria, they can do that today. In any lab, in any commercial lab, you can go and measure urinary cortisol. And if it spikes at night and not during the day when it's supposed to be, that's a pretty good proof. Along with the other criteria, it's non-24.

DR. FOUNTAIN: So maybe to kind of rephrase what Dr. Bastings said and/or the questions say, I might say that the consensus is, it is known to be an actual disorder based on DSM and so forth. But I guess the question is, that's a very specific sometimes laboratory-based diagnosis. And in clinical practice and in usual sense, is it recognized as a common disorder that has these diagnostic criteria that can be followed? Would that be a fair assessment of it?

DR. BASTINGS: Yes. Would people be able to correctly identify the patients? They see that

label, that indication; would the prescriber be able to decide whether the drug is right for the patient.

DR. FOUNTAIN: I'm not a sleep specialist, but I see lots of people with sleep disorders. I think I could generally recognize this within the broad realm of something I would give what seemingly is a safe drug for.

Dr. Mielke?

DR. MIELKE: I don't think you've touched on this. And maybe this has more to do with safety down the road. But are there any tolerance in these patients? So if you're going to plan on giving this drug for multiple years down the road, are they going to need a higher dose down the road? Or have you looked at that at all?

DR. POLYMEROPOULOS: Right. Dr. Dressman addressed this. And I will ask you to come up and show the data of the sequential design, people who were in the SET study and then moved onto the RESET study. And we have a seven-month experience of measuring tau again.

I cannot tell you what happens next that we are not -- Dr. Dressman?

DR. DRESSMAN: So I just remind you, the randomized withdrawal study, the RESET study, did look at patients who were on tasimelteon and then were withdrawn.

If I could have the slide up, please? These two patients show data collected over the period of 500 days. And if you look at it, they were during screening for the first 100 days, and then they were put on tasimelteon around day 130. And then they were dosed on tasimelteon until about day 450, 460. And throughout this entire time -- that's quite nearly a year -- they do seem to have significant improvement in their sleep and wake. And they are entrained.

So we don't believe that there is a tolerance issue or that there would need to be a dose adjustment with time.

DR. POLYMEROPOULOS: If I may add to that, the other mechanistic reason that you would not even expect tolerance is the rapid association with

the melatonin receptors and the half-life of about two hours. So in fact, most of the drug is completely out of your system within a few hours of dosing.

DR. FOUNTAIN: Thank you.

Is there any more discussion before we vote on the issue? So the specific discussion was, are the intended population and diagnostic criteria reasonable, which we kind of looked at a bit indirectly?

Are there other concerns with the way the condition is defined or represented? You might think about it now. And are you satisfied that non-24 is a bona fide sleep disorder with consequences for patients?

Any more discussion before we vote on that?

(No response.)

DR. FOUNTAIN: So the specific question we are voting on, is non-24 appropriate as an indication for an FDA-approved drug therapy? And at this time, the buttons will light up in front of you for yes, no, or abstain, and push the vote that

you select.

It'll continue to flash, but it'll register your vote. And it'll continue flashing until everyone has voted.

(Vote taken.)

DR. FOUNTAIN: So if you will select yes, no, or abstain for all the voting members. And why don't everyone push it again? It won't hurt to push it again, but one of us seems to not have pushed it hard enough.

(Vote retaken.)

DR. FOUNTAIN: Everyone has voted.

LCDR JOHNSON: I will now read the vote into the record. We have 10 yes, 1 no, zero abstain.

DR. FOUNTAIN: The votes are displayed now and we'll go around the room. And read your name, whether you voted yes or no, and if you'd like to make any comment. And let's start with Ms. Sitcov. If you will just state your name.

MS. SITCOV: State my name?

DR. FOUNTAIN: Your name and your vote. If you'd like, you can make a comment.

MS. SITCOV: Cynthia Sitcov. I voted yes. I feel as though the sponsor certainly sold me that it's a drug that should be considered for approval.

DR. HOFFMANN: Richard Hoffmann, and I voted yes because I think non-24 is an appropriate indication.

DR. SACK: Robert Sack. I voted yes. And clearly this is a very unrecognized diagnostic category at the present time and education is needed.

DR. VITIELLO: Michael Vitiello. I voted yes. This is breakthrough in terms of circadian rhythms being appreciated as a disorder. I think it's clear that it's a burden for the individuals we heard testimony for. And you need only look at the data graphs to see that sleeping at the wrong time can have a profound impact.

DR. EASTMAN: I'm Charmane Eastman. I voted yes. I think a lot of people can figure out if they're free-running and have non-24, blind and sighted.

DR. KRYSCIO: Dick Kryscio. I voted yes for

the reasons given by the clinicians on our left and the evidence presented by the sponsor.

DR. BAGIELLA: Emilia Bagiella. I voted yes. I think there is enough evidence that this is a disorder that should be treated.

DR. FOUNTAIN: Nathan Fountain. I voted yes. I believe this is a disorder. And I'm thinking of one -- or excited about one or two patients, if this is ever approved, to use it for.

DR. CLANCY: Robert Clancy. I also voted yes. I thought the sponsor gave a very nice story linking the neuroanatomy and neurophysiology, and the expected consequences, and what the data actually shows, and how this is mitigated by their intervention. So I thought, altogether, it was a very well-told story that's plausible and believable.

DR. ZIVIN: Justin Zivin. I voted no. And it's simply because I pressed the wrong button.

(Laughter.)

DR. MIELKE: Michelle Mielke. I voted yes. I think it's fairly clear that this disorder is

very burdensome to the patients that have it, and anything that can be done to treat it and help them should be.

DR. FOUNTAIN: Thank you. So moving on to question 2 now, the clinical endpoints used in the efficacy studies supporting the new drug application for tasimelteon in non-24 are novel. They have not been used to support the approval of the drug.

The point of discussion is to please discuss the appropriateness of the clinical endpoints, those that sought to measure directly how patients feel or function, specifically the lower quartile of nighttime total sleep time, and the upper quartile of daytime sleep duration, and that Clinical Global Impression of Change.

Maybe I'll make the first statement in that, while I certainly believe that having an abnormal circadian rhythm is the fundamental problem, we do want to make people feel better. Otherwise, what's the point of taking the drug? So it certainly makes sense you have a clinical endpoint.

I think maybe what everyone is wrestling with is what's the clinical endpoint? Because at face value it would be, you're sleepy during the day. But actually, as we heard, for patients with non-24 or circadian rhythm disorder, as we might have called it 25 years ago, the problems are pervasive beyond that. But it seems as though you could probably develop some ideas about that. And I don't know if Dr. Czeisler would like to comment on maybe that.

You mentioned the thesis from someone in England. And he looked across four data points as things besides, if I'm interpreting it right, some four data aspects that seemingly had clinical relevance. They were abnormal in people with non-24.

So the question would be, if you can identify in that type of study what are clinically bothersome data points, why not collect them while you're trying to figure out if the drug is useful in people with the disorder?

DR. POLYMEROPOULOS: As. Dr. Czeisler is

coming up, I wanted to address, though, the variability. You're pointing to the expression of the disorder across many spheres, not just sleep and wakefulness, but other items.

In the clinical study, we had to make a choice of collecting something as rigorous as we did over six months every day. Of course, there will be other items, but the burden, I want to emphasize, on the patients to call an IVRS system twice a day and collect the urine for a long period of time was sufficient burden.

But onto Dr. Czeisler.

DR. FOUNTAIN: Sure. But you could imagine maybe you could even, in the future, forego some of those and make something easier that was more clinically relevant, if you could think of something. So it just seemed to me that this has maybe already been done, at least in a very limited, small group.

DR. CZEISLER: Thank you for the question, Dr. Fountain. If I could have the slide up, please?

This was the slide that I showed of Dr. Joseph Hall's thesis from the University of Surrey. And these measures, the three measures that were correlated with the endogenous circadian rhythm and melatonin in this group of totally blind people that he studied were living in a laboratory.

They were free from all wake-promoting therapeutics like caffeine. And they were actually scheduled to a non-24-hour day here, going to bed and waking up four hours later each day, on a 28-hour day, so that their sleep and wakefulness could be characterized at all different circadian phases.

In these controlled laboratory conditions, this relationship between the timing of the melatonin rhythm, and the ability to sleep, and the ability to function effectively during wakefulness were assessed, as shown in these panels of the wake disturbance of the sleep at night and the impairment of their wakefulness during the day.

If I could go to the next slide. The problem is that in the outside world, when people

do have access to coffee during the daytime and other caffeine-containing products when they do try to function in the face of an imposed work schedule and school schedule, as we heard so poignantly from the people affected by non-24-hour disorder, the use of these agents can sometimes overcome, or the adrenaline and whatever, can overcome transiently the necessity to nap, and distort those measures that can be so beautifully seen in the laboratory.

So that's why I continue to believe that entrainment of the circadian system really has to be the primary determinant of whether or not a drug is seen to be successful in terms of a clinical trial like this.

However, of course, a clinician in an office can look at disturbance of sleep at night and these, what could even be regarded as non-optional naps during the daytime, as clinical symptoms that could help in the diagnosis of the disorder and should be, as reflected in the International Classification of Diseases diagnostic criteria as well as the DSM criteria.

DR. FOUNTAIN: I guess I'm just making a point for the previous slide that two of these measures, which I recognize now probably weren't spontaneously reported, were lapses of attention and something like level of alertness, the subjective alertness.

DR. CZEISLER: Yes. Slide up, please. This is the Karolinska Sleepiness Scale.

DR. FOUNTAIN: So in other words, it seems as though you could simply ask people how they felt, something analogous to a health sleep-related quality of life that would be either accepted in established measures or ones you develop for this purpose over time. And they would track with how far you were out of phase. And then you'd realize the clinical relevance of being out of phase.

DR. CZEISLER: Yes. And all I'm saying is that, yes, you could track that, particularly if you could study people under conditions as purely as they are in the laboratory. But the Karolinska Sleepiness Scale, if you've just gone to Starbucks and had a cup of strong coffee, is going to be

affected by that measure. That's all.

DR. FOUNTAIN: Right. But you're are you going to feel bad anyway. Right?

DR. CZEISLER: Overall.

DR. FOUNTAIN: Because you haven't gotten enough sleep, not just because you haven't gotten enough sleep, but because your circadian rhythm is off.

DR. CZEISLER: That's correct.

DR. FOUNTAIN: So you still feel bad.

DR. CZEISLER: Yes. That's correct.

DR. FOUNTAIN: So if you had somebody to capture that is what I'm getting at.

DR. CZEISLER: Yes. And there certainly could be measures that could allow you to capture that, just as you would be able to capture if you were in Singapore right now and you were trying to do this meeting at 4:00 in the morning biological time.

DR. FOUNTAIN: Dr. Vitiello?

DR. POLYMEROPOULOS: I wanted just to follow up on the same question on quality, because we

spoke about an amount and timing of sleep. We did collect sleep quality data on the SQ questionnaire. And I would like to ask Dr. Licamele to come up and present this.

DR. FOUNTAIN: So I guess, getting back to the FDA's point, is sleep quality a symptom that you're going to make people feel better about? I don't know the answer to that.

DR. LICAMELE: So as Dr. Polymeropoulos mentioned, we did collect sleep quality. Again, this was collected daily as part of the post-sleep questionnaire. The upper analysis here is the sleep quality. It's a 4-point rating scale from 1 as excellent to 4 as poor.

You see the sleep quality overall did improve in both analysis or the ITT star population. And more interestingly, if you look at the sleep quality in the lower two rows of the worst 25 percent of days of sleep -- so this is the nights that they reported their LQ-nTST -- the effect is as you would expect, even more statistically significant.

DR. FOUNTAIN: Dr. Vitiello?

DR. VITIELLO: Thank you. When I was talking earlier about how this is groundbreaking, when I first started reading the materials, I was somewhat skeptical about these measures because they're not traditional. But in the context of a circadian rhythm disorder being studied and potentially treated in what we're about today, I think they're remarkably clever. And I think that they very well address the issue and take advantage of the fact that you have a moving target, but you have a predictable moving target in terms of a person that free runs to a certain period, and they very well address the clinical appropriateness of the treatment.

So I was a convert, I guess, is what I'm saying.

DR. FOUNTAIN: Dr. Clancy?

DR. CLANCY: So I would like to ask about not so much the quality of sleep. The quality of sleep during the night is important. But when I look at these graphs, and after treatment I see

there's fewer and fewer naps during the day, it's hard for me to imagine that people were wide awake, zip-a-dee-doo-dah, and then they suddenly take a nap.

So the question is, if a large part of the disability is being too tired to do your job, to go to your kid's soccer game, and so forth, why were there not objective measures of daytime sleepiness like multiple sleep latency tests to say, "Look, you're not sleeping during the day, but how tired are you during those times?"

DR. POLYMEROPOULOS: If I may answer the question, of course, for excessive daytime sleepiness, there's a regulatory path and the MSLTs, which is a PSD test to look how fast one falls asleep, could be applied.

But for this cyclical remitting, relapsing disorder, it was very important to make observations over a long period of time that would not have been possible to do with MSLT test. And MSLT test ask only a very specific question. How fast are you going to fall asleep when you close

your eyes? And that is not the point here. The point here is whether we can avoid this huge magnitude of daytime sleep that advances as your circadian rhythm advances through the day in the black lines, which is completely superimposed with the acrophase.

What is critical also that we appreciated is that the length of observation of the data is what gave us strength in understanding this disorder. If you are looking at a pattern that repeats itself every 50, 60, or 80 days, you need to see it at least once, and you need to see it with enough confidence and enough density of the data. If you were to do one IPSD or an MSLT on a given day, that is very unlikely to capture the variability of the disorder.

DR. CLANCY: My question is, though, there is days when the daytimer is clean. There's no black bars. The person has not actually put their head down and slept. Why not do a subset of those patients. They have at least the illusion of being awake, but by an objective measure, like multiple

sleep latency tests, you could fortify the illusion by showing that, in fact, they don't fall asleep when they close their eyes and put their head down. Not for everybody, but just -- so how alert are these people when they're not napping?

DR. POLYMEROPOULOS: All I can tell you is some anecdotes. I know of one, and I'll tell you why we followed that up. And I will ask Dr. Lankford, actually, in a second to come up and tell us a couple of vignettes that point to what do these patients do after they feel better.

The one that I know is a patient that we noticed in the weight data, she started losing the weight and then stabilized. And she lost 20, 30 pounds. And of course, we're all researchers. We look at this data. We're trying to understand, "What is the meaning of this? What is the very simple meaning?" She was able to stay awake, go on a regular schedule of exercise, and lose weight.

So these are the things that happened when these people are alert, but Dr. Lankford can say a couple of stories.

DR. CLANCY: Well, I don't need stories. I mean, I know there's anecdotes, but all I'm saying is that I'm just not convinced that they are as awake as the graph shows them to be.

DR. FOUNTAIN: So how about this, Dr. Clancy? What if they just simply did Karolinska Sleepiness Scale every day each time they called into the IVRS or whatever they called into? That goes back to some measure of hardly any benefit.

DR. POLYMEROPOULOS: We do have this data. We have this data in Study 2101, which was a proof of concept study. That was a laboratory study that we could actually do this analysis. And we did an analysis of alertness using the VAS scale for the next day, after they had slept better than their placebo counterparts. But also, we did pharmacovigilance testing.

This PVT testing was done over 5 or 6 time points every 2 to 4 hours after you wake up. And what you measure is a blinking dot on a computer screen, and you see the reaction time and the lapse

is 500 milliseconds. And there was no difference from the placebo counterparts because we're looking for the next-day effects there.

So on the VAS scale, we had at least numerical trends of better alertness in this 5-hour phase advance simulation study that we have done. So I don't have this data in 3201, but we had it in a laboratory study.

Just to underscore what Dr. Czeisler was saying, some of the things like continuous VAS across the circadian clock, continuous PVTs, are more suited in the laboratory. And we had done it, but in the healthy volunteer phase advance study.

DR. CLANCY: Thanks.

DR. FOUNTAIN: Dr. Vitiello?

DR. VITIELLO: I was just going to comment. If you could bring back up the figure with subjects 3 and 4?

DR. POLYMEROPOULOS: The raster plots?

DR. VITIELLO: Yes, the rasters, because I was going to address Dr. Clancy's concern. It's not just the daytime naps. You also have to look

at the nighttime sleep, because if you look at the green, which matches the daytime naps when they're on treatment, they're sleeping much better at night. And we know that better nighttime sleep is going to predict better daytime arousal. So that and the PVT data that we just heard about certainly would convince me.

DR. POLYMEROPOULOS: Dr. Czeisler?

DR. CZEISLER: Yes. I just wanted to say in response to what Dr. Clancy asked, that Dr. Nakagawa, and Dr. Sack, and other colleagues in 1992 actually did this very study that you're asking about, in which they looked at sleep latency at all different circadian phases in a blind person and did essentially the equivalent of a multiple sleep latency test, except the test was given every 21 minutes.

They showed that it tracked very consistently with the phase of the melatonin rhythm. And that the ability to sleep when the melatonin rhythm was at the during-the-day phase, the biological day phase of the melatonin rhythm,

was almost completely absent, and that sleep propensity or the ability to sleep was much higher when the melatonin was being released.

So there are many other data in sighted individuals in the literature showing that the ability to sleep varies with the phase of the melatonin rhythm.

DR. FOUNTAIN: So in response in the discussion of question 2, we've talked about some other measures. Are there any concerns about the specific measures? It seems to me, based on the discussion we just had, the upper quartile of daytime total sleep duration would seem like the best analogy of how little you sleep during the day if you're going to use that as the marker for being better. But I'm not quite sure we ever got around to saying what's the clinical; is there a specific symptom or clinical measure reported by people to make them feel better.

I guess the aggregate view here is that -- well, I guess we'll leave that for the vote. Are there any specific aspects of the

measured factors anyone wants to discuss?

Dr. Bagiella?

DR. BAGIELLA: Did you collect any measure of quality of life in your trial? And did you correlate those measures with this other measure?

DR. POLYMEROPOULOS: Dr. Bagiella, the simple answer is we have not. And this is one of the plans we talked about, the close distribution system and the registry to collect data. One of our goals is to be able to collect this information. The only thing that we presented earlier was the patient-reported global impression of scale, and I know that is not a quality of life.

We also have had many discussions with a number of people on the appropriateness of activities of daily living. And for many reasons, this does not seem to be the appropriate method to collect. But there must be some quality of life that can measure eventually improvements, if they exist, and we want to continue to study that.

DR. FOUNTAIN: Dr. Kryscio?

DR. KRYSCIO: Yes. I would say the Clinical

Global Impression of Change is the weakest of the three because we've seen how many times it was changed while the protocol was being developed. And I just don't like those kinds of scores. They're just too soft.

The other two are really clever because, yes, they're more easily measured and they have low variance. And including all three of these in one package, I would suspect the lower quartile and the upper quartile are fairly highly correlated. So why would you want to, in a next trial, say pay the price of adjusting your alpha level for multiple endpoints? So a package deal is a little iffy from that perspective.

DR. POLYMEROPOULOS: If I may address the correlation, it is true, as we can see from the pictures, that there is a significant correlation, but there is not a 1 to 1 relationship. And if I may have this slide up, I will ask, actually, Dr. Laska (ph) to address this issue of correlation versus complete independence of the items.

What we see here is a table comparing lower

quartile with all the other measures, upper quartile. And you can see that the values are .44, .55, sometimes .73.

Dr. Koch, would you like to continue?

DR. KOCH: Gary Koch, biostatistics department, University of North Carolina. My only financial relationship with the sponsor is as principal investigator for a cooperative agreement for statistical methodology between the sponsor and my university. I have no other financial relationship.

So as was shown, they are correlated. Actually being correlated and also being expected to show a difference formally does not require a multiplicity penalty. There is a method whereby you rank each of the endpoints from good to bad. High ranks go to good and low ranks go to bad. You average the ranks together across the two endpoints and you assess that average. So it's using the information in both of the endpoints as well as their correlation.

If that is statistically significant at

alpha, you can then proceed to test each of the endpoints separately at alpha. That's a closed testing procedure that is due to Lehmacher and colleagues that was published a number of years ago.

It is only successful when all of the endpoints have signal, as is the case here. You want to take an alpha penalty when one or more of the endpoints clearly have signal, but one or more others have no signal. Then you want to order them and test them sequentially. But in this particular setting, there would be a statistical method that would let you look at both of them without any alpha penalty.

DR. FOUNTAIN: Thank you. Any more discussion on the clinical endpoints used in the efficacy studies? Dr. Bastings?

DR. BASTINGS: Yes. Just a comment. So for this question, we ask you to consider the three endpoints that we propose. And if you think some combination of these endpoints would be appropriate, we would expect that you vote yes.

Let's say you think CGI is not a good endpoint, but you think the other two would suffice, we would expect that you vote yes. We don't mean that you have to use all three endpoints in a package together. We just mean, is some combination of these endpoints appropriate.

DR. FOUNTAIN: Do you want us to discuss it for future reference or as particularly in reference to the data here? That is, I'll just say my comment is that, in the data here, either way, it would be acceptable to me, and they both seem to have essentially the same outcome.

DR. BASTINGS: No. It's really for the indication. If you use these endpoints in a clinical study, could you get approved for that indication? That is the question.

DR. FOUNTAIN: So I think, in retrospect, then, we would do it differently, even though this way turned out okay either way. And so the question would be, what would be more logical? Start from the beginning with a logical way to analyze it.

DR. BASTINGS: Yes. And there could be other endpoints that you may think are preferable. But in this case, from the endpoints that were used, is that enough? Would these endpoints be sufficient? They may not be the best. There may be better endpoints. But out of the one we had, if we take these, is that valid to support approval.

DR. FOUNTAIN: Dr. Zivin?

DR. ZIVIN: Have you done any studies to determine whether one endpoint is better than the other? And if so, what was your finding?

DR. POLYMEROPOULOS: Actually, we looked at every endpoint, and they look about the same. If I could have the tau slide, please?

In this slide, I will show you all the data for the 84 patients on tasimelteon and placebo. And if you bear with me for a second, each column is one of the different categorical contributors to the non-24 CRS. It was entrainment and then the four items, LQ, UQ, MoST, and CGI. And on the left, we have tasimelteon, on the right, placebo. It's raw. It's a single patient. And every blue

mark, it says if they succeeded.

So you can see, first of all, from the totality of the picture, what we see with the statistics, that the results favor tasimelteon. Now, if we start taking out one item at a time and we're left either with a single item or any combination, the results continue to behave the same. And that is that, statistically, most of the combinations favor placebo -- favor tasimelteon.

Can we see the slide without MoST? One of the questions with the clinical reviewer was, what is the clinical significance of MoST? Should that be part or not? And in fact, we went back and we removed MoST from the scale. And we did this analysis. I will ask Dr. Licamele to come up and present.

DR. FOUNTAIN: Although I'd point out, as the statistical analysis goes, it does depend to some degree on which population you look at because it is slightly different with the full ITT population as traditionally defined as anybody who got one dose and the ITT populations you defined,

which is repeated dosing.

I think what you defined makes sense to me. You just have to get more than one dose to have any effect. But nevertheless, it does change. And so the question would be, is there a single one of these that's better than the others, or most appropriate, or could supplant the others, or make some more sense, or has more clinical relevance, or is simply better.

DR. POLYMEROPOULOS: Just to address three things, one is, on the ITT question, we want to actually show a couple of slides that explain the difference between the populations. And on conclusion, they are very similar, but we wanted to explain the logic. So on excluding the MoST, I would like to ask Dr. Licamele to present.

DR. LICAMELE: Slide up. So as you remember, Dr. Dressman presented the results for the clinical response step-down primary endpoint that was entrainment plus an N24CRS score of 3 or greater.

If you actually remove MoST and perform the

same analysis, whether with entrainment or sensitivity analysis of the next three rows there, even without entrainment, the N24CRS would be positive, show a statistical difference between treatment for tasimelteon compared to placebo, with N24CRS of a score of 3.

So this would mean that they would have to actually respond on LQ-nTST, greater than 45 minutes, UQ-dTSD, a reduction of 45 minutes, and a CGI-C score of 1 or 2. As you see, regardless of the cutoff or if you took the new non-24 CRS after throwing out MoST on the bottom, you would still be significant.

If you want to go --

DR. POLYMEROPOULOS: The ITT, you want to show that.

DR. LICAMELE: Sure. Maybe we'll go to the next slide.

DR. FOUNTAIN: I don't think you need to discuss the ITT unless someone else wants to. I was just making the point it does make a little difference. So therefore, that might be a basis

for deciding if one thing is better than another.

DR. LICAMELE: Sure.

DR. FOUNTAIN: I don't think we need to review it, though.

DR. LICAMELE: Well, very quickly, if you were to perform that same analysis with the ITT star population, you would again have very significant results.

DR. FOUNTAIN: So if there's no more discussion, I think we can probably vote on the issue at hand. And the specific vote will be, are the clinical endpoints used in the tasimelteon development program appropriate to support an indication in non-24? Once again, yes, no, and abstain will light up. And you can press it once and change your mind if you would like.

(Vote taken.)

DR. FOUNTAIN: Everyone has voted.

LCDR JOHNSON: I will now read the vote into the record. We have 10 yes, 1 no, zero abstain.

DR. FOUNTAIN: We can now go around the room again, and just as before, if you will state your

name, and your vote, and any comment you'd like to make. Let's see. Let's start with Dr. Mielke.

DR. MIELKE: Michelle Mielke. I voted yes. Specifically, I think the lower quartile of nighttime total sleep time and the upper quartile of daytime total sleep duration are probably the best endpoints and, as was mentioned, are very novel and unique, but I think very appropriate for this indication.

DR. ZIVIN: Justin Zivin. I voted no, and the reason I did is because I think this scale is unnecessarily complex. And the more complex it is, the more likely it is to be irreproducible.

DR. CLANCY: I'm Bob Clancy. I voted yes because I felt that if I was a patient confronted with these issues, two things I'd probably want to change is to have more sleep at night and less during the day. And that's what these variables capture. So it sounded reasonable to me.

DR. FOUNTAIN: Nathan Fountain. I voted yes for the same reasons. I think if you were to start over and develop it again, I'd really like some

clinical measure. And I agree, I wouldn't make it this complex.

DR. BAGIELLA: Emilia Bagiella. I voted yes for the same reasons that have been already said.

DR. KRYSCIO: I'm Dick Kryscio. I voted yes for the same reasons.

DR. EASTMAN: I'm Charmane Eastman, and I voted yes. I think the sleep measures are good for most free-running non-24-hour people. But entrainment is better because there's a few, lucky free-running non-24-hour people who may be very flexible sleepers, very phase tolerant, and not have so much trouble sleeping, but they still have occasional days and months of circadian misalignment, and eating at the wrong phase, and having cognitive deficits, and all the other things that go along with doing things at the wrong circadian phase.

DR. VITIELLO: Michael Vitiello. I like the two sleep measures. It's nice to have the entrainment measure. Going forward, I would love to see a true daytime function measure, perhaps a

PVT, a vigilance test.

DR. SACK: Bob Sack. I voted yes. I would also advocate that someday there be like a rhythm available that would add power to this diagnostic and evaluation testing. And I guess, as just a comment, it seems like one of the problems with this particular study was that it drew upon the FDA's regulatory experience with hypnotic medications, or at least, that was overshadowed. So they needed a different kind of sleep measure to be appropriate.

I think that will be true for future studies. And there needs to be considered seriously a different category of pharmacology, that is, phase shifting, circadian phase-shifting drugs, and what sort of outcome measures would be appropriate to that, that are different from outcome measures related to hypnotic or stimulant medication use.

DR. HOFFMANN: Richard Hoffmann. I also voted yes. I felt that the clinical endpoints were adequate, but I also believe that entrainment is

also correlated with clinical response.

MS. SITCOV: Cynthia Sitcov. I voted yes for reasons already stated.

DR. FOUNTAIN: We are scheduled for a break, but I think maybe we'll just move ahead, since we're on a roll. We've already discussed many of these other things to come up, but I want to make sure we have plenty of time for full discussion to present all the information we need to.

The next question is, please discuss the evidence of efficacy presented, and particularly, are there any concerns with the design, conduct, or analysis of the efficacy trials. So this is specifically with regard to efficacy; that is I suppose by that we mean did the design demonstrate the outcome measure that was examined.

I guess you previously heard it referred to as a clever design. I'd agree with that. I'm more used to thinking about epilepsy, which is also a kind of episodic disorder, but not in any regular way. And so trying to define how things change over time is very difficult. And so it's very

clever, I think, to think of looking at just the worst days for sleeping during the day and just the worst days for sleeping at night.

I suppose you might think of the more sophisticated way to analyze that, to put it also in a time spectrum. So that has kind of a quality spectrum, but I guess you could imagine putting it over how things change over time.

Any comment, Dr. Farkas?

DR. FARKAS: Yes. I just wanted to clarify. For question 3, maybe it wasn't totally clear, but we had thought that we would have answered questions about the endpoints, say, in question 2 and question 3, was issues of, well, there were two studies, and one study was a randomized withdrawal study. And it enrolled certain patients from the first study, or whatever, that kind of thing.

I mean, I'm not saying that we have any particular concern about that, and I might even say that randomized withdrawal studies seem to be a very powerful way to confirm findings from the first study.

So with that amount of priming, I guess, I would say that was kind of the main direction we wanted to talk about in question 3.

DR. FOUNTAIN: Okay. Dr. Bagiella?

DR. BAGIELLA: So I think that the only issue there -- I think the designs were appropriate, both the first one and the second one, with the usual randomized trial and the withdrawal randomized trial. I think that the only question is about the ITT analysis and the exclusion of those few subjects from the analysis and the use of the ANCOVA, or the randomization, or the permutation ANCOVA.

I didn't see a lot of problems with that. I think that the analysis with some variability were pretty consistent and that the use of the ITT or the other population pretty much were comparable on that.

DR. POLYMEROPOULOS: If I could actually see the definition of the populations in the scatter plot, it is important to visualize what the statistical reviewer from the FDA discussed about

the inclusion or exclusion of some patients.

If I could have slide up, please. So these are the three populations. Eighty-four patients were randomized in the study and received at least one dose. And that is the population that the FDA used for their sensitivity analysis. The ITT-defined population of 78 were people that had at least tau measured for the primary endpoint. So they were in the study for about a month at least.

Finally, the analysis population was defined as people that were there for 70 percent of their cycle at least, which means they had the opportunity to come in, in phase and then enough opportunity to be out of phase, because if we are to design a study that people stayed in the study only 30 percent of the circadian cycle, everybody would improve beautifully. Both on drug and placebo, we'd not see a difference.

So what's the difference of these 12 people? And I think the table that the FDA showed is very accurate, just to show this in a graphic way. So the analysis population has 72 people, and all of

them have 70 percent of their cycle post-randomization and at screening. The 78 are people who had tau. So that means, by definition, they have at least about a month of observation, that it took us that long to calculate out. The difference in our numbers is between ITT and ITT star, so these six people. Who are these six people? They are highlighted in blue. And it as suspected these are people that had little observation. We agree with the FDA that, in any other study, having 20 or 30 days of observation is a lot. And for sensitivity analysis, it's great. But because all of this data falls in less than 50 percent of the cycle, we agree also with the FDA that 50 percent is insufficient to do the cyclicity analysis.

But the next slide shows that, regardless of who is right and who is wrong -- this is a forest plot comparing ITT with a prespecified model because we talk about sites and how to use them, the ITT star, using the same site model, and the FDA's ITT star, where it did not use pooled site.

We can sit here and argue what's the right

way of pooling sites or not pooling sites, but I guess the results are pretty clear that, no matter what, all the analysis favored tasimelteon and even the magnitude seems to be just about the same.

DR. FOUNTAIN: Thank you. Dr. Vitiello?

DR. VITIELLO: Yes. Sadly, intent to treat means intent to treat. And fortunately, the pattern of results obviates the question, and I don't think we need to go over it anymore.

DR. FOUNTAIN: That sounds accurate.

So are there any concerns in other regards in particular to having -- it certainly is unique to have patients, subjects, in one study that are then used directly in the next study or the withdrawal study. The need for that in a long-term study is maybe somewhat obvious.

But I don't have any concerns about that. I don't know if anyone else does. We don't have to discuss it. Dr. Sack?

DR. SACK: I guess I'm still a little bit unclear as to what the response rate is. The 20 percent response rate was for the first round of

analysis, but then in order to get different response rates, subjects were included for the run-in part of the withdrawal study, et cetera.

So is there kind of a bottom line as to what could be considered the efficacy response rate?

DR. FOUNTAIN: Just before you answer that, just to refine that more, so we don't go over anything else, so we can answer the question, we saw boxes that had responders and non-responders across the five different measures of entrainment, MoST, LQ, and so forth.

Are you asking for the aggregate numbers of people who responded, or the number who just entrained, or something different?

DR. SACK: I guess I'm thinking along the lines of entrainment more than other measures of response.

DR. FOUNTAIN: So what are the numbers that entrained in the first study and the numbers that un-entrained in the second study?

DR. SACK: Yes. If there is a kind of bottom line that one could count on if you're

seeing a patient in the clinic, what are the chances that, that person will be a responder? What's that number?

DR. POLYMEROPOULOS: That number is half or more of the patients, 50 percent or more. And this evidence comes from two areas, 10 out of 17 patients that had drug and that were evaluated in month 1 and month 7, that's 59 percent, and then, in the screening phase of the RESET study, 24 of 58 who came in and entrained. So the answer is 50 percent or more.

DR. SACK: I might just make a comment. In published literature for melatonin, the response rate for entrainment is about 70 percent. Obviously, there are no head-to-head trials comparing these two, but I just wanted to put that in the record.

DR. FOUNTAIN: Now, once entrained in the second study, isn't it true that the majority, like 80 or 90 percent, became un-entrained when you took them off it?

DR. POLYMEROPOULOS: Correct, 90 percent.

DR. FOUNTAIN: So the opposite, once you're entrained, you come off it, you're really likely to be entrained, which is a little different than how many will actually entrain to begin with when you give it to them.

DR. POLYMEROPOULOS: I understand Dr. Sack's comment, that it is very clear that we tend to underestimate the entrainment because of design. So if I was to change anything in the design of the study, I would measure entrainment not just at month 1, but maybe at month 3, month 4, and month 5. And then most probably, the results would be that the majority of patients, with few exceptions, should be able to entrain.

DR. FOUNTAIN: Thank you. Dr. Kramer?

DR. KRAMER: I would just comment on the question that you said about design and that you're not used to seeing these. Almost all maintenance trials in neuroscience, or psychiatry, or whatever, are responders that are re-randomized.

For you to determine what's the likelihood of a patient failing if you stop therapy, you have

to do that kind of design. You have to have a responder to start with. And it's true in maintenance trials, in GI, and in every area.

So there's many circumstances of re-randomization of the same patient.

DR. FOUNTAIN: So maybe we'll vote on the issue unless there are other comments. So the specific issue at hand is, has substantial evidence of efficacy been presented for tasimelteon in non-24? Please register your vote.

(Vote taken.)

LCDR JOHNSON: I will now read the vote into the record. We have 10 yes, 0 no, and 1 abstain.

DR. FOUNTAIN: We will now go around the room, if you will announce your name and your vote. And if you'd like, you can make a comment. I think we're starting with you, Ms. Sitcov.

MS. SITCOV: Cynthia Sitcov. I believe its efficacy has been established. I think it's a great thing that there has been entrainment, even if it's 50 percent of the population.

DR. HOFFMANN: Richard Hoffmann. And I also

voted yes because I think the efficacy results were robust.

DR. SACK: I voted yes with somewhat mixed feelings in that I suspect that we're on the road to approving this drug to be licensed. There is quite strong evidence that an already available agent, namely melatonin, is about as effective. I understand that there's no commercial support for going through the expensive trials that would be required for melatonin to be approved by the usual FDA criteria.

Consequently, it has remained relatively underutilized. Clearly, what this field needs is more education about non-24, more understanding of blind people who have this problem, and I certainly sympathize greatly with the people who are here, who talked about the troubles that they've had.

On the other hand, I can't in good conscience feel great about introducing a drug that's foreign to the body, which a person might be taking for a lifetime, when there is another agent available that would probably do the same thing.

DR. VITIELLO: Michael Vitiello, and I voted yes.

DR. EASTMAN: Charmane Eastman. I voted yes. About efficacy, when I first heard the results of this study at the National Sleep Meeting APSS, I was shocked at how low the entrainment rate was until I realized it wasn't a long enough study. It was low compared to melatonin.

But I'm sure that if the patients are treated long enough, that entrainment rate would go up and it would be as good as melatonin, even though it will cost more.

DR. KRYSCIO: Dick Kryscio. I voted yes, robust results and standard design.

DR. BAGIELLA: Emilia Bagiella. I voted yes for the same reason.

DR. FOUNTAIN: Nathan Fountain. I voted yes for the same reasons.

DR. CLANCY: Robert Clancy. I voted yes. I thought it was a lovely study and that the results were very compelling.

DR. ZIVIN: Justin Zivin. I abstained. It

failed on its primary endpoint. It succeeded on subsequent compound endpoint, which I have problems with. And therefore, I can't decide whether this drug is effective or not.

DR. MIELKE: Michelle Mielke. I voted yes for many of the reasons previously stated.

DR. FOUNTAIN: Now, we'll turn to the last question in regards to safety. The discussion is, please discuss the safety evidence presented for tasimelteon. And the question we'll vote on is, has the safety of tasimelteon in non-24 been adequately addressed?

So does anyone have any comments about the safety of the drug? Dr. Vitiello?

DR. VITIELLO: We've heard compelling safety data, and we also heard that a dose of 15 times prescribed is safely handled, so I think that's fairly compelling.

DR. FOUNTAIN: Any other comments? Dr. Kryscio?

DR. KRYSCIO: I thought perhaps -- and again, it's an orphan drug, as we don't have near

enough experience to declare it a drug to be perfectly safe because some of the things that can go wrong go wrong on a very small, small percentage of patients.

DR. FOUNTAIN: I was waiting for someone to say that. You don't have that much exposure, but I wouldn't have any concern about that. So I guess we can turn to the vote unless there's any other discussion or concerns.

Has the safety of tasimelteon in non-24 been adequately addressed? And the lights are blinking now, so please vote yes, no, or abstain.

(Vote taken.)

DR. FOUNTAIN: All the votes have been registered.

LCDR JOHNSON: I will now read the vote into the record, 11 yes, zero no, zero abstain.

DR. FOUNTAIN: We will now go around the room. Please read your name, your vote, and you can make a comment if you'd like. Dr. Mielke?

DR. MIELKE: Michelle Mielke. I voted yes. I think there appears to be a very low percentage

of adverse events, but as mentioned, this is a small number of individuals, so there will have to be postmarketing follow-up and whatnot as this is administered to more people.

DR. ZIVIN: Justin Zivin. In the file information that we have -- granted, it's relatively small and probably things will come up postmarketing. But as it stands, I don't see any reason to feel that it's reasonably unsafe.

DR. CLANCY: Bob Clancy. I voted yes. I think within the next few weeks, we'll see a product called Similac with tasimelteon, so this should be pretty good.

DR. FOUNTAIN: Nathan Fountain. I voted yes.

DR. BAGIELLA: Emilia Bagiella. And I voted yes. I think there is enough evidence that the toxicity profile is pretty safe.

DR. KRYSCIO: Dick Kryscio. I voted yes for similar reasons.

DR. EASTMAN: Charmane Eastman. I voted yes. And just for the record, melatonin is also

safe with relatively few side effects, except for sleepiness.

DR. VITIELLO: Michael Vitiello. And I voted yes and agree with the caveat around numbers.

DR. SACK: I voted yes. Given the response rate of around 50 percent, I think that the clinician will be tempted to increase the dose as the first move for a non-responder. And so a safety profile may change with time and should be monitored.

DR. HOFFMANN: Richard Hoffmann. I voted yes because it looks like it is well tolerated, but we do need postmarketing surveillance.

MS. SITCOV: Cynthia Sitcov. I voted yes.

DR. FOUNTAIN: That concludes the voting on issues. Any other discussion?

DR. BASTINGS: I would like to thank the committee for very clear advice and for a very good discussion. I would like to thank the patients who testified today. And again, Dr. Fountain, I would like to thank you very much for your participation throughout the advisory meetings.

Adjournment

DR. FOUNTAIN: Thank you. And also, a particular thank you also for me -- personally, but I'm sure the committee -- to the people who came to testify. It's a lot of work to come here, and get here, and stand up in public. I was remiss in not saying that earlier, how that's valued and appreciated by the committee. And thank all of you for coming. That concludes the meeting.

(Whereupon, at 3:03 p.m., the meeting was adjourned.)