FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEETING (PDAC)

Virtual Meeting

Thursday, November 4, 2021

8:45 a.m. to 3:05 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Joyce Frimpong, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:46 a.m.)

Call to Order

DR. NARENDRAN: Good morning and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her email and phone number are currently displayed.

My name is Raj Narendran, and I will be chairing this meeting. I will now call the November 4, 2021 Psychopharmacological Drug Advisory Committee meeting to order. Dr. Joyce Frimpong is the designated federal officer for this meeting and will begin with the introductions.

I'll hand it over to Dr. Joyce Frimpong.

Introduction of Committee

DR. FRIMPONG: Good morning. My name is Joyce Frimpong, and I'm the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Robert W. Baker?

(No response.)

DR. FRIMPONG: Dr. Robert Baker?

DR. BAKER: Hi. It's Robert Baker from Eli Lilly. Sorry. I was having trouble with my mute button.

DR. FRIMPONG: Dr. Walter Dunn?

DR. W. DUNN: Walter Dunn, assistant professor, University of California, Los Angeles and the Greater Los Angeles VA Medical Center.

DR. FRIMPONG: Dr. Jess G. Fiedorowicz?

DR. FIEDOROWICZ: Yes. Hello. This is Jess Fiedorowicz, professor at the University of Ottawa and with the Ottawa Hospital.

DR. FRIMPONG: Dr. Satish Iyengar?

DR. IYENGAR: Yes. This is Satish Iyengar. I'm professor and chair of the statistics department at the University of Pittsburgh.

DR. FRIMPONG: Dr. Jessica K. Jeffrey?

DR. JEFFREY: Hi, everyone. Jessica Jeffrey, associate professor of psychiatry with the University of California, Los Angeles.

DR. FRIMPONG: Dr. William R. Keller?

DR. KELLER: Dr. William Keller, assistant professor of psychiatry, Dartmouth College, Geisel School of Medicine.

DR. FRIMPONG: Dr. Sonia L. Krishna?

DR. KRISHNA: Hi. This is Sonia Krishna. I'm affiliate faculty at the University of Texas, Dell Medical School at Austin.

DR. FRIMPONG: Dr. Rajesh Narendran?

DR. NARENDRAN: Hi. This is Raj Narendran. I'm a psychiatrist at the University of Pittsburgh Medical Center, professor in the Department of Radiology and Psychiatry, University of Pittsburgh, Pittsburgh, PA.

DR. FRIMPONG: Dr. Patrick S. Thomas?

DR. THOMAS: Hi. This is Dr. Patrick Thomas, assistant professor at the Baylor College of Medicine in Houston, Texas, and staff psychiatrist at the Menninger Clinic in Houston, Texas.

DR. FRIMPONG: Ms. Kim O. Witczak?

(No response.)

DR. FRIMPONG: Ms. Kim Witczak?

MS. WITCZAK: Good morning. Kim Witczak, a consumer representative, Woodymatters out of Minneapolis, Minnesota.

DR. FRIMPONG: Dr. Charles J. Billington?

DR. BILLINGTON: Good morning. This is Charles Billington. I'm an endocrinologist at the Minneapolis VA Health Care System and professor of medicine at the University of Minnesota.

DR. FRIMPONG: Dr. James J. McGough?

DR. McGOUGH: James McGough, professor and child psychiatrist at UCLA.

DR. FRIMPONG: Dr. Alice Shapley?

DR. SHAPLEY: Hi. This is Alice Shapley, the patient representative. I'm also a professor and the vice chair for Astronomy and Astrophysics in the UCLA Department of Physics and Astronomy.

DR. FRIMPONG: Dr. James F. Troendle?

DR. TROENDLE: Hi. This is James Troendle. I'm a statistician in the Office of Biostatistics Research in the National Heart, Lung, and Blood Institute.

DR. FRIMPONG: For our FDA participants, Dr. Billy Dunn?

DR. B. DUNN: Good morning. I'm Dr. Billy Dunn, director of the Office of Neuroscience.

DR. FRIMPONG: Dr. Tiffany R. Farchione?

DR. FARCHIONE: Hi. This is Tiffany Farchione. I am the director of the Division of Psychiatry.

DR. FRIMPONG: Dr. Bernard Fischer?

DR. FISCHER: Good morning. Bernie Fischer, deputy for psychiatry.

DR. FRIMPONG: Dr. Paul Bossie?

DR. BOSSIE: Hi. I'm Paul Bossie, the clinical reviewer for this application.

DR. FRIMPONG: And Dr. Andrew Potter?

DR. POTTER: Hi. I'm Andrew Potter, the statistical reviewer for this application.

DR. NARENDRAN: This is Raj Narendran.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this 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 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, 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.

I will now turn it over to Dr. Joyce Frimpong.

Conflict of Interest Statement

DR. FRIMPONG: The Food and Drug

Administration is convening today's meeting of the Psychopharmacologic 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 special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for 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 discussion of new drug application 214812, for carbetocin nasal spray, submitted by Levo Therapeutics, Incorporated, for the proposed treatment of

hyperphagia, anxiety, and distress behaviors associated with Prader-Willi syndrome. This is a particular matters meeting during which specific matters related to Levo Therapeutics' new drug application 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.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Robert Baker is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Baker's role at this meeting is to represent industry in general and not any particular company. Dr. Baker is employed by Eli Lilly.

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 relationships that they may have with the firm at issue. Thank you.

DR. NARENDRAN: This is Raj Narendran. We'll now proceed with the FDA's opening remarks from Dr. Tiffany Farchione.

FDA Opening Remarks – Tiffany Farchione

DR. FARCHIONE: Hi. Good morning, everyone. Welcome to this meeting of the Psychopharmacologic Drugs Advisory Committee. As Dr. Narendran said, I'm Tiffany Farchione, and I am the director of the Division of Psychiatry here at FDA. Today we'll be discussing Levo Therapeutics' application for intranasal carbetocin for the treatment of hyperphagia associated with Prader-Willi syndrome.

Prader-Willi syndrome is a rare and serious genetic disorder that's caused by loss of expression either through deletion or uniparental

disomy of paternally derived genes on chromosome 15q11 to 13. Individuals with Prader-Willi syndrome experience cognitive, behavioral, and endocrine symptoms and have characteristic physical features.

Hyperphagia is a prominent and characteristic feature of Prader-Willi. In childhood, individuals with PWS progress through different nutritional stages, with classic hyperphagia presenting at phase 3 around age 7 or 8, and continuing through adulthood.

Hyperphagia is characterized by profound lack of satiety and constant preoccupation with food and food-seeking behavior. Hyperphagia and decreased resting energy expenditure lead to obesity. But more importantly, shortened life expectancy in Prader-Willi syndrome appears related mainly to hyperphagia and obesity, including cardiopulmonary or gastric complications such as choking or esophageal rupture.

There are no medications available to treat hyperphagia, so management consists of restricted

calorie diet and strict environmental controls. Families will lock refrigerators and garbage cans. They'll avoid social events when food might be present. They can't go to restaurants. The need for constant vigilance around food has a significant impact on quality of life.

In addition to food-related behavioral and emotional difficulties, individuals with Prader-Willi syndrome also experience what their families describe as anxiety and obsession. They engage in compulsive behaviors and have difficulty with changes in routine, mood lability, and skin picking.

With that background, allow me introduce the subject of our meeting today, intranasal carbetocin. Carbetocin is a synthetic neuropeptide analog of oxytocin. Compared to endogenous oxytocin, carbetocin binds more selectively to oxytocin receptors with less affinity for vasopressin receptors.

The proposed formulation is intended for administration 3 times daily via nasal spray,

2 pumps per nostril per dose. The applicant has proposed an indication of treatment of hyperphagia, anxiety, and distress behaviors associated with PWS. During today's meeting, the agency presentations will focus primarily on hyperphagia and whether or not the applicant has provided substantial evidence of effectiveness for that indication.

So what exactly do I mean by substantial evidence of effectiveness? The statutory definition is a good place to start. As defined in the Food, Drug, and Cosmetic Act, it is "evidence consisting of adequate and well-controlled investigations, including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

For more insight on what exactly this means in practice and how we evaluate this standard in our reviews, we can refer to the FDA evidence guidance. This document was provided as an appendix to the FDA background documents for this meeting, and it's publicly available on the FDA website.

As noted in the guidance, FDA generally interprets the phrase "adequate and well-controlled investigations," plural, to mean at least two adequate and well-controlled trials. The characteristics of an adequate and well-controlled trial are also outlined in the Code of Federal Regulations and include things like having a clear statement of objectives; using designs that permit comparison; assessments that are well defined and reliable; et cetera.

Although we typically need two such trials for substantial evidence, the guidance also outlines the circumstances under which we might rely on a single study. For example, we could rely on a single large multicenter trial if the trial

demonstrates a clinically meaningful and statistically very persuasive effect on mortality, or severe irreversible morbidity, or prevention of a disease with a serious outcome. In those circumstances, a second trial would be impractical or unethical.

Another option for establishing substantial evidence is with one adequate and well-controlled trial plus confirmatory evidence. That could mean an adequate and well-controlled trial in a related disease area or compelling mechanistic evidence in the setting of well understood pathophysiology. However, in this case, the applicant has not identified any confirmatory evidence.

Finally, the statutory standard includes both a statement of the kind of evidence, as we've discussed, and an element of expert judgment. The line about "it could fairly and responsibly be concluded by experts," the guidance also outlines circumstances when some flexibility can be exercised. It states that "FDA may fairly and responsibly rely on designs that produce less

certainty when a better design is not feasible or ethical such as in the case of a life-threatening disease with an unmet medical need like Prader-Willi syndrome."

We recognize the need to exercise flexibility in applying the statutory standards when it comes to medical products for serious diseases with unmet medical needs, while also making sure that these are effective and have favorable benefit-to-risk profile.

Our task for today is to consider how the evidence provided by the applicant fits within this framework. They have submitted data from two studies; first, Study 114, a small proof-of-concept study evaluating the effect of 9.6 milligrams of intranasal oxytocin 3 times daily versus placebo. The change from baseline in hyperphagia was evaluated at day 15 in this study.

We also have a single adequate and well-controlled study, Study LV-101 to 301, which we'll refer to as Study 301. This study evaluated the previously tested 9.6-milligram dose, as well

as a lower 3.2-milligrams, 3 times-a-day dosage. Here, the change from baseline to week 8 on hyperphagia and obsessive-compulsive symptoms were evaluated.

The primary analysis compared 9.6 milligrams to placebo and did not detect a difference. Because the prespecified testing plan stopped when the primary was negative, the secondary analyses were considered post hoc, but these analyses do suggest there may be a difference between 3.2 milligrams and placebo.

Study 301 also included a long-term follow-up phase during which all patients received active treatment. We primarily reviewed this portion of the study as a source of safety data, but will also discuss the efficacy data from that portion of the study and the limitations inherent in interpreting data without a placebo comparator.

Taking all of this together, the evidence presented, our statutory standard and guidance, we'll ask the committee to consider a single question. Has the applicant provided substantial

evidence of effectiveness for carbetocin nasal spray in the treatment of hyperphagia associated with Prader-Willi syndrome?

With that, I will turn things over to the applicant for their presentation. Thank you.

DR. CORMIER: Thank you, Dr. Farchione.

Prader-Willi syndrome is a rare, serious genetic disorder affecting approximately 8 to 10,000 Americans. Its most striking symptom is an unrelenting false sense of starvation referred to as hyperphagia, which can be life-threatening. Patients with PWS also experience life-limiting anxiousness and distress behaviors that, together with hyperphagia, prevent them from leading independent lives. Most importantly, there are no approved treatments for these significant symptoms.

CAPT WAPLES: Hi. Good morning. This is Yvette Waples.

Can you please pause? Can you please pause for your presentations?

DR. CORMIER: Sure.

CAPT WAPLES: Dr. Narendran, you do have

something to say prior to the sponsor's presentation.

DR. CORMIER: I apologize. Sorry.

CAPT WAPLES: No problem, sir. Thank you.

DR. NARENDRAN: This is Raj Narendran.

Both the FDA 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 applicant's non-employee presenters, to advise the committee of any financial relationships they may have with the sponsor 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 presentation to advise the committee if you do not have any such financial

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

With that, we will now proceed with presentations from Levo Therapeutics. You can go ahead.

DR. CORMIER: Sorry about that, and my apologies. Thank you very much.

Applicant Presentation – Jay Cormier

DR. CORMIER: So I'll just pick up where I left off.

Most importantly, there are no approved treatments for these significant symptoms of PWS.

My name is Jay Cormier, and I'm the senior vice president of Levo Therapeutics. I've been involved in drug development for over 20 years, including as a reviewer at FDA, as well as a consultant in the development of drugs for orphan programs. I'm currently at Levo Therapeutics, where I help lead the development of treatments for PWS. I'm very excited to be here today to work

with this committee to bring forward the first product to address previously intractable hyperphagia of PWS.

PWS is a rare, life-threatening, neurodevelopmental genetic disorder that's typically diagnosed in neonates with failure to thrive. PWS has a uniquely complex medical phenotype, including shortness of stature, hypogonadism, and intellectual disability. It also has a psychiatric phenotype that includes hyperphagia, anxiousness and distress behaviors, and obsessive-compulsive symptoms.

Importantly, these psychiatric symptoms do not fit neatly into standard psychiatric diagnosis. The heterogeneous manifestations of PWS can vary with age and often overlap with autism and autistic-like behaviors. PWS has a high morbidity and mortality with an average life expectancy of approximately 30 years. Patients with PWS experience respiratory failure, cardiovascular events, GI events, which can include life-threatening gastric rupture, obesity,

diabetes, and renal failure.

While growth hormone has been approved to normalize linear growth in patients with PWS, currently there are no therapies approved for PWS' most life-limiting symptoms. Patients with PWS are often prescribed psychiatric medications such as SSRIs, anti-psychotics, stimulants, and others. Patients also receive non-prescription interventions such as vitamins and supplements in an effort to reduce the most problematic manifestations of PWS.

Importantly, none of these medications and interventions have been shown in a controlled clinical trial to provide benefit to PWS, nor do they address the underlying deficiencies linked to the ideology of PWS and its pathophysiology.

With an absence of effective treatments for PWS, caregivers resort to instituting rigid controls over their loved ones. By following strict daily routines, caregivers can avoid some of the outward manifestations that can be experienced with patients with PWS, including meltdowns and

tantrums that proceed well into adulthood, not just in the younger age groups.

The controls that are used with patients with PWS are often referred to as environmental controls. These things include locking refrigerators, cabinets, trash bins in the home, limiting the type and amount of food consumed at mealtimes and snack times, and avoiding social situations that include food.

Given the abundance of food in our society and its inevitable presence in social gatherings, families with PWS often retreat from society, as such situations present life-threatening risks to their loved ones, as well as to the social trauma that comes with any tantrum that may occur. The need to enforce these rigid controls around the clock exacts a major toll on caregivers. The burden for caregivers of individuals with PWS has been measured and assessed to be greater than that of caregivers for even Alzheimer's disease.

We at Levo have one singular mission: develop impactful therapies for the PWS community

that empower PWS patients to lead more independent lives. While other products in our pipeline look to address other aspects of the pathophysiology of PWS, today we'll be talking about an oxytocin receptor agonist.

The neuroendocrine hormone oxytocin is known to be involved in the hunger/satiety pathways within the paraventricular nucleus of the hypothalamus, where it is released concurrent with mealtime. Animal and human data demonstrates that there is a functional oxytocin deficiency in patients with PWS. Based on this understanding, the PWS community has had a long-standing interest in oxytocin hormone replacement therapy as a potential treatment for patients with PWS. However, treatment with the oxytocin has had mixed results largely thought to be due to off-target vasopressin effects of oxytocin. Carbetocin, on the other hand, is an oxytocin receptor agonist that has been designed to have greater oxytocin receptor affinity. Carbetocin has a longer half-life and, importantly, it has lower activity at the

vasopressin receptors.

The clinical development program for intranasal carbetocin consists of two adequate and well-controlled clinical trials. The phase 2 study, Study 114, was conducted by Ferring Pharmaceuticals and was a 2-week study of 9.6-milligram intranasal carbetocin in 37 patients with PWS. The phase 3 study, what I'll refer to as CARE-PWS, was conducted by Levo Therapeutics. It is an 8-week study investigating two different doses, 3.2-milligram and 9.6-milligram intranasal carbetocin, along with placebo.

CARE-PWS was originally planned to enroll 175 patients, however, the study was truncated due to the COVID-19 pandemic and resulted in 119 evaluable patients. Importantly, CARE-PWS includes a 56-week long-term follow-up period, and patients who complete that long-term follow-up period are given the choice to continue to receive drug through an optional extension period.

The phase 2 clinical studies showed statistically significant improvements in

hyperphagia, according to the prespecified primary endpoint, which evaluated hyperphagic changes from baseline to day 15. Significant improvements were also observed for obsessive-compulsive symptoms, as well as clinical global impressions.

The phase 3 study, CARE-PWS, did not achieve statistical significance on its primary endpoints. However, the 9.6-milligram dose showed numeric improvements in hyperphagia, obsessive-compulsive symptoms, and clinical global impressions.

The reason we're here today is that the 3.2-milligram dose, which was specified as the first secondary endpoint, achieved nominally significant improvements in hyperphagia, anxiousness and distress, and clinical global impressions.

Both studies demonstrate that intranasal carbetocin provides clinically meaningful reductions in hyperphagia, which is consistent with the hypothesis that addressing the observed functional oxytocin deficiency in patients with PWS would be beneficial. Importantly, the

3.2-milligram dose was found to be the lowest effective dose studied. The 9.6-milligram dose has no greater efficacy and was observed to have greater discontinuations during the phase 3 study, which may be the result of off-target effects that could also mask efficacy in some patients.

The benefits observed in the phase 3 study in the 3.2-milligram dose were seen across multiple endpoints throughout not only the placebo-controlled period, but over the course of the 56-week follow-up period, as well as when evaluating the results using multiple sensitivity analyses. These results are compelling given the rarity and complexity and difficulty of studying PWS and should be considered in context of the safety profile.

The most common events observed with carbetocin were transient and mild to moderate in severity. Those events included flushing, which is consistent with the known basal dilatory effects of oxytocin receptor agonism and the events related to intranasal route of administration. As expected

with oxytocin receptor agonists, intranasal carbetocin should not be used during pregnancy, and physicians should be advised to use caution when administering intranasal carbetocin with patients who are also taking concomitant prostaglandins due to the potential to cause uterine cramping.

The safety and efficacy data supports a proposed indication of intranasal carbetocin for the treatment of hyperphagia and anxiousness and distress associated with PWS. We recognize that the data are not without complexities and that there's a complicated situation between COVID and a rather unique and rare syndrome, so we value the expert judgment of the committee with respect to our demonstration of substantial evidence of effectiveness.

As presented in FDA's substantial evidence guidance, the agency recognizes the importance of facilitating the development of and access to safe and effective treatment options for life-threatening and severely debilitating diseases. As stated in that guidance, which can be

found at the back of FDA's briefing document for this meeting, the substantial evidence standard is interpreted flexibly when reviewing treatments for rare diseases and considers the harmful consequences of not only false positive, but also false negative results, and the amount of evidence that can practically be acquired.

The degree of certainty supporting a conclusion of substantial evidence depends on the clinical circumstances such as the severity and rarity of the disease and the unmet medical need. In these circumstances, less certainty of effectiveness is acceptable when balanced against the risk of rejecting or delaying the marketing of an effective therapy.

After this introduction, Dr. Shawn McCandless, chair of Clinical Genetics and Metabolism from the Children's Hospital of Colorado, will describe the impact of PWS on patients and their families, as well as the significant need for treatments to address their life-limiting hyperphagia and behavioral symptoms.

Dr. McCandless is a leading geneticist, working with patients with PWS and was the lead author of the American Academy of Pediatrics' clinical report regarding health supervision for children with PWS. He has been an investigator in numerous studies with potential PWS interventions, including the phase 3 CARE-PWS study.

Then I will return to review the efficacy data that demonstrate the benefits of the 3.2-milligram dose. Dr. Davis Ryman from Levo will show the favorable safety and tolerability of hormone replacement therapy with intranasal carbetocin.

Finally, Dr. Cheri Deal from Sainte-Justine University Hospital in Montreal will provide a clinical perspective on the benefits of intranasal carbetocin to patients with PWS and their families. Among other things, Dr. Deal led the development of the consensus guidelines for the use of growth hormone therapy in patients with PWS. She was also an investigator in the CARE-PWS study.

Thank you very much, again, for your time

today, and with that, I'll turn it over to Dr. McCandless.

Applicant Presentation – Shawn McCandless

DR. McCANDLESS: Thank you, Jay.

My name is Shawn McCandless from the University of Colorado and Children's Hospital Colorado. I have a long-standing interest in Prader-Willi syndrome as a geneticist, as a treating clinician for more than 20 years, and as a clinical researcher.

My university has been compensated for my time in this effort and I was an investigator in the study, but I have no financial interest in the company or the outcome of this meeting. And quite frankly, I will help anyone who has a promising approach to treating this frustrating and terrible disease.

Prader-Willi syndrome is a rare, life-threatening, genetic neurodevelopmental disorder with a complex and unique phenotype. Prader-Willi syndrome is an orphan disease that occurs in approximately 1 in 10,000 to maybe 1 in

30,000 births, and recent estimates in the U.S. suggest that there may be between 8 and 10,000 individuals total living with Prader-Willi syndrome in the U.S.

Approximately half, or under the age of 18, may tend to live with their families. As individuals with PWS age, along with their parents, it often becomes necessary for the young person to live in a group home setting with specialized care. These factors, and other things including location, access to care, and family's ability to commit to the time involved in a clinical trial, significantly limit the population available to participate in clinical trials in Prader-Willi syndrome.

This gene map helps explain how the lack of expression of a group of genes on chromosome 15 -- the ones shown in blue in the map -- are the cause of Prader-Willi syndrome. Typically, the genes that are shown in blue are silenced on the chromosome 15 inherited from the mother, a process called imprinting, which is

primarily due to DNA methylation. Only the chromosome 15 inherited from the father has acted unmethylated copies of these genes.

PWS is caused by the absence of the active copies of these genes, shown in blue, either from a deletion of the paternal allele or a complete absence of the paternal allele with two silenced maternal copies, or due to an error in switching the imprint on the paternal allele.

This is a truly unique orphan disease, where patients are subjected to hyperphagia or that false state of perceived starvation that is persistent throughout their lifespan. Hyperphagia permeates all facets of their lives and is a hallmark symptom of this syndrome. In addition to the hyperphagia, PWS has broad medical behavioral and developmental impacts on the lives of patients and families. There are varying degrees of intellectual disability, as well as behavioral challenges and broad and different abnormalities.

PWS is life-threatening and life-limiting. Morbidity and mortality risks arise in a variety of

ways. Patients have a tendency to overeat, even gorge, when there's an opportunity. They tend to eat rapidly and often end up choking. As many as 7 percent of deaths in young people with Prader-Willi syndrome have been reported to be related to rupture of the intestines or the stomach, resulting from an episode of food gorging. Their desperate sense of starvation also drives them to risk their lives in order to obtain food, which can result in food-seeking accidents.

Despite many advances in management over the past 20 years, a claims database analysis we presented two years ago showed that the average age of death has not changed significantly and is still around 30 years of age. The intellectual disabilities and behavioral challenges, combined with the intense hyperphagia and inability to regulate food intake on their own, make it impossible for PWS patients to lead independent lives.

Individuals with PWS typically begin to experience hyperphagia around the age of 7 or 8,

though it can start earlier or a bit later. While there's inherent variability, longitudinal data from multiple data sets show that, on average, hyperphagia remains relatively constant as measured by the validated consensus instrument, the Hyperphagia Questionnaire for Clinical Trials or HQ-CT. This is seen in broad age ranges, including adolescence and early adulthood. Although there is heterogeneity in many manifestations of PWS, hyperphagia is one symptom from which essentially no individual with PWS is spared.

The consensus definition of hyperphagia is a constant, inexorable hunger that is all-consuming and encompasses severely problematic behaviors. It's worth pointing out this is not the feeling of being hungry that you or I feel at the end of a long day where we missed lunch. This is a pathological drive to eat that is intense in a way that we cannot fully appreciate.

These children and adults truly believe that they're starving. That's what their bodies are telling them. They have a desperate, urgent,

overwhelming physiological drive to get food tied to their survival instinct. It's all-consuming, persistent, and intractable, and eating does not make the intense hunger go away. Even an individual who has free access to food, although they may stop eating for a short period of time, that person will continue to focus on food, and if food is available, they'll gather it, hide it, and hoard it.

I've tried to relate this to an experience that we've all had and might be able to understand, and although it's somewhat indelicate and it's not directly tied to survival the way food is, the best I could imagine to understand the feeling that these individuals have is the situation where we have a bladder that's full, but we don't have access to a bathroom. The sense of urgency from this physiological need grows and becomes overwhelming. It's hard to think about anything else.

Imagine if that's how you felt all day long, every day, and all night long, every night, and an

hour after you use the restroom, you are right back to feeling that same level of intense physiologic need to go. Then imagine the people around you saying, "Umm, you don't actually need to go to the bathroom now; you just went. So you can go to the bathroom again in 3 hours. Don't ask again."

Our ability to function in the world would be extremely impacted by that. We would have a very difficult time shifting our concentration away from that overwhelming physiological drive that we felt. Some of us may be feeling that way now. Now, imagine what it would feel like if this was how you would spend every day of your life, constantly thinking about food; continuing to eat if portion size is not limited; and waking up from sleep early thinking about food.

I had one young man in my practice who lived in a group home. He woke up in the middle of the night because he heard a noise in the kitchen. A staff member had left the door unlocked and he was able to get in and get some food. For the next 6 months, he couldn't sleep at night because he was

just lying in his bed ruminating about whether he might be able to access food, steadily becoming more and more anxious and unable to sleep, hoping, feeling that if he could just get up, he might be able to get more food. It was devastating for him and for the group home workers.

This is not a unique story. Children with Prader-Willi syndrome, given the opportunity, will eat huge amounts of food very rapidly. After a meal, they become hungry again within a very short period of time, typically 30 to 60 minutes. Stealing food or stealing money to buy food is very common, as well as running away from home to get access to food, which can be quite dangerous.

Another risky behavior is breaking into houses to access food. Sometimes the creativity shown by individuals with Prader-Willi syndrome finding ways to get food is shocking relative to their other intellectual disabilities. One patient that I've cared for, a young man, noticed the neighbor making something in a large bowl in her kitchen, so he went and rang the front doorbell,

then ran to the back of the house and went in the kitchen while she was answering the front door, and he ran off with a large bowl of cookie dough.

The neighbor called the police, and they quickly sorted out what had happened, but the boy was nowhere to be found. That led to two hours of family and police searching and his parents being terribly worried before he was eventually found asleep in the crawl space under the neighbor's house with the mostly empty bowl of cookie dough. That story ended safely, but others don't. We know of children having been hit by cars while running away to try to get food.

There's also a classic phenotype of eating food from the garbage can, which most children with Prader-Willi syndrome will do if given the opportunity. Families learn quickly to lock up garbage cans, but that can't be done when you're out.

Also typical are meltdowns or behavioral episodes, where a person loses control of their behavior, rapidly becoming extremely upset and

anxious. These episodes are frequently related to food or, more often, when access to food is prevented. And again, the various morbidities related to food-seeking behavior have been shown to contribute to mortality in a third, one-third, of patients under the age of 18 who died. Accidental deaths at all points of life continue to be a common cause of death. Very often these accidental deaths are related to food-seeking behaviors.

As a result of all of this, patients with this degree of intense hyperphagia require constant supervision from an adult, or more than one adult in many cases. And to be clear, at any given age, the likelihood of death in a person with Prader-Willi syndrome is about 3 times that of typically developing child and adult peers.

Unfortunately, there is no treatment for this feeling of starvation. Drugs for diet management that reduce appetite in most typically developing children and adults have not been effective in individuals with Prader-Willi syndrome, and stimulant medications for

hyperactivity that are often used in young children, and often associated with reduced appetite and weight loss, have no apparent effect on the hyperphagia or weight management in Prader-Willi syndrome.

Clinicians and families recognize that environmental controls can mitigate the obesity phenotype by reducing calorie intake, but this does not reduce the underlying hyperphagia that patients experience, and it comes at the cost of intense 24-hour vigilance on the part of caregivers.

Caregivers resort to locking not only cabinets, but locking bedrooms and kitchens to prevent PWS patients from accessing food, and they have to monitor their children continuously, making it difficult to go to a restaurant, attend a birthday party, or participate in daily routines at school. Most importantly, you can't judge an individual's degree of hyperphagia by looking at their weight. Our thin patients are just as hyperphagic as our heavy patients; they just have better control of calorie intake by other people.

Restricting access to food does not affect the experience of starvation that the child or the adult with Prader-Willi syndrome feels, and it only partially mitigates the risks associated with food-seeking behaviors.

The need for constant supervision and strict environmental controls is one of the major contributors to the high levels of caregiver burden reported for PWS, and it also contributes greatly to the low levels of both patient and caregiver quality of life reported for the syndrome. In our clinic, questions about how folks are coping and the stressors at home frequently lead to parents breaking down in tears. I'd say we see this once or twice a day in our clinic. This need significantly limits the independence of patients.

People with Prader-Willi syndrome could function in society and live more independently with modest assistance or in group homes that don't have PWS specific food procedures in place if the hyperphagia were controlled. However, without adequate hyperphagic control and without the

external controls that are currently required with constant 24-hour-a-day supervision, an individual with Prader-Willi syndrome cannot live independently, and the controls required in the home are impossible to replicate outside of the home: locked doors, constant supervision, and lack of opportunity to go out. Together, the severity of the external controls effectively turns the home into an institution for both the patients and their families.

Furthermore, the behavioral issues in Prader-Willi syndrome, although characteristic, don't easily fall into the classical diagnostic categories for psychiatry. There are high levels of anxiousness and distress, and in the teen years, an increased risk of psychiatric disorders, including psychotic episodes characterized by auditory and visual hallucinations.

There are a number of characteristic issues that develop in adolescents and young adult life, including repetitive thinking and questioning and ritualistic and compulsive behavior symptoms. The

person struggles with social interactions due to their cognitive rigidity and maladaptive behaviors.

Individuals with PWS experience interpersonal challenges that limit engagement in their environment. They typically have poor peer relationships and lack empathy. Patients with PWS also have a lack of insight, which along with intellectual disabilities and their strong desire to please makes them very unreliable self-reporters.

Their insistence on routines, concrete thinking, rigid behavior, and intolerance of change make it difficult to adapt to new circumstances. People with PWS often have mood lability. When their routine is disrupted or they do not get what they want, they often have temper outbursts. All of these manifestations and challenges result in a very high burden of disease for both the patient and their family.

A recent systematic review of 4,000 children and adults with neurogenetic disorders associated with intellectual disability documented the

frequency of psychiatric symptoms in each condition. Of the 10 different conditions considered in that study, individuals with Prader-Willi syndrome had the greatest burden of psychiatric and behavioral issues.

There are no approved therapies to treat the behavioral symptoms of Prader-Willi syndrome. Psychiatric medicines are frequently prescribed without any specific data documenting their effectiveness in patients with PWS. Many individuals with Prader-Willi syndrome, out of desperation, receive a wide variety of non-prescription, over-the-counter interventions, nutritional supplements and vitamins, hoping these will have an effect on behavioral symptoms. None of these substances have been shown in any clinical study to provide a benefit for individuals with Prader-Willi syndrome.

The majority of teens and adults at some point in their life will have been exposed to drug therapy for a psychiatric condition, and many are chronically exposed to multiple psychoactive drugs

with all the risks of polypharmacy that go with that. Some children are being treated with as many as four different drugs, even in their late childhood and early teen years, despite the lack of evidence and mechanistic relationship to PWS.

There's also a broad disruption of the endocrine system underlying most of the PWS phenotype. There are functional deficiencies of multiple hormones at the root of many of the medical, psychiatric, and behavioral symptoms. Hormone replacement therapy has been highly effective in PWS, although the only FDA-approved treatment for any aspect of Prader-Willi syndrome is the use of a concomitant human growth hormone which specifically addresses the underlying growth hormone deficiency that has been well documented in Prader-Willi syndrome.

Growth hormone has been shown to increase linear growth and to help produce a more normal appearing body habitus when used in conjunction with very strict dietary control. This is important because growth hormone deficiency is

characteristic of PWS, but it's only one of many functional hormonal deficiencies that we see, including thyroid insufficiency, hypothalamic, hypogonadism, and central adrenal insufficiency.

While hormone replacement therapy is already being used for some of these medical issues, there's a growing body of evidence that there is another hypothalamic hormone deficiency that is not yet being treated, oxytocin deficiency, which underlies some of the behavioral issues. Oxytocin deficiency appears to contribute to several different unmet needs in individuals with PWS.

We know from brain autopsy studies that there's a marked reduction in the oxytocin-producing neurons in the paraventricular nucleus of the hypothalamus in adult brains of individuals with Prader-Willi, measured at both the protein and messenger RNA levels in independent studies.

In the image show, the bright spots in the control sample on the left indicates staining for oxytocin mRNA in oxytocin-producing neurons. You

can see on the right a significant reduction in oxytocin-producing neurons in a similar slice of hypothalamus from a subject with Prader-Willi syndrome.

Likewise, a mouse model that has disruption of the MAGEL2 gene, which is one of the imprinted genes that is non-functional in people with Prader-Willi syndrome, shows a significant reduction in oxytocin-producing neurons in the hypothalamus. In that mouse model, there is a 50 percent neonatal mortality that was completely rescued by treatment with oxytocin.

Further, normal infant mice, control mice, injected with oxytocin receptor antagonists showed almost identical feeding problems. Together these data strongly suggest that the oxytocin deficiency contributes significantly to not just the appetite phenotype, but also the early infantile phenotype that we see in children with Prader-Willi syndrome, these very floppy babies who don't feed well.

Consensus exists that there is a functional oxytocin deficiency in patients with PWS, which is

important because the known functions of oxytocin overlap many of the issues experienced by people with PWS. Oxytocin is well known as a hormone that impacts social-emotional behaviors. It's a hormone that's released during breastfeeding in both the mother and the child. It's the hormone that's released when individuals have skin-to-skin contact and is involved in social bonding. It's also been shown to be a potent anorectic hormone.

Low doses of oxytocin injected intraperitoneally or intracerebrally in animal models reduce food intake. We also know that mice that are null for either the oxytocin peptide sequence or the oxytocin receptor develop adult on-set obesity. These functions of oxytocin overlap with a number of important symptoms of PWS, including hyperphagia, anxiousness, and distress.

Despite the important role of oxytocin in appetite regulation, the functional deficiency of the hormone in PWS, and anecdotal reports of benefit in human infants treated with oxytocin, results from clinical trials of efficacy of

oxytocin in PWS have been mixed. When the dose is escalated, behavior worsens with increasing temper outbursts observed. It's been hypothesized that there's an off-target effect of oxytocin, which has a very similar peptide structure to another hormone, vasopressin.

Oxytocin interacts quite free with vasopressin receptors and they limit the therapeutic window of oxytocin in individuals with Prader-Willi syndrome because the delivery can't be as precise with an externally delivered drug as it can be with a normally modulated, endogenous hormone release. So to get the effect of concentrations of oxytocin at oxytocin receptors, where and when they're needed, requires a non-physiologic dose that is likely also activating vasopressin receptors, likely contributing to the intolerance for higher doses of oxytocin.

The vasopressin 1a receptor in particular is implicated in anxiety and depression. Its off-target stimulation by oxytocin may exacerbate PWS behavioral symptoms that mute or negate any

positive effect of the drug. Activation of the vasopressin 2 receptor is associated with antidiuresis and a risk of hyponatremia, which may have very severe health consequences.

In summary, Prader-Willi syndrome is complex in a unique way. It is a rare but very serious life-threatening, genetic disorder. Individuals with Prader-Willi syndrome typically die by the time they reach 30 years of age. Without treatment for hyperphagia and the most significant behavioral issues, particularly anxiousness, patients are unable to lead independent lives.

They have a need for constant supervision and management, which is incredibly taxing on their caregivers, and I might add incredibly expensive if they were to move to a group home because they often need one-to-one attention anytime they're awake, and someone needs to be attentive to them even when they're sleeping.

While a consensus exists that there's a functional oxytocin deficiency in Prader-Willi syndrome, the use of oxytocin itself as a

replacement therapy has been challenging due to potential off-target effects, particularly through the vasopressin receptors.

There's clear evidence that oxytocin agonism would be extremely helpful based on mechanistic evidence, and there's a need to try to develop a drug that will overcome some of the limitations of oxytocin itself so that we can use this very promising pathway to treat the condition.

I'll now turn the discussion back to Jay Cormier.

Applicant Presentation – Jay Cormier

DR. CORMIER: The clinical development program demonstrated the efficacy of intranasal carbetocin in two randomized, placebo-controlled clinical trials. The data substantiate the hypothesis that oxytocin receptor agonism with carbetocin is effective in treating hyperphagia and other behavioral symptoms of PWS.

Carbetocin was originally developed in the 1980s by Ferring Pharmaceuticals as an oxytocin receptor agonist with greater selectivity for the

oxytocin receptor than the native hormone. It was developed as an alternative to oxytocin for use in reproductive health and was first approved in Canada in 1997. It is now approved in over 90 countries for the prevention of uterine hemorrhage following labor and delivery. Over the last 24 years, carbetocin has been administered to over 11 million women worldwide with a notably safe profile.

Given the interest in oxytocin hormone replacement therapy in PWS and the need for more selective oxytocin receptor agonists, carbetocin was a natural choice with its existing safety data set and its availability outside the U.S. as a marketed product. Accordingly, Ferring developed an intranasal form of carbetocin as a potential treatment for PWS. In 2017, Levo in-licensed the product, now referred to as LV-101, to treat patients with PWS. For this indication, FDA has granted it orphan product designation, rare pediatric disease designation, and fast-track designation.

Carbetocin was developed specifically to have a longer half-life and a wider therapeutic window than the endogenous oxytocin hormone, with greater on-target activity at the oxytocin receptor and less off-target activity at the vasopressin receptors. The EC50 for oxytocin receptor is 3-fold lower than that of oxytocin itself, but carbetocin's EC50 for the vasopressin 1a receptor is 4 times higher than oxytocin, and the EC50 for the V2 receptor is almost 25 times higher.

Oxytocin has known dose-limiting effects on cardiovascular homeostasis, which were thought to be mediated via off-target activation of the V2 receptor. No such effects have been observed with the use of carbetocin.

As mentioned in Dr. McCandless' presentation, negative behaviors have been observed when using higher doses of oxytocin in the patients with PWS, which may be mediated in patients with PWS via activation of the V1a receptors. As a result of the lower propensity to activate such receptors, carbetocin's wider therapeutic window

reduces the chance that an individual with PWS will experience the negative behavior seen with the use of oxytocin that limited its effectiveness.

Intranasal carbetocin is dosed 3 times per day with meals to mimic the body's normal release of oxytocin concurrent with meals. Each dose consists of 4 sprays, 2 in each nostril, and delivers a total of 3.2 milligrams of carbetocin. The effects of treatment are measured by caregiver and clinician questionnaires.

Direct assessment of PWS patients is difficult because patients exhibit varying degrees of intellectual disability and developmental delay. Individuals with PWS also have limited insight into their symptoms and tend to be unreliable reporters. Accordingly, there's a broad consensus that behavioral assessments for PWS need to be via caregiver- or clinician-reported questionnaires.

Furthermore, because of the unique constellation of symptoms in PWS, traditional psychiatric instruments are of limited value, necessitating questionnaires that are specifically

designed to measure the observable manifestations of PWS. These PWS specific instruments have been developed and validated for the patient population in alignment with FDA guidance on clinical outcome assessments.

The phase 2 and phase 3 studies used two different but related caregiver-reported questionnaires to assess hyperphagia. The phase 2 used an 11-item questionnaire, the Hyperphagia in PWS Questionnaire, referred to as the HPWSQ-R. This instrument was developed by Vanderbilt University and is related to the HQ-CT, which was revised following FDA input and validated by another sponsor, Zafgen, along with help from RTI Health Solutions. The validated HQ-CT instrument is a 9-item caregiver-reported outcome measure.

Obsesssive-compulsive symptoms were assessed using the children's version of the Y-BOCS. This clinician-administered instrument takes approximately an hour to complete. Because the CY-BOCS was not designed for PWS, it is not used in the clinical management of patients and was

unfamiliar to the vast majority of the raters in these studies.

In the phase 2 study, there was evidence of benefit of the CY-BOCS, which was the secondary endpoint in Study 114. During discussions of the design of CARE-PWS with the FDA, the agency questioned the use of CY-BOCS as a secondary primary endpoint in the phase 3 study, preferring that the study focus the analysis solely on the assessment of hyperphagia rather than on both HQ-CT and CY-BOCS endpoints.

Despite adding a complexity to the second 3.2-milligram dose, the phase 3 study, CY-BOCS was ultimately retained as a second primary endpoint in CARE-PWS with the hope of demonstrating improvements in the obsessive-compulsive symptoms of PWS, in addition to improvements in hyperphagia.

The unique anxiousness and distress experienced by PWS patients manifest differently than what is captured by available measures of generalized anxiety and psychological distress. Such classical measures often query physical

symptoms not experienced in PWS and are missing concepts central to PWS.

There are also patient-reported instruments, and therefore not appropriate for use in a population that is unable to self-report. As a result, and in collaboration with RTI Health Solutions and the Foundation for Prader-Willi Research, Levo developed the PWS Anxiousness and Distress Behaviors Questionnaire.

The PADQ is a 15-item, caregiver-reported instrument designed to capture the observable signs of anxiousness and distress that are common among subjects with PWS. With data collected during the phase 3 CARE-PWS study, the PADQ has met the requirements for a validated observer-reported outcome measure under FDA guidance.

Other efficacy measures employed include clinical global impression scales which have a long history of use in various product development programs. Specifically, both the CGI severity and CGI change instruments were included to provide the clinician's perspective at each visit on global PWS

symptom severity, both at the time of the visit and improvements from baseline in global PWS symptoms.

Finally, the Food Safe Zone is a PWS-specific questionnaire developed by Vanderbilt University as a caregiver-reported, standardized method for surveying the use of environmental controls to help manage both behavioral symptoms, as well as hyperphagia in individuals with PWS. Scores reflect both the caregiver burden of hyperphagia and the degree of restrictions imposed on the patient for their safety and well-being. Reductions in Food Safe Zone scores over time reflect an ability to relax environmental controls due to improvements in hyperphagia.

Two clinical studies support the efficacy of carbetocin as a treatment for PWS, the phase 2 study, Study 114, and the phase 3 study, Study 301, which we refer to as CARE-PWS. As expected, these studies had many similarities. Both studies were randomized to double-blinded, placebo-controlled, parallel-group multicenter studies. Both studies evaluated the 9.6-milligram dose administered

3 times daily with meals versus placebo. Both were designed to evaluate the effects of intranasal carbetocin on behavioral symptoms in PWS, specifically hyperphagia and obsessive-compulsive symptoms. Both studies enrolled male and female subjects with genetically confirmed PWS.

While the design of the phase 2 and phase 3 studies were similar, key differences exist, the most obvious of which are the size and duration of the studies. Study 114 enrolled 37 patients with PWS, whereas CARE-PWS targeted 175 patients. Due to the COVID pandemic, 130 patients were enrolled and 119 were evaluable for efficacy.

Study 114 evaluated patients for 15 days, whereas CARE-PWS included an 8-week placebo-controlled period was a 56-week, long-term follow-up period and an optional extension period. Based on FDA feedback and the potential for off-target effects of carbetocin on the vasopressin system, a lower 3.2 milligram -- that is one-third of the 9.6 milligram dose -- was added to the CARE-PWS study design, whereas Study 114 included only the higher

9.6-milligram dose.

In Study 114, there was a single primary efficacy endpoint related to hyperphagia, whereas in CARE-PWS, there were two primary efficacy endpoints, the HQ-CT and CY-BOCS instruments. Accordingly, a minimum entry criterion for screening and baseline scores for CY-BOCS was added to CARE-PWS.

In addition to an increase in study size, the number of clinical study sites enrolling patients increased from 3 sites in Study 114 to 24 sites in CARE-PWS. Lastly, as discussed earlier, the specific instrument to measure hyperphagia differed between the two studies.

Study 114 was conducted at Vanderbilt, the University of Florida Gainesville, and at NYU Winthrop. It was designed to be a 1-to-1 randomization of patients to either 9.6-milligram carbetocin or placebo. The primary analysis considered changes in hyperphagia from baseline to day 15. Of the 37 patients enrolled, 20 were randomized to placebo and 17 to 9.6-milligram

carbetocin. Baseline demographics were well balanced between the two arms.

Subjects enrolled in the study and randomized to the 9.6-milligram carbetocin arm experienced an average placebo-adjusted improvement of 6.9 points on the HPWSQ-R instrument with a one-sided p-value of less than 0.025. Statistically significant improvements were also observed with other secondary instruments, specifically the HPWSQ-R-C, which was the clinician-rated version of the primary endpoint; the Clinical Global Impression of Improvement, CY-BOCS; and the Reiss Profile food domain, which is a subset of caregiver-reported instruments not specific to PWS. Improvements were observed across the subdomains of the caregiver and clinician versions of the hyperphagia instrument.

In summary, patients randomized to carbetocin experienced significant and clinically meaningful reductions in hyperphagia. Benefits were also seen across other secondary instruments, including clinical global impressions and

obsessive-compulsive symptoms. Adding to the animal, in vitro, and human mechanistic data, Study 114 confirms that selective oxytocin receptor agonism is able to address the functional oxytocin deficiency in PWS; and consistent with what is known about oxytocin's role in human behavior is able to reduce both hyperphagia and behavioral symptoms of PWS.

Building on these data, in 2017, Levo began work on what would become the CARE-PWS study. After we were able to meet with FDA to discuss the study design and the protocol was finalized, CARE-PWS opened enrollment in November of 2018 with the intent to enroll 175 patients, which would have made it the largest PWS study ever conducted. Unlike more common diseases, enrollment of clinical studies in rare diseases is a much longer and more arduous task.

Throughout 2019, CARE-PWS enrolled approximately 9 patients per month across a total of 24 clinical study sites. Unfortunately, we were unable to complete the attended enrollment when the

COVID-19 pandemic halted the vast majority of clinical research.

In March of 2020, we were forced to pause enrollment at study sites and close our hospitals to clinical studies such as ours. After consulting with FDA in April 2020, and with FDA's concurrence, the difficult decision was made to truncate the study, enrolling only 130 of the original 175 study subjects. Even at that reduced number, 130 patients represents the second largest clinical study in PWS history.

The last patient completed their placebo-controlled period in May of 2020 and the study database was locked, and Levo employees were unblinded in July of that year. Following analysis of the results, all study subjects were transitioned in October and early November to the 3.2-milligram dose. The last of the 130 subjects to reach the end of the long-term follow-up period and enter into the extension period occurred in May of this year.

Critically, for patients with PWS, the

disruptive circumstances of the pandemic presented a perfect storm, as they and their families rely heavily on strong daily routines to manage and lessen the negative behavioral symptoms of the syndrome. Images of grocery store shelves during the beginning months of the pandemic increased concerns regarding food security among the general population and was a particular concern to people with PWS.

These unexpected changes had the potential to confound CARE-PWS data during this period since all efficacy measures in this study were observer-reported outcome measures of the outward and observable manifestations of hyperphagia, obsessive-compulsive symptoms, and symptoms of anxiousness and distress, all behaviors at risk of being affected by the pandemic.

Importantly, the amount of time that caregivers spent with study participants suddenly and substantially increased as schools closed and local areas went into lockdown. Given the importance of caregiver observations and the

efficacy endpoints of the study, this change represented a fundamental shift.

After discussion and in agreement with FDA, but before study unblinding, a primary analysis set was defined to remove any potential confounding impact of the pandemic. As a result, efficacy data were evaluated through March 1, 2020, resulting in 119 evaluable subjects.

CARE-PWS is a phase 3, randomized, placebo-controlled, double-blinded study, consisting of an 8-week placebo-controlled period, a 56-week period of long-term follow-up, and an optional ongoing extension period.

Subjects were randomized to receive 3.2-milligram carbetocin, 9.6-milligram carbetocin, or placebo during the first 8 weeks. Patients randomized to placebo were further randomized prior to baseline to later receive either the 3.2 -milligram carbetocin or 9.6-milligram carbetocin during the long term follow-up. All patients, caregivers, and study site personnel were blinded to dosing and all remaining participants

were transitioned to open-label 3.2-milligram carbetocin in October of 2020. Subjects who completed their week 64 visit were given the option to continue to receive intranasal carbetocin during an extension period, again, which is still ongoing.

The CONSORT diagram for the PAS population is shown here. The 130 enrolled subjects were evenly distributed across study arms. Even when considering the 119 evaluable subjects for efficacy analyses, parity is maintained with 39 in the 3.2-dose arm, 40 in the 9.6-dose arm, and 40 in the placebo arm.

The only two subjects to discontinue from the study during the placebo-controlled period were in the 9.6-milligram dose arm. Because both discontinuations occurred prior to March 1, 2020, both are included in the PAS. Of the 40 placebo patients included in the PAS, 20 went on to receive 3.2 milligram in the long-term follow-up period and 20 received 9.6 milligram.

A greater proportion of subjects that ultimately discontinued from the study were

receiving the higher dose. Specifically, when blinded to dose, 71 percent of study discontinuations are patients who are receiving the 9.6-milligram dose of carbetocin. As with the 114 study, baseline demographics were generally well balanced in CARE-PWS.

Improvements in hyperphagia as measured by the HQ-CT were observed for both doses. Improvements were seen in the 9.6-dose arm, but those improvements did not statistically separate from placebo. At this point, formal statistical testing ended and subsequent p-values are all nominal. Subjects receiving 3.2-milligram carbetocin, however, showed greater improvements in HQ-CT total scores that attained a nominal p-value of 0.016.

While the study missed its specified success criteria, patients taking 3.2-milligram carbetocin experienced consistent benefits across primary and secondary endpoint measures. Specifically, the 3.2-milligram dose arm showed nominally significant improvements in HQ-CT total scores, again, a

p-value of 0.016; PADQ total scores, a nominal p-value of 0.027; clinical global impressions of change, also a nominal p-value of 0.027; and a subset of HQ-CT questions that are less likely to be confounded by caregiver-imposed environmental controls, a phenomenal p-value of 0.011.

The 3.2-milligram dose arm further showed numerical improvements in CY-BOCS total scores in HQ-CT question 9, a question that measures the extent to which subject's hyperphagia interferes with daily life.

While the two primary endpoints of HQ-CT and CY-BOCS changes in the 9.6 arm were not statistically significant, subjects randomized to the 9.6-milligram dose experienced numerical improvements in all primary and secondary instruments, except for the PADQ total scores, which favored placebo. Of the other 12 prespecified primary and secondary analyses, the results favored carbetocin in all but the PADQ for the 9.6 dose. The 3.2-milligram dose consistently outperforms the 9.6-milligram dose with greater

magnitudes of effect and lower p-values.

Digging into the 3.2-milligram data more deeply, we can show the data as a forest plot. The results of all primary and secondary endpoints for the 3.2-milligram showed consistency of effect with all point estimates showing improvements from baseline compared to placebo for both caregiver- and clinician-reported outcomes.

The confidence intervals exclude zero for HQ-CT, PADQ, CGI change, and the HQ-CT subset. Question 9 and 5 are point estimates to show improvement, but the confidence intervals do not exclude zero for these two outcomes. A responder analysis can demonstrate the clinical meaningfulness of improvements in hyperphagia among patients receiving the 3.2-milligram dose of carbetocin.

The validation dossier for the HQ-CT defines a responder threshold of 7.7 points, which equates to an 8-point improvement threshold. Looking at the proportion of patients who showed improvements of at least 8 points, on the left, there is

significantly more in the 3.2-milligram dose group than in the placebo group, whereas greater proportions of placebo patients are found in groups of patients with 1 to 3-point improvements and among those with no change or worsening over the 8-week placebo-controlled period.

For the 8-point responder threshold, one-third of patients on 3.2 are responders, whereas 12.5 percent of those on placebo are responders. The difference between 8-point responders in the 3.2-milligram arm versus placebo translates to a p-value of 0.034 with an odds ratio of 3 and a half. Furthermore, the study was designed to enable comparison of the experience of patients originally assigned to placebo to those patients' experience after they transitioned to receive active treatment.

These patients were prospectively randomized to make this transition at week 8, either to 9.6- or 3.2-milligram carbetocin for the dose-blinded, long-term follow-up period. As you can see on this slide, those patients originally on placebo who

transitioned to 3.2-milligram carbetocin experienced a significant and clinically meaningful improvement in hyperphagia scores in a matching time period of 8 weeks with a p-value of 0.0004. The meaningful effects of carbetocin continued to accrue in the long-term follow-up period and are maintained through the week 64 visit.

Here we see the longitudinal data for HQ-CT scores from week 8 to week 64. For simplicity, of the 103 patients who completed the study through week 64, only the patients originally assigned to carbetocin -- that is, not the placebo patients -- are included in this chart. Over time, patients in all treatment groups show clinically meaningful improvements in hyperphagia that are sustained through their week 64 visit.

Specifically, 65 percent of the 103 patients experienced an 8-point improvement in HQ-CT scores at the end of the study, meeting the within-patient responder threshold. Even when conservatively counting all patients who discontinued from the study as non-responders, still 52 percent of

patients are responders at week 64.

Importantly, while these long-term follow-up data are not placebo-controlled, the sustained and substantial improvements observed are inconsistent with the natural history of PWS that Dr. McCandless described. This is seen again with longitudinal PADQ total scores where, conservatively, 53 percent of all patients experienced an 11-point improvement at week 64, which represents, again, the within-patient responder threshold for this validated anxiousness and distress questionnaire.

While the 3.2-milligram dose was not chosen as the primary endpoint, it nonetheless achieved significant and clinically meaningful improvements in both hyperphagia, as well as anxiousness and distress. The results of the study are internally consistent and robust to sensitivity analyses. Importantly, both caregiver assessments, as well as clinical assessments, show benefits to patients with PWS. The long-term follow-up data provide additional evidence of the importance of the

observations in the placebo-controlled period.

Patients who took placebo and then cross over to receive 3.2-milligram carbetocin experienced significant improvements by week 16, and the clinically meaningful benefits experienced by patients are maintained for over a year, through the week 64 visit.

In conclusion, the phase 3 study identified the safe and effective dose of carbetocin, specifically 3.2 milligrams. The phase 2 study, while testing only the higher dose, demonstrated pharmacologic proof of principle and, at a minimum, should be considered confirmatory evidence. The phase 3 results are further supported by the mechanistic data, demonstrating the functional oxytocin deficiency in PWS and the long-term follow-up analyses, which are inconsistent with the natural history of PWS.

While there may be debate regarding the appropriate statistical conclusions from the data, in their totality, and particularly in light of the truncation of care PWS due to the pandemic, the

clinical data provides substantial evidence that administration of intranasal carbetocin confers significant, sustained, and clinically meaningful efficacy in addressing the previously intractable hyperphagia in PWS behaviors. These clinically meaningful and durable benefits clearly outweigh the minimal risks, which Dr. Davis Ryman will describe next in his presentation of the safety data.

Dr. Ryman?

Applicant Presentation – Davis Ryman

DR. RYMAN: Thank you, Jay.

My name is Davis Ryman, and I'm the vice president of Clinical Development for Levo Therapeutics. I'm a neurologist and geneticist by training, and I've led the clinical development of intranasal carbetocin as an investigational treatment for Prader-Willi syndrome throughout the startup and completion of the CARE-PWS phase 3 study.

The safety of intranasal carbetocin has been thoroughly characterized and is favorable for use

in PWS. The safety presentation is based primarily on data from the placebo-controlled period of the CARE-PWS phase 3 study, supplemented by additional data from the phase 2 study, Study 114, and by data from the long term for treatment-emergent adverse events that were transient and mild to moderate, and self-limited in nature.

These events most prominently included flushing, which is an expected event of transient vasodilation that's been observed with oxytocin and with other oxytocin receptor agonists, as well as several events that could be potentially related to the intranasal route of delivery such as headache and epistaxis, or nosebleeds.

The favorable observed safety profile for intranasal use is consistent with the previously established clinical safety experience from intravenous use of carbetocin for obstetric indications outside the U.S.

Intravenous carbetocin is currently approved in over 90 countries outside the United States, where it's primarily used for prevention and

treatment of uterine atony and excessive bleeding for one Cesarean section. It's been administered for this use, to date, in over 11 million women worldwide over the last 24 years. Notably, the 3.2-milligram intranasal dose results in similar total exposure to the intravenous dose that's used for these obstetric indications.

Although PWS is a rare orphan indication, the phase 2 and phase 3 pivotal studies together have gathered data on extensive exposure to carbetocin in patients with PWS. As of June 18, 2021, Levo has accumulated approximately 188 subject-years of exposure, including 110 subjects with 6 months or more of exposure and 102 subjects with one year or more of exposure from the CARE-PWS phase 3 study.

Levo continues to accumulate additional subject exposure data as the extension period for the CARE-PWS study is ongoing. These data have consistently shown a profile of predominantly mild to moderate treatment-emergent adverse events.

During the placebo-controlled period of

CARE-PWS, the rate of treatment-emergent adverse events was broadly similar between the placebo group and the carbetocin groups, although rates were somewhat higher in the carbetocin arms, particularly for the 9.6-milligram group.

The best majority of TEAEs were mild to moderate in severity with the sole exception of one severe event of transient sinus pain in the 9.6-milligram arm. This occurred as the family's flight was landing and was due to a sinus infection that entirely resolved with antibiotics.

There were no deaths during the CARE-PWS PWS study and no serious adverse events occurred during the placebo-controlled period. The most commonly observed TEAEs were events expected either due to the activity of carbetocin or the intranasal route of delivery. Though transient flushing is an expected event that's consistent with transient vasodilation that has been observed with oxytocin and other oxytocin receptor agonists, in CARE-PWS, 20 percent of patients on 9.6- milligram carbetocin and 14 percent on 3.2-milligram carbetocin

experienced transient flushing, which was mild to moderate in severity and self-limited.

Other events, including nasal discomfort and epistaxis, or nosebleed, upper respiratory infections, and headache may be potentially related to the intranasal route of delivery, with epistaxis being notably more increased in the 9.6-milligram dose arm. These events were also mild to moderate in severity and were self-limited in nature.

Discontinuation for adverse events were infrequent and occurred only in the 9.6-milligram arm. One subject discontinued during the placebo-controlled period due to an event of impulsivity when a patient had impulsively swallowed some coins after an argument with her mother; one patient discontinued due to experiencing tachycardia and feeling flushed following the initial administration of study medication; and one patient had an event of hypersexuality, or sexual acting out, which the investigator assessed as mild that began during the placebo-controlled period, and the patient

eventually discontinued during the long-term follow-up period.

During the CARE-PWS long-term follow-up and extension period, the nature and severity of the events observed were largely similar. All patients have now transitioned to receive open-label 3.2-milligram per dose carbetocin during the ongoing open-label extension period.

Though these data reflect prolonged participation in the CARE-PWS study, there are currently patients in the ongoing extension period of the study who have been exposed for over three years as of the most recent safety update. The overall rate of TEAEs and the rate of moderate TEAEs was somewhat higher in the 9.6-milligram group. The majority of events have continued to be mild to moderate in severity, and there have been no deaths during the study. The overall pattern of most commonly observed events was probably similar to that observed in the placebo-controlled period.

Interestingly, rates of flushing fell below 5 percent during the long term follow-up and

extension periods, suggesting that flushing may be an event that may diminish over time. Events potentially related to the intranasal route of delivery, such as headache, epistaxis, and nasopharyngitis, continue to be observed during these periods but remain mild to moderate and self-limiting in nature.

Unlike the 8-week placebo-controlled period, the multiyear, long-term follow-up and extension periods did include some serious adverse events, but no deaths. Serious adverse events were reported at rates of 7.4 percent in the 3.2-milligram group and 12.5 percent for the 9.6-milligram group, but with no particular pattern and no event occurring with frequency above 3 percent.

The most commonly observed SAE in the 9.6-milligram group was pneumonia, so there is an elevated rate of respiratory infections in PWS, which is often related to choking and subclinical aspiration. The most common SAE in the 3.2-milligram group was scoliosis surgery, which

related to elective admissions for orthopedic surgery to correct pre-existing scoliosis due to PWS. The majority of these events did not result in discontinuation.

During the long term follow-up and extension periods, there was a somewhat higher rate of discontinuation due to TEAEs overall in the 9.6-milligram group, with a rate of 7.8 percent versus 2.8 percent in the 3.2-milligram arm. The majority of the events leading to discontinuation in the 9.6-milligram group were emotional or behavioral in nature, and as you've heard, this may be potentially related to off-target effects on vasopressin receptors occurring at higher doses.

The previously completed 2-week phase 2 study also explored the safety and efficacy of the 9.6-milligram dose versus placebo. Safety was also largely consistent with that observed in the placebo-controlled period of CARE-PWS.

The overall rate of TEAEs was similar in the carbetocin and placebo groups in the phase 2 study. No deaths or serious adverse events occurred during

the study and TEAEs were exclusively mild to moderate in severity. One patient experienced TEAEs of aggression and ulnar fracture during an aggressive behavioral outburst at school where the patient needed to be restrained, leading to discontinuation from the study. This patient was determined to be in the placebo group.

The most common events observed were those potentially related to the intranasal route of delivery. Most common TEAEs overall was headache, which occurred at similar frequencies in the 9.6-milligram and placebo arms. Both headache and sinusitis may be potentially associated with the intranasal route of delivery. The other event rates were largely similar between the groups.

Across studies and study periods, intranasal carbetocin was consistently safe and well tolerated in patients with PWS. The most common events observed were transient and mild to moderate and primarily included flushing, which is an expected event due to transient vasodilation associated with oxytocin receptor agonism and also a number of

other different events potentially related to the intranasal route of delivery. The overall nature and severity of the events observed were consistent across studies and across the three periods of CARE-PWS.

I'm now honored to introduce Dr. Cheri Deal from the Sainte-Justine University Hospital in Montreal, who's an experienced clinical researcher and physician, taking care of patients with PWS over many years, and will now provide her clinical perspective on intranasal carbetocin.

Applicant Presentation – Cheri Deal

DR. DEAL: Thank you, and good morning. I'm Cheri Deal, and I've been an academic pediatric endocrinologist for 30 years. My primary affiliation is with the Université de Montréal and the Research Center of Sainte-Justine Montréal university teaching hospital here in Montreal, Canada. I participated in the CARE-PWS trial, and I've been involved in several other phase 2, 3, and 4 trials during my career, including the large Millendo study in PWS, which unfortunately did not

meet the efficacy endpoints.

Levo provided funding to my institution for participation in the CARE-PWS trial, and I have received compensation for my time to help them with this meeting. However, I have no financial interest in the company or in the outcome of this meeting.

For this part of the presentation, I'll give you my clinical perspective of these trial data and of the patients and their families living with PWS for which I've had a long career interest and experience with the care of over 70 individuals diagnosed with this rare syndrome.

I can honestly say that Prader-Willi syndrome is the most challenging clinical condition that I've been treating over my career, and unlike many of the other diagnoses that I follow that require a pediatric endocrinologist such as pediatric brain tumor survivors, congenital disorders of the hypothalamus and the pituitary, endocrine tumors, differences in sex development, Prader-Willi syndrome is a uniquely complex

disorder.

Caring for patients living with PWS requires multiple healthcare professionals and subspecialists. Here, I've shown this as a large forest of trees indicating the usual healthcare participants. Endocrinologists, geneticists, and psychiatrists/psychologists are among the most important.

Coordinating care and keeping the healthcare teams harmonized in their approach, as well as up to date with the clinical care guideline, is a significant challenge. The impact of PWS spreads far beyond the patient, their families, and their caregivers. These patients are reliant on the interactions between the caregivers and the physicians caring for their children, as well as the interactions between the caregivers and their allied healthcare teams, the children's educators, and the local social services. And like a forest that looks so dense from a distance, up close you see that there are still many holes and gaps in that forest that can compromise care.

Based on everything that I've observed over my career, as well as what we see in the literature, PWS continues to have many unmet needs, and the greatest need is for treatments for hyperphagia and behavioral symptomatology. These manifestations exert the most impact on long-term morbidity and mortality in PWS, as well as on interpersonal interactions.

One of the reasons there are so few options for patients living with PWS is because of the challenges of drug development for this very rare syndrome, and these challenges are numerous. I want to emphasize that these families are already giving multiple treatments without much success both on and off label, including health supplements, vitamin supplements, and other unregulated treatments that may even pose health risks, and this concerns me as a clinician. There are also large numbers of confounders, which lead to heterogeneity of the clinical manifestation.

Also, while our tools for probing behavioral manifestations of PWS are useful, they are not

ideal. Given the intellectual disability of this population, they require caregiver and clinician reporting of behavior, which are prey to external and environmental factors that we as clinical investigators can't control. So we must make due with the incremental development of tools and techniques to study PWS, and we can't let the perfect become the enemy of the good for this important patient population.

Current studies aren't perfect either, but they are telling us something very clear, and we can't wait for the perfect study. The perfect study would need to be three times larger to be prospectively powered to detect the differences seen in CARE-PWS, and this number of subjects from the small population is simply unattainable. Patients and families already are unlikely to live in places where clinical trials are run, making participation particularly burdensome, and the pool of participants willing and able to participate would be further reduced by inclusion/exclusion criteria.

LV-101 is the first treatment for pediatric hyperphagia to get this far, despite these challenges and the challenges presented by the need for oxytocin hormone replacement therapy. As you've heard before, oxytocin is homologous with vasopressin, and oxytocin replacement can result in activity at the vasopressin receptor isoforms. So the physiological crosstalk of the oxytocin and vasopressin systems present unique challenges in this regard, and these hormones are known to elicit opposing anxiolytic and anxiogenic effects.

To give you an important example of this coming from animal studies, which have administered oxytocin to induce scratching behavior in mice using models, for instance, when administered to oxytocin receptor knockout mice, this scratching behavior continues unabated. However, when administering oxytocin to vasopressin 1a receptor knockout mice, the scratching behavior ceases, showing that this negative behavior is mediated through the vasopressin 1a receptor.

This crosstalk results in a narrow

therapeutic window, which makes oxytocin very difficult to deliver exogenously. In contrast, carbetocin's greater receptor selectivity has the effect of widening the therapeutic window by permitting greater oxytocin receptor agonism and lessening, but not eliminating, off-target vasopressin receptor agonism.

I was therefore not at all surprised to see that the higher dose of carbetocin did not perform as well as the lower dose in the phase 3 study. I do not think that this is only a sample size issue between the two trials but is consistent with our clinical experience with other hormones that share multiple receptors, and with the heterogeneity of the human response to the exogenous hormones.

To me as an endocrinologist, these data are not discordant but represent the reality of the changing treatment landscape that we face. But before I speak about efficacy, I just want to say that for me, the physician, safety data is always my primary concern; first, do no harm to your patient. And we had a good precedent with IV

carbetocin, which has been on the market for over 20 years and used in my own mother-child hospital to successfully treat and prevent postpartum hemorrhage by controlling uterine atony.

Turning to intranasal carbetocin, my clinical impression from my patients and from the study data presented today has not given me any safety concerns. Here are my takeaways from studying the efficacy data, which come from two randomized, placebo-controlled trials.

There are benefits across multiple endpoints, and both trials gave clinically meaningful improvement. The efficacy gains through week 16 in the phase 3 trial were clear. Most importantly, the persistence of this benefit has occurred through week 64. All of this supports the efficacy through patient participation in the extension period, and the greatest efficacy is observed for the 3.2-milligram dose.

You've also seen the data demonstrating consistency of the 3.2-milligram carbetocin effects during the placebo-controlled period in the

symptoms measured in this study using the various standardized questionnaires, expressed here as the point estimate. The lower bound of the confidence interval doesn't cross zero for HQ-CT, PADQ, and the two CGI scales. Critical results here for hyperphagia, anxiousness and distress behaviors, as well as clinical global impressions of change, all instill high levels of confidence.

You've seen that there is marked improvement in the HQ-CT scores, as shown here during the 8-week placebo-controlled period on the left, with a mean 5-point drop in HQ-CT score, as well as week 16 in the long-term follow-up period on the right.

From a clinical perspective and to understand the meaning of a score reduction of, say, 5 points in a subject's life, this could describe one of several possible sets of improvements. For our example, that the child stopped foraging through trash for food and went from talking about food daily for one hour to less than 5 minutes a day; or for a second example, that

food-related behavior went from interfering every day with daily activities to non-interference with school, self-care, or recreational activities with the family, and at the same time, the individual's behavior around food and meals went from very distressed to mildly distressed; or to give you a final example, that smaller improvements are seen but in several domains: food stealing, manipulative behavior to obtain food, perseveration in food-related demands, improved ability to partake in daily activities without as many meltdowns, and in a decrease in night waking for the purpose of seeking food.

Another way to assess the proportions of patients who benefit compared to placebo is the number needed to treat. By the end of the 8-week double-blind period of CARE-PWS, 33 percent of patients on the 3.2-milligram dose had an improvement of 8 points or more on the HQ-CT compared to 12.5 percent of patients on placebo.

You heard me explain the clinical impact of a 5-point decrease in the HQ-CT score. Imagine

what an 8-point or greater improvement could mean for patients and their families. This high bar of 8 points translates into an NNT of 5 for efficacy, which puts it squarely into the range of treatments we would want to use.

No matter which of the approaches being discussed today about calculating clinically significant changes that you prefer, these HQ-CT results have the greatest benefit-risk ratio we've ever seen in PWS. But for me, this is one of the most important data slides.

The improvement in HQ-CT scores occurred relatively early and showed a stable and sustained response curve as seen by the consistent decrease over time in all patients who receive carbetocin, shown in purple. We see that 103 of the 130 trial participants elected to stay in the study through week 64.

And let me just say, in the PWS community, families are savvy and very attuned to the condition of their child with PWS. I truly believe that patients speak with their feet and are telling

us something that we need to listen to. They will not keep giving a 3-times-per-day treatment that's not helping. But for those patients who do show an improvement in hyperphagia, they will, and many of the patients on intranasal carbetocin have benefited substantially from treatment.

We haven't spoken about the Food Safe Zone data, but this is also very important when speaking about a clinical benefit. This is a scale that assesses the extent of environmental controls and restrictions caregivers need to implement for their loved one with PWS.

The average scores of screening of this population, of a possible 80 total, were very high, reflecting a substantial level in environmental controls employed by families to protect their children. But what the message is, is that for the 100 patients who completed the Food Safe Zone questionnaire at the week 64 visit, there was an overall relaxation in environmental controls, which translates into a more independent life experience for the individual with PWS and less for the need

for vigilance on the part of caregivers. This is shown here as a spaghetti graph with the individual changes, as well as the overall decreased mean change in their Food Safe Zone score.

Furthermore, of the 17 patients who terminated early and completed the Food Safe Zone questionnaire, they were unable to relax environmental controls, as shown on the right in the table as the average change in Food Safety Zone questionnaire scores in both the completers and the non-completers. And this is consistent with what we would expect; once instituted, environmental controls are not relaxed unless caregivers are given a very good reason to do so.

I'd like to finish with this patient. This markedly ill child with a severity score of 5 was one of our most challenging patients because of his behavioral symptoms that made every clinic visit, prior to the CARE-PWS study, incredibly difficult. The relationship between the child's parents was also very rocky for a long time because of the child's behavior and its impact on the couple. He

was labeled as autistic and severely intellectually disabled with severe expressive dysphasia, in addition to its other long list of comorbidities, which included central sleep apnea not related to his growth hormone, but most probably to his abnormal brain development.

I really want you to note the relaxation of his Food Safe Zone in the middle graph, as well as his improvement on the HQ-CT on the upper graph, and the PADQ on the bottom graph. This represents a new found freedom for the parents, for the siblings, and most importantly for the child who can live a more normal life.

I confess to thinking initially that there was very little hope for this boy's future, and this is the email we received from the mom several weeks into the carbetocin trial. And I read, quote, "One day, the associate director of my 7-year-old son's school said that 'the place of my child was not in school but in a psychiatric institution,' because according to her, he will never be able to learn academically. I was

devastated, but I didn't believe her."

And this is what I received yesterday. The child's now 8 years, several weeks after being in the carbetocin trial from a teacher and social worker. "Your son is a model of the class. He's always on top of his work and we congratulate him so often that he's proud, calm, and ready for learning."

Parents are now feeling better about leaving their son with caregivers in order to have personal and couple times, and of course this has strengthened the couple and no doubt helped their son even further. So the impact goes far beyond questionnaire scores and their p-values. If this patient was the 1 patient in 5 needed to treat, I maintain that this family merited that benefit.

This is of course an anecdotal testimony, but everything I'm seeing is consistent with what I know as an endocrinologist and the established hormone replacement approach we use in PWS to address the hypothalamic pituitary dysfunction that underlies the syndrome. Growth hormone, sex

steroid hormone, and sometimes thyroid hormone and cortisol are now routinely prescribed as replacement therapy to correct deficits.

Of particular importance for the day is that the experience with all of these hormones, and other smaller hormones such as LHRH, has shown us that more is not always better, not just because of potential side effects, but also because of receptor downregulation and because of off-target effects.

Oxytocin is one of the missing hormones for which we now have exceedingly compelling data pointing to molecular explanations and molecular interactions. Prominent evidence examples are reductions in oxytocin-producing neurons, animal data showing a rescue of the phenotype with oxytocin administration, and prohormone convertase 1 deficiencies resulting in a processing defect of critical neuroendocrine hormones, including pro [ph] oxytocin. Given the difficulties with exogenous oxytocin replacement, the best tool that we have is carbetocin.

Intranasal carbetocin addresses the oxytocin deficiency and fits into our hormone replacement paradigm in PWS.

Those are our goals to answer the top unmet needs as voiced by patients and by their caregivers, reducing hyperphagia and improving behavior. Despite COVID and despite all the challenges that this trial has presented to caregivers, to the investigators, and most probably to the company, intranasal carbetocin fulfills this unmet need.

The safety data is reassuring with now up to two and a half years in the ongoing long-term extension study, and the data demonstrate effectiveness, as do clinical observations of physicians and their families. These clinically meaningful improvements are seen across multiple endpoints, and the effects can be really dramatic and life-changing for patients and families. And finally, patients and families express a desire and a need for access to intranasal carbetocin.

Depriving the PWS community a safe and

effective treatment because the sponsor chose the wrong statistical analysis would be inexcusable in light of the tremendous unmet need, the strong mechanistic rationale, and the demonstrated benefits already seen in two double-blind, randomized, placebo-controlled trials in this rare disease. In my professional opinion, carbetocin does not need further studies prior to approval. Thank you.

DR. CORMIER: Thank you, Dr. Deal.

I will now lead our responses to any questions you may have. In addition to the presenters, we have additional experts available, including Dr. Blumenstein, a statistical consultant who has overseen the analysis of the data from the clinical trials; Dr. Lisa Cole Burnett, director of Early Research and Development at Levo; Dr. Sheri Fehnel from RTI Health Solutions -- hello?

Clarifying Questions to Applicant

DR. NARENDRAN: Hi. This is Raj Narendran.

We will now take clarifying questions for Levo Therapeutics. Please use the raised-hand icon

to indicate that you have a question and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you, and end your follow-up question with, "That is all I have for my questions," so we can move on to the next panel member.

In terms of questions, the first question is going to be from Dr. Alice Shapley.

DR. SHAPLEY: This is Alice Shapley. Thank you so much to everyone from Levo for your presentations. I'm particularly impressed by the results, based on the 3.2-milligram dose and also the safety profile of carbetocin overall.

My question has to do with the fact that given that the phase 2 study led with a

9.6-milligram dose, I was wondering about the factors that guided Levo to introduce the 3.2-milligram arm of the phase 3 trial and also to determine this lower dose level. I'm not sure if this question should be for Dr. Cormier or Dr. Ryman. Thanks.

DR. CORMIER: Thank you. I'm happy to take it. The discussions with FDA during our end-of-phase-2 meeting, the agency encouraged us to do further dose exploration during the phase 3 study. Given the known potential issues with higher doses of oxytocin, we decided to go with a lower dose as opposed to a higher dose, and given the rarity of the condition, studying any more than two doses, it was already hard to enroll the kinds of patients we would need to do two doses. One-third of the dose was selected because we wanted to have sufficient separation with respect to the two doses as we went into the phase 2 study.

DR. SHAPLEY: Thank you very much for your answer. Thank you.

DR. NARENDRAN: Our next question is from

Dr. James McGough.

(No response.)

DR. NARENDRAN: Dr. McGough, I think you might be muted.

DR. McGOUGH: How about now? Can you hear me now?

DR. NARENDRAN: Yes, I can hear you now. You're on.

DR. McGOUGH: That's weird. I apologize. Anyway, Dr. McGough. Two questions, first to Dr. Deal.

Thank you for giving us the information about the number needed to treat. That's very helpful, and 5 is about the same as we see with treating depression in teenagers. Could you give us more of a dimensional effect size, such as what would the Cohen's D be on the primary measure for the 3.2 dose at week 8? That ought to be calculated easily. It would be helpful if someone could come up with that if it isn't at the tip of your fingers.

My second question also has to do with the

statistics. I'm a little troubled by the fact that you used a one-sided T test in the initial study. That strikes me as a little unusual and it will bias a positive result in your direction.

What was the justification for the one-sided T? Was that a priori? And I would also like some comment from some of the other statisticians, as well as maybe the FDA, as whether that is acceptable in terms of accepting efficacy for a trial. So one, do you have a Cohen's D; and two, some justification for the one-sided T –test.

DR. CORMIER: Thank you. I don't believe we have Cohen's D immediately available. That's not something that we have analyzed, but I can see if our team can maybe do that during the day here and have that for you later. I'm not sure if we can do that this quickly, but we'll try our best.

As far as the one-sided T test goes, that was a prespecified approach by Ferring, the sponsor at the time. And when you're analyzing by a one-sided T test, what you're doing is you're saying we're only going to look at the benefit side

of the two sided normal distribution.

So the alpha control, rather than being 0.05 is 0.025, so you can still maintain the same level of type 1 error control using a one-sided test. You just reduce the thresholds down, and that's in fact what we see with the primary efficacy there being less than 0.025. In the one-sided, it's common to do that kind of thing in these small proof-of-concept phase 2 type studies.

DR. McGOUGH: I just, either now or later, would want to hear that the FDA finds that acceptable, that that's a standard, because it's not usually how I would do things. But I just want a little reassurance that that's ok, and it still meets the standard for accepting efficacy. Those are my questions. Thank you.

DR. NARENDRAN: Thank you, Dr. McGough.

I think we could have the agency comment during their question period.

The next question is from Dr. Baker.

DR. BAKER: Thank you, Dr. Narendran.

This is Robert Baker. I'm the industry rep

and a psychiatrist. I have a question for Dr. Cormier.

During the sponsor presentation, we heard a bit about the challenges with COVID, and Dr. Deal also mentioned challenges with this patient population. You referenced the FDA guidance on evidence and the flexibility considerations for orphan populations, which do speak specifically there in the consideration of doing a second trial about feasibility, of doing such a trial.

Now, you've done two, but one of the potential questions would be another or bigger study. So I'm wondering if the sponsor has conclusions on whether that is doable or feasible.

DR. CORMIER: Thank you, yes. Conducting another study in this patient population would be very difficult for a number of reasons, including substantial operational challenges. Given the rarity of the disease, it's difficult to find sufficient patient numbers to have the appropriate prospective statistical power that would normally be relatively easy to find in a larger clinical

study.

So from our perspective, another study, even if it could be adequately powered, it would not really be justified based on the data that we already have in hand, showing that intranasal carbetocin is a safe and efficacious treatment for patients with PWS.

DR. BAKER: Thank you. I don't have any other questions.

DR. NARENDRAN: The next question is from Dr. Dunn.

DR. W. DUNN: Hi. This is Walter Dunn. I have a two-part question but related to the same issue. I'm trying to better understand the off-target effect to explain the lack of efficacy in the 9.6-milligram dose in your phase 3 study. So to that end, the first question is, do you have any question-level breakdown for the HPWSQ-R for questions 1A and 1C that particularly speak to the possibility of increased aggression in that Study 114?

In your briefing document, you were able to

break it down for your phase 3 study, but I didn't see anything for phase 2. So I want to see if any type of trend-level data is available for that, for 114.

Then my second question also relates to this issue, to the off-target effect. For your long-term follow-up, do you have any data looking at the 9.6-milligram cohort that was randomized from placebo to the 9.6-milligrams for that 8- to 16-week period, looking at those who remained in the study during that period and those who dropped out; and was there any evidence of increased anxiety and aggression at your instrument-level data?

So not a treatment adverse event of aggression, but looking at the actual instrument that you used, again, breaking it down to question-level data; is there any evidence for those questions that could lead to aggression? Was there any evidence that those who dropped out in that 8- to 16-week period had higher levels than those who were retained in the study?

DR. CORMIER: As far as the question-level information from the phase 2 study, I don't have a slide on that, but I can see if I can try to pull that data for you. I'm really sorry, I don't have that slide available.

When thinking about the phase 3 study data, the best question to really get at this issue is question 12 of the PADQ.

If I could have slide 1 up, this shows all the various questions in the PADQ, but if you look at question 12, which is highlighted here in the box, it's asking about whether emotional outbursts occur when their desires are followed, and we can see in those data that individuals on the low dose outperformed placebo, whereas those who were on the 9.6 dose actually do worse than placebo during that time.

That question is very similar to what Einfeld was asking, based on the intranasal oxytocin study in patients with PWS that showed statistically significant higher levels of temper outbursts with the higher levels of oxytocin use.

Importantly, when we think about -- if I could have slide 2 up, if you look at what the dose is being delivered during the phase 3 study in carbetocin and what that is equivalent to with oxytocin dose delivery, we estimate that the V1a activation with the high dose is equivalent to what Einfeld was seeing with his higher doses; whereas the low dose of carbetocin in our study has an equivalent of about, say, one-quarter to one-half the level of V1a activation that Einfeld was getting with his higher doses of oxytocin.

I know that doesn't directly answer question. I just don't have the phase 2 data for you, so I apologize for that, but hopefully you can see kind of where the data is coming from.

DR. W. DUNN: And what about the data for the long-term follow-up, specifically week 8 to week 16 for those who started off in placebo and then were randomized to 9.6.? Specifically to question 12, do you still see that trend?

So I guess what I'm trying to figure out here is -- your explanation is certainly plausible.

I'm just trying to see, again, from your phase 2 data and from your long-term follow-up data, this explanation, is it been replicated; is this phenomenon of potentially increased agitation and aggression at that 9.6. arm, is that being seen in other populations in different phases of your studies.

DR. CORMIER: Yes. No, I appreciate the question. Thank you. It's very helpful. Again, with respect to the long-term follow-up data, I don't have a slide with the question-by-question analysis. What we do know from analysis of the data is that those who are discontinuing come out of the high dose, and they tend to be showing lack of efficacy as they discontinue.

So to the extent that that lack of efficacy can be driven by these reciprocal behaviors that are elicited by vasopressin 1a receptors that look like lack of efficacy, it's just the opposite of what you're trying to effect with the drug. That's kind of how we see the data and what the data are showing us with respect to that off-target effect

in the long term follow-up period.

DR. W. DUNN: Thank you.

DR. NARENDRAN: Our next question is Dr. Billington.

DR. BILLINGTON: Thank you. Charles Billington in Minnesota. Two questions, and in regard to the first one, the background is that in most other areas where we're studying hyperphagia and obesity, either preclinically or clinically, we have objective measures.

In the case of short-term studies, we would do something akin to a food buffet and measure reductions in food intake. For long-term studies, we looked at weight. And in the case, I think modestly parallel to the one we're presented with here -- that is congenital or genetic leptin deficiency -- hormone replacement, as we are encouraged to think about this being, results in measurable decreases in both food intake and weight.

So question number one is, can you talk about the rationale for why that type of measure

was not done and seemingly does not seem to be appropriate?

I'll just go ahead and ask question number two. This is in regard to Dr. Deal's, I think, striking case presentation, which showed a really remarkable relaxation in environmental controls. But I'm having trouble integrating that with a rather modest effect on environmental control relaxation that we see otherwise, and I'm wondering if Dr. Deal or Dr. McCandless can help me put that in perspective. Thank you.

DR. CORMIER: Thank you. With respect to your first question about why not measure weight or why it would not be appropriate, I'll give you a brief bit of data from the phase 3 study baseline information, and then I'll have Dr. McCandless weigh in about why things like food buffets or measurement of weight is really not appropriate or not informative in this patient population.

If I could have slide 2 up, we see that given the environmental controls that patients with PWS are placed under, their caloric intake is

severely restricted and controlled by the caregiver. As a result, weight -- or BMI, or in this case, BMI Z- scores to control by gender and age -- is really decoupled from the experience of hyperphagia. So unlike other diseases of obesity where people are able to eat more ad libitum, caregivers severely restrict that caloric intake, and that affects what they're doing.

But I'd like to maybe ask Dr. McCandless to share his perspective on ad libitum type studies and also use of weights in PWS.

DR. McCANDLESS: Thank you. This is Shawn McCandless. I'm a clinical geneticist and run a Prader-Willi syndrome clinic. I've had the same thought and really would love to use a food buffet, but that was done 25 years ago in Prader-Willi syndrome in a study from the UK, and there was a generalized consensus after that that it was both unethical and unsafe for individuals with Prader-Willi syndrome. And for that reason, the food buffet approach has not been used since then in clinical trials. Although several of us have

argued for it, it's really just not been generally acceptable, so it's not been used.

To answer the other question about weight, it's just worth reminding people, first off, that the hyperphagia, the obesity, when it occurs, is a result of the primary problem of the increased appetite and sense of starvation that leads to hyperphagia. And because of the environmental controls -- and if I could have slide 1 up, please, again -- that we use, you can see that most of the patients enrolled in the phase 3 trial that had weights that were well controlled were less than two standard deviations above the mean for age, for BMI.

So there was really very little room, and to get to see significant weight reduction, we would have had to further restrict calories in addition to measuring the hyperphagia because, again, the amount of calories -- we would have had to reduce calories probably to 6[00] to 800 calories per day for the teenagers in this study to have seen any weight loss, and that wasn't really the goal of

this study. The goal of this study was not to lose weight; the goal of this study was to control hyperphagia. Thank you.

DR. NARENDRAN: Our next question is from Dr. Shapley.

DR. BILLINGTON: Excuse me. Hang on. I didn't get my answer to the second question about environmental control relaxation.

DR. NARENDRAN: Sure. Go ahead. Sorry.

DR. CORMIER: Sorry. No problem.

With respect to the environmental controls, as Dr. Deal had mentioned, once instituted, it is rare for a caregiver with an individual with PWS to relax a given environmental control; it's instituted reluctantly and only in the face of the need to further put in place that environmental control for a given child or individual with PWS.

So you expect -- and if I could have slide 1 up just to show the data one more time -- that this would be flat over time. And in fact, if you look at the individuals who terminate the study early, of the 17 individuals that return for an early

termination visit and did the study, their scores actually went up a little bit on average, but you generally consider that to be flat. You could think about that as just being flat over time.

So this reduction of environmental controls is just something you just don't really see, and we see that if you compare the two, there's a net reduction of 10 points on the Food Safe Zone score. But perhaps I could have Dr. McCandless also speak to the meaningfulness of that kind of reduction in environmental controls and what that might mean to families.

DR. McCANDLESS: Actually, I'd like to ask Dr. Billington for a little clarification about what you're looking for just to make sure that I'm addressing the question.

DR. BILLINGTON: Sure. Dr. Deal showed a case report in which the environmental controls, I think, were quite strikingly relaxed, and that resulted in quite an improvement for that particular individual patient, but the overall degree of relaxation is quite modest. It's not

striking in the way that that single patient was, so I was trying to get a feel for how important the medication effect might be on something like this. I guess to put it quite simply, if giving the medication does not allow any environmental relaxation, then explain what the benefit is.

DR. McCANDLESS: I understand. Thank you for that clarification. I think it's really important to point out that those of us who manage individuals with Prader-Willi syndrome in the families that take care of them, these environmental controls have been in place for years, and we've learned that we just have to be strict and constant about them.

I think I speak for most, if not all, of the investigators in this study, that it was not part of the study protocol to intentionally reduce the environmental controls on food access. In fact, part of the protocol was asking the families to maintain all of their pre-existing approaches.

So it's not really fair to judge this clinical trial on that, with that as an outcome

measure, because that was not the intention of the trial. We saw the relaxation in the Food Safe Zone just as we did in the Zafgen trial, by the way. That was entirely by the families just doing it on their own, and I think each of us have our own examples from the patients that we enrolled in the study of families who were able to relax controls without asking us for permission, who just did it, and then we learned about it later. I think that's reflected in that, really, quite substantial change in the Food Safe Zone scores.

DR. CORMIER: Maybe I could also ask Dr. Deal to give her color on the changes, what those might mean.

Dr. Deal?

DR. DEAL: If I could pull up the spaghetti slide that I showed during my last talk? In the meantime, I will tell you that, as I said, the maximum score is 80, and you might say reduction, as shown in the table of 7 to 8, is that clinically meaningful when you do your statistics well.

Let me tell you that of the questions, of

the 20 questions, with a response from 0 to 4, let's just pick, for instance, questions 1 and 2. A family that all of the time kept their pantry and cabinet, where food is kept, locked, or their refrigerator and freezer locked, if they went from all the time to none of the time, removed the locks, that would give them a drop of minus 8.

So yes, I consider that very significant. Similarly, there are other questions in the Food Safe Zone; avoid taking a child to a restaurant, or taking a child to a grocery store. If they are now taking that child when they didn't ever take them to those two places, and they are now taking them, that would be a drop of minus 8. So yes, I think it's very clinically significant, even though to you, on this graph, a drop of 8 points doesn't seem very much.

Does that answer your question?

DR. BILLINGTON: Thank you.

DR. NARENDRAN: Thank you, Dr. Billington. Our next question is from Dr. Shapley.

DR. SHAPLEY: Yes. Thank you so much.

Dr. Cormier, this is a question for you based on your slide. I think it's slide 54 that shows the bar graph distributions for the three different arms of the phase 3 trial. I don't know if you want to bring that slide up.

DR. CORMIER: If we could bring that slide up, I just want to make sure this is the right slide for you.

DR. SHAPLEY: Yes. I'm really struck by the distinction between the orange histogram and the gray histogram. My question has to do with the right-hand set of bars, the no change or worsening part of the distributions. I guess I'm just wondering whether you can speak to a subdivision of that in terms of the carbetocin 3.2-milligram cases, how many of them were no change versus worsening. I guess I'm wondering what the subdivision of that part of the distribution is --

DR. CORMIER: Sure. Certainly --

(Crosstalk.)

DR. SHAPLEY: -- the first-do-no-harm idea.

DR. CORMIER: Sure. And as with any

clinical trial, there are patients who do worse, patients who do better, and this is no different. And some of that's going to be some of the variability in the instrument, and there are individuals on both the 3.2 and the 9.6 who are zeros, and there are also patients on both that are higher. I believe we may have a waterfall plot that will show you that data very distinctly so you can see that. But again, while the carbetocin has much less activity at the off-target receptors, it's not none.

If I could have slide 1 up, you can see in slide 1 -- it may be a little hard to see the zeros; we had trouble representing them -- you can see the worsening is on the right. These are the increases in HQ-CT over time, and then the improvements are on the left. There's a distribution of each of the dose arms throughout the response curve, but the orange bars are much more heavily weighted on the left-hand side, as you would expect, based on the histograms you just saw.

DR. SHAPLEY: Yes. No, I can see that.

That's great. Thank you so much. Thank you.

DR. NARENDRAN: Dr. Dunn?

DR. W. DUNN: This is Walter Dunn. This question is related to I think, really, the reproducibility of some of the effects that you're seeing. I'm wondering, again, specifically for these off-target effects that you were seeing for the anxiety and aggression in your briefing document, and also when you answered my initial question, you highlighted question 12 about the emotional outburst when the desire is not followed. But when you look at the other questions in the PADQ and even in the FHC-QT [ph], some of these other questions also kind of speak to aggression and anxiety, but it doesn't appear to have that significant of an effect or signal there.

For example, question 15 in the PADQ, it's not trending in the other direction. Question 13, anxiety, if you look at the HQ-CT, question 1, being upset when denied food, I imagine that would be a significant trigger for this patient population. If progression was being triggered by

an off-target effect, I would have expected to see a much more dramatic signal there.

So I guess my question is, is there anything specific about question 12 that speaks more accurately to the type of aggression that you might see with the off-target effect? Because it seems if I exclude that one, and I look at all the other questions that potentially could relate to anxiety and aggression, I don't see that. I'm not seeing that signal of that off-target effect.

DR. CORMIER: Sure. None of the questions in these instruments, as you know, were really designed to try to target the specific off-target effects of an oxytocin receptor agonist like carbetocin. We can show the data. We would bring up slide 1 just to show the PADQ data. I think you had mentioned question 15, and I think it was -- I'm sorry. I didn't get them all written down, but --

(Crosstalk.)

DR. BILLINGTON: Yes, question 15, question 13, and question 10, I think these all speak to

potential anxiety and aggression.

DR. CORMIER: Right. Question 10 is a little bit less clear, but in each of those cases, you're seeing the 3.2-milligram dose outperforming the 9.6-milligram dose in each of those issues, and when we think about the temper outbursts that we're talking about that were observed by Einfeld in his study as a potential off-target -- how these off-targets would manifest, looking specifically at these things.

But question 15 is an interesting one that you point out because this question is sort of an overall question. It's not included in the total PADQ score because it's an overall anxiousness and akin -- it's kind of like a CGI type issue, and that data is very robust with respect to 3.2 compared to placebo, whereas 9.6 doesn't get us there.

So the overall Gestalt that question 15 tries to get at is consistent with the idea, or the conclusion, that 3.2 milligram is outperforming placebo, whereas 9.6 is really not able to

distinguish itself when looking at these kinds of symptoms.

I wish I had a better tool to target this specific issue, but it's not one that's -- we're working with caregiver- and clinician-reported instruments, and it's a difficult syndrome from that perspective to get clear answers to these kinds of very specific questions that are obviously very interesting and worth thinking a lot about.

DR. BILLINGTON: Thank you.

DR. NARENDRAN: Okay. I think we're right on time, so we will now take a quick 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic with other panel members during the break.

Let's plan to resume at 11:20 -- that's like a 10-minute break -- so we can start on time, 11:20. Thank you.

(Whereupon, at 11:08 a.m., a recess was taken.)

DR. NARENDRAN: We will now proceed with the FDA presentations, starting with Dr. Paul Bossie.

FDA Presentation – Paul Bossie

DR. BOSSIE: Thank you. My name is Paul Bossie. I'm the reviewer for the application. Today I'm going to discuss the relevant regulatory history, overview of efficacy results of Studies 114 and 301, and an overview of safety results. My colleague, Dr. Andrew Potter, will present his statistical assessment before concluding remarks.

As mentioned earlier, intranasal carbetocin has not been approved or marketed in the United States or elsewhere. The applicant acquired a license to develop intranasal carbetocin in 2017 after the former sponsor had conducted Study 114. Since then, the agency and the applicant have had multiple interactions, but I'll focus on two relevant meetings.

At the 2018 end-of-phase 2 meeting, the agency provided feedback on the primary and secondary endpoints and other design elements for the proposed phase 3 study, which I'll describe in further detail later.

As Study 114 had included only one dose, the agency recommended a dose-finding study noted that a longer-term safety study would be required prior to approval. The agency provided statistical comments for Study 301 at several timepoints, which Dr. Potter will discuss in further detail.

At the 2020 pre-NDA meeting, the agency and the applicant discussed the results of the two studies. The agency expressed concern that, based on the prespecified primary analysis, Study 301 was not a positive study. The agency noted that the conflicting results between Study 114 and Study 301 are difficult to reconcile. However, when the applicant submitted the application in April 2021, the agency decided to file the NDA to comprehensively review all of the available data.

Moving on to the phase 2 and 3 studies, Study 114 was a phase 2, randomized, double-blind, placebo-controlled, proof-of-concept study of carbetocin 9.6 milligrams, 3 times daily versus placebo, conducted at three sites in the United States. The study included a 14-day treatment

period with final assessments on day 15.

It was planned for 38 subjects, aged 10 to 18 years, genetically confirmed Prader-Willi syndrome, nutritional phase 3 -- that is when hyperphagia has begun -- with screening and baseline Hyperphagia in Prader-Willi Syndrome Questionnaire-Responsiveness scores, HPWSQ-R, greater than 13. I'll talk more about this scale on the next slide.

Psychotropic medications such as antidepressants, antipsychotics, or wakefulness-promoting drugs must have had stable doses for at least 6 months before screening. Overall, the study design and eligibility criteria appear reasonable for this proof-of-concept study, although the relatively brief duration isn't adequate to support efficacy in a chronic condition on its own.

The primary endpoint was the change from baseline to end of treatment day 15 on the HPWSQ-R, which is an 11-item observer-reported outcome measure for hyperphagia-related behavior over the

preceding one week. Each item is rated on a 5-point scale for total scores ranging from 11 to 55, with higher scores indicating there are frequent hyperphagia-related behaviors.

The scale includes hyperphagia, drive, and severity domains. Examples of items include such questions as how upset was your child when denied desired food; how persistent was your child in asking or looking for food after being told no; how often does your child try to bargain for more food, or forage through trash for food, or get up at night to food seek, among others.

The agency had agreed with its use in an exploratory phase 2 study, which would also provide evidence for the scale's ability to detect change. Secondary endpoints included the Clinical Global Impression-Improvement score at day 15; change from baseline to day 15 on domain scores for the HPWSQ-R and the HPWSQ-R clinician total and domain scores; the change from screening to day 15, Children's Yale-Brown Obsessive-Compulsive Scale, CY-BOCS; and the Food Domain of the Reiss Profile.

I'll focus my results discussion on the CGI-Improvement, as it may be considered supportive of the primary endpoint findings and on the CY-BOCS, as the applicant used it in the phase 3 study based on these findings.

The CY-BOCS is typically used in obsessive-compulsive disorder and includes a severity scale, 5 obsession items, and 5 compulsion items, each rated 0 to 4 for a score ranging from 0 to 40, again with higher scores indicating more severe frequency. At the time of protocol submission, the agency didn't comment on secondary endpoints for this proof-of-concept study, although the agency did express concerns with the CY-BOCS later for the phase 3 study, as I'll get to.

Study 114 was designed to include 38 subjects to provide at least 80 percent power, to detect a treatment difference of 5 points, with a standard deviation of 6 points, one-sided alpha level of 0.1. There was no prespecified plan to control the type 1 error rate for multiple comparisons over primary and secondary endpoints,

which is acceptable for a proof-of-concept study but may limit efficacy conclusions. The primary analysis was conducted using an analysis of covariance model.

Thirty-eight subjects were randomized. After excluding a screen failure who was randomized in error, 37 subjects were dosed in the full analysis set, including 17 with carbetocin and 20 with placebo. In terms of disposition, all subjects completed the study, except one in the placebo arm who discontinued for adverse events.

The mean age of subjects was around 13-and-a-half years; 62 percent of subjects were female and 38 percent male; 97 percent identified as white and 97 percent as not Hispanic or Latino. Mean baseline HPWSQ-R scores were slightly more severe at 39.7 for the placebo arm versus 35.6 for the carbetocin arm. As a reminder, the score ranges from 11 to 55. Mean baseline CY-BOCS scores were similar across arms, around 15 to 16. As a reminder, the score ranges from 0 to 40.

During agency inspection of one of the

studies sites, an investigator noted a discrepancy between the paper source and the electronic study database, for one subject in the placebo arm, primary endpoint HPWSQ-R, day 15. The applicant reanalyzed the corrected data set which resulted in changes that I'll discuss on the following slide.

This table displays the primary endpoint results with the originally reported data in the left-hand column, and results from the updated data in the right-hand column, with the updated p-values highlighted in yellow. Treatment with carbetocin showed a 6.9-point improvement on the HPWSQ-R compared to placebo for a one-sided p-value of 0.0244.

As you can see, the original results on the left were already well below the study's one-sided 0.1 threshold for significance, which was promising, and the updated results, based on the inspection finding reanalysis, were below the typical one-sided 0.025 threshold for significance.

This table displays the secondary endpoint results for the CGI-Improvement at day 15 and the

change in the CY-BOCS. Both show treatment improvement for carbetocin over placebo, with p-values also below the typical one-sided 0.025 threshold for significance, although there was no prespecified plan to control for multiple comparisons across endpoints.

In summary, Study 114 provided preliminary evidence for the effect of carbetocin 9.6 on hyperphagia. Clinical meaningfulness of the observed treatment effect is unclear given that the 2-week study duration is insufficient to assess efficacy for chronic disease in which subjects/patients would be taking the medication perhaps lifelong. But the results were promising, proof-of-concept result, and further data from the phase 3 study would be required to better understand carbetocin's effects.

Moving on to Study 301, it was a phase 3, randomized, double-blind, placebo-controlled trial with carbetocin 9.6 or 3.2 mg three times daily versus placebo. The study took place at 24 sites, mainly in the United States, with a few sites in

Canada, and one in Australia. The study included an 8-week, double-blind, placebo-controlled treatment period, followed by a 56-week long-term follow-up with option for extension.

In the long-term follow-up, all participants were unblinded to receiving carbetocin but were blinded to which dose. At study baseline, subjects were randomized 1 to 1 to 1 9.6 milligrams, 3.2 milligrams, or a placebo-treatment sequence; that is placebo to 3.2 milligrams or placebo to 9.6 milligrams, this switch occurring at week 8 when entering the long-term follow-up. Subjects in the carbetocin groups would stay on their original dose for the long-term follow-up.

The applicant planned to enroll 175 subjects ages 7 to 18 years with genetically confirmed Prader-Willi syndrome and nutritional phase 3; screening and baseline, Hyperphagia Questionnaire for Clinical Trials; HQ-CT scores greater than or equal to 13; CY-BOCS scores greater than or equal to 9. The applicant noted that the inclusion cutoffs were chosen to allow demonstration of

change, and I'll talk more about the endpoints on the next slide.

In terms of differences from Study 114, the agency had previously suggested decreasing the lower age limit from 10, and age 7 aligns with the mean onset of hyperphagia, and in addition from Study 114, subjects were excluded for any new food-related interventions, requirements, or dietary restrictions within one month of screening; no changes during the study.

As in Study 114, subjects were to have stable, chronic, concomitant medications prior to the study start and throughout. Overall, the design elements of the study appear reasonable. There were two primary endpoints of the study, including the change from baseline to week 8 on the HQ-CT in the 9.6 arm and the change on the CY-BOCS in the 9.6. arm. The HQ-CT is a 9-item modified version of the HPWSQ-R, which removed two items, one asking how clever or fast was your child in obtaining food, and the other asking how easy was it to redirect your child away from food to other

things. Recall period was also increased from 1 to 2 weeks.

The agency had agreed with the use of the HQ-CT primary hyperphagia endpoint at the end of phase 2 meeting. As used in Study 114, the clinician-administered CY-BOCS includes a 10-item severity scale with 5 obsession and 5 compulsion items. The agency initially questioned the fitness for purpose of the CY-BOCS given its primary use in obsessive-compulsive disorder, but after discussion with the applicant, the agency agreed that the CY-BOCS was a potentially appropriate endpoint.

The first secondary endpoints were the same as the primary endpoints, change from baseline to week 8 on the HQ-CT and CY-BOCS, except this time for the 3.2-milligram arm. Other secondary endpoints for both doses included the change on the PWS Anxiety and Distress Behaviors Questionnaire, PADQ; the Clinical Global Impression-Change score at week 8; change on an HQ-CT subset; and the change on the HQ-CT item 9 alone.

At the end of the phase 2 and pre-NDA

meeting, the agency had disagreed with the PADQ's adequacy as an observer-reported outcome. The Division of Clinical Outcome Assessments noted that some items on the PADQ may not be directly observable by caregivers. Feelings of anxiety and distress are best known to patients, whereas caregivers or clinicians may only report observable signs, behaviors, and verbalizations.

Regarding HQ-CT item 9, the applicant noted that item 9 holds value in assessing overall burden by asking how often behaviors interfere with normal daily activities. Regarding the HQ-CT subset, the applicant noted that the subset removed items that might be susceptible to environmental control. For example, if the refrigerator is locked, item 4 about getting up at night to food seek may be confounded.

In general, the subset and item 9 alone may be redundant with the primary endpoint total score on the HQ-CT. At the meetings, the agency disagreed with the use of HQ-CT subset and item 9, noting that such measures could only be considered

exploratory without sufficient analysis of psychometric properties, and that removal of items might affect the content validity HQ-CT. For the subset, the agency noted the confounding effect of environmental controls would be addressed by randomization.

This slide contains a brief overview of the statistical analysis, although I know it doesn't look brief, so Dr. Potter will go into greater depth later. The overall type 1 error was specified at a two-sided 0.05 level of significance, and the prespecified control for multiple comparisons, included a combined Hochberg procedure and an hierarchical testing procedure. The applicant proposed 175 subjects would provide 90 percent power for the HQ-CT and 99 percent power for the CY-BOCS, assuming that the phase 2 results held in phase 3.

It's important to examine how meaningful a change on a scale is to a patient, known as clinically meaningful within-patient change. The 2016 psychometric validation report suggested a

7.7-point improvement on the HQ-CT as a within-patient responder threshold, meaning that it correlated to the average change experienced by subjects who were described on the CGI change as moderately better in the validation study.

Not to get ahead of myself, and I'll be discussing the mean changes in each treatment group shortly, but this slide shows you the proportion of subjects who met this responder threshold in each arm. As you can see, the highest crude rate occurred in the 3.2 group, followed by 9.6, then placebo. Dr. Potter and I will discuss the results.

Because of the pandemic, the applicant held enrollment on March 12, 2020 and defined two analysis sets. The primary analysis set included 119 randomized subjects who received at least one dose of carbetocin and completed either the week 2 or week 8 visit before March 1st. To be clear, if subjects' week 2 visit occurred before that date but the week 8 visit occurred after, only the week 2 data was used in the primary analysis set.

The full analysis set included 130 randomized subjects who received one dose of carbetocin.

In proposing the COVID-19-related amendment to the study, the applicant noted that the events of the pandemic could have impacted efficacy results in multiple ways; for example, by affecting enrollment, use of remote visits, a larger amount of time that caregivers would be able to observe subjects' behavior, and grocery store shortages that could heighten food security concerns that are already an issue. The agency did not object to the applicant's primary analysis set proposal, and I'll note that we were able to examine all of the available data for both sets.

This table displays the treatment group distribution among the full analysis set, the same as the safety; the primary analysis set; and the applicant's per-protocol analysis set.

This CONSORT subject disposition diagram looks complicated, as it includes both the full analysis set and the primary analysis set numbers, so I will try to keep this simple. Of the three

groups -- 9.6, placebo, and 3.2 -- nearly all completed the placebo-controlled period at week 8. There were only 2 subjects in the 9.6 arm who discontinued during the placebo-controlled period, both for adverse events.

After week 8, subjects in the placebo arm continued in their pre-assigned treatment sequence to 9.6 or 3.2. So in total, 64 subjects in each group in the full analysis set entered the long-term follow up.

This portion of the CONSORT diagram displays subject disposition through the long-term follow-up and ongoing extension as of the June 2021 cutoff date. These two groups here at the top are the same as the bottom of the previous slide. I'll just point out that the total number of discontinuations from the long-term follow-up here on this tier, 25 total, including 17 for the 9.6. arm and 8 in the 3.2 arm.

I should note that after data unblinding and analysis, the applicant transitioned all of the subjects in the 9.6 arm to open-label 3.2 starting

in October 2020. So as you descend this flowchart, subjects in the 9.6 arm transitioned over to the 3.2 arm at various points, depending on the subject and where they were in the study. It was a bit complicated to represent that just because of different durations of time that they were in each phase. But here at the bottom, you can see that a total of 89 subjects remain in the extension, at this point all on open-label 3.2 milligram.

Mean age of subjects was 12 years across all arms. Eighty-five percent of subjects identified as white and 91 percent identified as not Hispanic or Latino across all arms. In terms of sex distribution, the 9.6 arm was fairly balanced, although the 3.2 and placebo arms included somewhat more females than males.

This table displays mean baseline scores on the HQ-CT and CY-BOCS. As a reminder, the HQ-CT has a score range of 0 to 36; CY-BOCS has a score range of 0 to 40, higher scores indicating more severe or frequent symptoms in both scales.

The 9.6 arm, in the second column from left,

had a slightly higher mean baseline score on the HQ-CT than both the other groups, and a higher mean baseline score on the CY-BOCS than the 3.2-milligram arm, which Dr. Potter will talk about later.

To summarize the key results of this study, 9.6 milligrams of carbetocin showed a 1.2-point treatment difference compared to placebo on the HQ-CT score and a 0.6-point difference compared to placebo on the CY-BOCS. Both p-values were greater than 0.05, so the primary endpoints provide no evidence of efficacy for 9.6 milligram.

On the first secondary endpoint, 3.2 milligrams of carbetocin showed a treatment difference of 0.8 compared to placebo on the CY-BOCS. However, 3.2 milligrams showed a 3.1-point difference compared to placebo on the HQ-CT with an unadjusted p-value of 0.0162.

For this slide and the next several slides, I note that because of the prespecified statistical testing plan, these secondary endpoint p-values are nominal or unadjusted for multiple comparisons.

Dr. Potter will discuss further.

Although formal statistical testing had stopped at this point, the finding on the HQ-CT 3.2 milligram raised the possibility that this dose could have an effect on hyperphagia and prompted further examination of the study results in our review and our discussion this morning. And as Dr. Cormier pointed out, that's why we're here today.

In addition to further detail regarding the primary endpoint week 8 results for 9.6 I just reviewed, highlighted here in yellow, this table also presents the week 2 results for 9.6. Although week 2 results were not primary endpoints, they are useful to compare with Study 114 and to understand how the results change over time.

At week 2, there was a 0.425-point treatment difference in the 9.6 arm compared to placebo on the HQ-CT, with a wide confidence interval that includes zero. These week 2 results are inconsistent with the findings of Study 114, in which 9.6 appeared to show a treatment effect at

15 days. Overall, it would appear that Study 301 did not confirm the results of Study 114 for 9.6 in either week 8 or week 2.

Similar to the previous table, this table provides further detail regarding the first secondary endpoint week 8 results for 3.2 milligrams, highlighted here in yellow, and also presents the week 2 results.

At week 2, there was a 3-point improvement for 3.2 milligrams compared to placebo in the HQ-CT, a similar estimated effect to week 8. There was a 1.8-point improvement for 3.2 compared to placebo on the CY-BOCS, which is a larger estimated effect than at week 8, but still with a wide confidence interval that does include zero.

For the additional secondary endpoints for 9.6 milligrams, none showed any signal of improvement compared to placebo. For 3.2, several of the other secondary endpoints showed a potential signal of improvement, although I will note again that the p-values reported here are unadjusted and must be considered descriptive statistics only.

Also, the agency had concerns about the PADQ and use of the HQ-CT subset and item 9, as I mentioned earlier.

To review the program's findings, Study 114 provided preliminary evidence of efficacy on the primary endpoint HPWSQ-R for 9.6. However, the clinical meaningfulness of the treatment difference was unclear, as the 2-week duration of the study was insufficient to assess efficacy in a chronic condition.

Study 114 also provided preliminary evidence of efficacy on secondary endpoint results of the CGI-Improvement and the CY-BOCS, but secondary endpoints were not controlled for multiplicity. Study 301 did not provide evidence of efficacy for 9.6 on its primary endpoint results for the HQ-CT and CY-BOCS. Also, the week 2 results were inconsistent with results of Study 114 for 9.6 milligrams.

Statistical testing stopped after the primary endpoint. Descriptive findings for the first secondary endpoint included a potential

signal for improvement for the 3.2-milligram arm on the HQ-CT, but not the CY-BOCS.

Moving on to the long-term follow-up phase of Study 301, just as a quick refresher. Subjects in the placebo arm switched to 9.6 or 3.2 based on their treatment sequence randomization that occurred at baseline and remained blinded to which dose they received, at least until the transition to open-label 3.2 in October 2020. Assessments were collected throughout the follow-up and subjects could continue an optional extension.

Dr. Potter will discuss the efficacy results and some of the complexities in interpretation, and I'll focus on the safety results for the whole study, including the placebo-controlled period and the long-term follow-up and extension.

Besides providing long-term safety data, the long-term follow-up safety findings are pertinent to the applicant's hypothesis regarding a U-shaped dose-response curve, to be discussed later. No deaths or other serious adverse events occurred during Study 114 or the placebo-controlled period

of Study 301.

In terms of discontinuations for adverse events, in Study 114, one subject in the placebo arm discontinued. For the placebo-controlled period of Study 301, 2 subjects in the 9.6 arm discontinued, one for an adverse event of tachycardia, the other for impulsive behavior. An additional subject in the 9.6 arm had an adverse event of hypersexuality that led to later discontinuation during the long-term follow-up.

Regarding the most common adverse events, that is those that occurred with 5 percent incidence and at least twice the rate with placebo, none occurred in more than one subject in Study 114. During the Study 301 placebo-controlled period in the 3.2 arm, the most common adverse events included headache, flushing, diarrhea, abdominal pain, pyrexia, fatigue, and nasal discomfort. In the 9.6 arm, the most common adverse events included flushing, epistaxis, and headache. There were no findings regarding nasal examinations, vital signs, or laboratory

assessments that suggested a safety signal.

For long-term follow-up and extension, 17 serious adverse events occurred in 16 subjects. Of those, scoliosis surgery and pneumonia occurred in more than one. Nine adverse events led to discontinuation in 8 subjects, including emotional disorder in 2 subjects. Most of those were primarily psychiatric, including one subject each for aggression, agitation, behavior disorder and one subject for obsessive thoughts and separation anxiety disorder.

More discontinuations for adverse events occurred in the 9.6 arm compared to 3.2, 5 versus 3 subjects. During the long-term follow-up and extension, the most common adverse events were generally similar to the placebo-controlled period. Overall, carbetocin appeared to be generally safe and well tolerated across the development program.

In evaluating efficacy and safety findings for Study 301, the applicant hypothesized that the 9.6 dose at the longer duration in Study 301 compared to 114 resulted in more off-target

vasopressin effects, leading to psychiatric adverse events that counteract treatment effect. It's true that a higher number of psychiatric adverse events occurred in the 9.6 arm compared to 3.2, but it's somewhat difficult to draw any definitive conclusions, as the overall number of psychiatric serious adverse events and discontinuations for adverse events was small, there was no placebo-controlled arm in the long-term follow-up for comparison, and many of the psychiatric adverse events overlapped with symptoms seen in Prader-Willi syndrome.

I'll now pass the baton to my colleague, Dr. Potter, who will discuss his statistical assessment of the studies and overall conclusions.

FDA Presentation – Andrew Potter

DR. POTTER: Thank you, Dr. Bossie, for that informative discussion about Studies 114 and 301.

I'm Andrew Potter, the statistical reviewer for this NDA, and I will discuss the statistical assessment of this application. Our key statistical findings are that for Study 114, it's

an acceptable but short proof of concept, but it is a small study with changes in a single subject on a single item in the primary hyperphagia symptom scale, impacting the results. There were no additional statistical issues impacting the findings from this study.

For Study 301, the statistical review confirmed that the study was negative on both primary endpoint in the 9.6-milligram dose arm. Therefore, based on the prespecified statistical test and plan, the interpretation of any statistical inference that was about the 3.2-milligram results became post hoc, and it is challenging to interpret the findings.

As you may recall, here are the results for the 9.6-milligram dose. For this deeper dive, we want to pay attention to the p-values at week 8 in the HQ-CT and the CY-BOCS for both the 9.6-milligram dose and the 3.2-milligram dose. Next, we will use these four p-values -- two primary 9.6-milligram dose and two secondary endpoints on the 3.2-milligram dose -- and the

prespecified statistical testing point.

The prespecified statistical testing plan first started by testing 9.6-milligram dose arm endpoint. It used two p-values for the 9.6-milligram dose, the HQ-CT at a p-value of 0.3493 and the CY-BOCS at a p-value of approximately 0.6.

The results of this prespecified testing plan were that neither the null hypothesis associated with the HQ-CT endpoint, nor the CY-BOCS endpoint, for this dose were rejected because both p-values were greater than 0.05. Therefore, based on the prespecified statistical testing plan, formal statistical testing stops at this point, and the interpretation of whether 3.2-milligram dose represents a chance finding becomes post hoc. In other words, we cannot determine whether or not a potential signal in the 3.2 milligram dose is a chance finding.

Why is this the case? To better understand why, we evaluated the prespecified statistical testing plan or multiple comparison procedure.

This plan consisted of a combination of Hochberg's procedure and hierarchical testing. At this point, note that these are both accepted statistical procedures that control the type 1 error rate when properly applied.

In Study 301, the prespecified plan determined to first test both hypotheses on the 9.6-milligram dose using Hochberg's procedure; then, if positive on either, 9.6 milligram endpoint, proceed to the second step. The second step was to again test the null hypothesis associated with HQ-CT and CY-BOCS in the 3.2-milligram dose using Hochberg's procedure. If at this point, any of these tests had enough of tested rejected, all of the secondary endpoints were to be tested in a fixed-sequence hierarchy.

During FDA's evaluation of the applicant's proposed multiple comparison procedure, we found that, yes, it may control type 1 error for just the 9.6-milligram dose, but it also may inflate the overall type 1 error rate. This is caused by property of the Hochberg procedure to exhaust all

of the prespecified alpha unless both primary hypothesis tests are rejected.

In addition, the applicant's prespecified testing plan does not allow for assessment of the 3.2-milligram dose if no signal is seen on the 9.6-milligram dose. It's important to note that this full multiple comparison procedure was first received with the NDA submission. A shortened statistical analysis was contained in the protocol, but it was insufficient to fully assess this MCP.

Now that we've discussed our prespecified statistical testing plan, we go on to evaluate the primary analysis. The primary prespecified analysis was a longitudinal data analysis called constrained longitudinal data analysis.

For example, in the constrained longitudinal data analysis, or cLDA, or considering just the HQ-CT endpoint, baseline HQ-CT scores are used as a response similar to the week 2 and week 8 observations rather than a covariate as is commonly used in either ANCOVA or mixed-effects models for repeated measures. All of these models will

provide equivalent results.

For here, treatment differences are estimated by the least-squares mean from this model. Why is this called constrained longitudinal data analysis? Well, there's a constraint in the model that all three treatment arms have the same baseline mean and expectation.

In order to interpret p-values from this primary analysis, there's an important assumption about how observations within a subject co-vary. In the prespecified model, this assumption was that all observations within a subject have the same covariance. This is called compound symmetry.

Compound symmetry may not be met in any clinical trial, and violations of compound symmetry may underestimate the standard errors, causing overly optimistic p-values. A viable approach to adjust for such underestimation of the standard errors is applying either the sandwich estimator together with compound symmetry, or simply using an unstructured covariance structure where no assumptions are made about the covariance between

observations within a subject.

To understand the potential violations of compound symmetry, FDA conducted a set of sensitivity analyses that looked at different covariance structures. This table shows changes in nominal p-values, in the far-right column, and treatment differences for multiple covariance structures. The top row shows the results for compound symmetry covariance with an adjustment to the test statistic. However, this nominal p-value, even with this adjustment, is the same as the unadjusted case, and this nominal p-value of 0.026 can be used as reference.

In this table, also note that we're only discussing the results of the sensitivity analysis for the HQ-CT endpoint in the 3.2-milligram dose. Remember, Study 301 has two endpoints in the 9.6-milligram dose and an additional endpoint, the CY-BOCS, in the 3.2-milligram dose.

To better understand the nominal p-values in this table, consider a world, or a study, in which the 9.6-milligram dose was not studied. In this

case, using Hochberg's procedure, it would have compared the nominal p-value of the 3.2-milligram dose on the HQ-CT with 0.025 because the CY-BOCS had already failed at 0.05 for this dose.

As you can see, for the HQ-CT, the nominal p-values in sensitivity analyses are all greater than 0.025 starting in row number 2. However, the applicant p-value of point 0.0126 is subject to underestimation of the standard errors, causing an overly optimistic p-value. In summary, the sensitivity analyses indicate that the 3.2 dose likely did not demonstrate a statistically significant treatment effect.

Going into more details, we see that the more robust cases, e.g., using compound symmetry with the sandwich estimator, were using unstructured covariance matrices with both equal variances between arms, unequal variances between arms; and the Kenward Rogers adjustment to the degrees of freedom lead to p-values in the range of 0.03 to 0.05. In summary, the prespecified cLDA model may be sensitive to the choice of covariance

structure.

Our statistical conclusions for the placebo-controlled period are that Study 301 lacked evidence for the 9.6-milligram dose at both week 2 and week 8 and in all of the primary and secondary endpoints for the 9.6-milligram dose. This is inconsistent with the results of Study 114 that indicated preliminary evidence for the 9.6-milligram dose at 2 weeks after study initiation.

For the 3.2-milligram dose, Study 301 suggests that there may be an efficacy signal. However, these statistical inferences are post hoc, implying that it's challenging to determine if these findings are due to chance. In addition, sensitivity analyses increase the uncertainty of these findings.

Finally, it is very challenging to interpret findings in the 3.2-milligram dose because of lack of evidence for the 9.6-milligram dose, lack of evidence for the CY-BOCS in the 3.2-milligram dose, and the absence of a convincing rationale for a

U-shaped dose-response relationship. And while we have secondary endpoints in both doses, they do not provide independent confirmation of efficacy, as primary and secondary endpoints may be correlated.

Now, the study did not terminate at the end of the double-blind period but contained a long-term follow-up period, which allows us to take another deep dive into the data and explore efficacy over time. This period contained multiple exploratory analyses.

Here, I focus on placebo crossover analysis for the HQ-CT in both the 3.2-milligram dose and the 9.6-milligram dose of carbetocin. The exploratory placebo crossover analysis compared changes in the HQ-CT from study baseline to week 8, which I will call period 1, and change from HQ-CT from week 8 to week 16, period 2.

Subjects were randomized at study baseline to one of two treatment sequences, placebo followed by the 3.2-milligram carbetocin or placebo followed by 9.6-milligram carbetocin. In the placebo follow-up period, both dose groups improved in the

period after switching from placebo to carbetocin. However, we can see in the treatment sequence, starting with placebo followed by 3.2-milligram dose, that in period 1 there was effectively no change in the HQ-CT. However, during period 2, there is an approximately 9-point change in this same group. In contrast, the treatment sequence of placebo followed by 9.6 milligrams shows an approximately 5-point decline during period 1 and an approximately 5-point decline in period 2

To better visualize what these changes mean, we can look at the mean HQ-CT over time in both the placebo-controlled period and the long-term follow-up period for patients who started on placebo and then followed a treatment sequence to switch from placebo to 3.2-milligram dose, indicated by the purple line, or switch from placebo to the 9.6-milligram dose, indicated by the gray line.

In this graph, we have along the X-axis study visit starting at baseline and continuing to week 64. On the Y-axis, we see mean HQ-CT. The

placebo-controlled period is on the left of the red dashed line and the long-term follow-up period is on the right of the red dashed line. During the placebo-controlled period, both treatment sequences declined during the first two weeks.

However, from week 2 to week 8, the treatment sequence of placebo, followed by 3.2 milligram, rebounds -- increases in symptom severity while the treatment sequence of placebo followed by 9.6 milligrams continues to decline. At week 8, there's a separation of around 5 points on the HQ-CT between these two groups.

Following switch to carbetocin, both groups declined from week 8 to week 10 and have approximately similar HQ-CT scores, ranging from about 14 to 15 points. By week 16, the groups look roughly similar, with an HQ-CT score ranging from about 12 to 14 points. After week 28, the sample size shrinks to the point where estimates and inferences may become unreliable.

The long-term follow-up period has multiple limitations that impact interpretation of the

analyses. First, the long-term follow-up period lacks placebo control, so while subjects were blinded to which dose of active drug they received, subjects were not blinded to whether they were going to receive active drug after week 8. Second, the randomization at study baseline led to an imbalance in the placebo crossover subjects at week 8, leading to challenges of interpretation between group comparisons in the placebo crossover subjects.

All of the long-term follow-up analysis may be subject to confounding by potential expectation bias -- i.e., patients expect to receive an active drug after week 8 -- and other sources of bias. Finally, the sample size becomes rather small in the later long-term follow-up period.

Now, I'll briefly discuss our overall conclusions. In conclusion, Study 114 provided preliminary evidence of hyperphagia for the 9.6-milligram dose, but with unclear clinical meaningfulness of the results given the 2-week study duration in a chronic condition. Study 301

did not show efficacy for the 9.6-milligram dose, which is inconsistent with the results of Study 114. In addition, it is challenging to interpret 3.2-milligram dose findings because of the lack of efficacy on the 9.6-milligram dose and the prespecified statistical testing plan.

Finally, the lack of placebo control and potential biases in the long-term follow-up period impact any potential findings from this data. Thank you.

Clarifying Questions to FDA

DR. NARENDRAN: We will now take clarifying questions for the FDA. Please use the raised-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raised-hand icon again after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Our first question is Dr. Shapley.

DR. SHAPLEY: Thank you. This is Alice Shapley. Thank you very much for your presentations. This is a question for Dr. Potter.

You mentioned a couple minutes ago that it's challenging to interpret the positive 3.2-milligram findings in the phase 3 study given the lack of efficacy for the 9.6-milligram dose in the same study. However, we actually heard from multiple presenters earlier this morning how a, quote, "inverted U dose-response" might arise for carbetocin, i.e., that the 3.2-milligram dose would work better than a 9.6-milligram dose because of the more specific signaling to oxytocin receptors alone for the 3.2-milligram dose.

So I wonder if taking into account these explanations that we heard earlier this morning

makes it less, quote, "challenging" to interpret the 3.2-milligram results.

DR. POTTER: Yes. Thank you, Dr. Shapley, for that question, however, I may not be the best person on the FDA side to answer this question.

Dr. Bossie or Dr. Farchione, would you prefer to help me out here a little bit?

DR. FARCHIONE: Yes, sure.

This is Tiffany Farchione. I'm the director for the division. I know that we did here some discussion of that this morning, but I think that we need to bear in mind a few things.

One, a U-shaped curve is extraordinarily rare. We just don't see it very often, so it's difficult to really justify that as a mechanism of action here when, after the fact, we're looking at this, and have the data in hand, and trying to apply a hypothesis that might fit the data.

There doesn't really seem to be any mechanistic or pharmacological explanation as to why we would have a U-shaped curve in this case. When we talk about the off-target effects, I think

that you heard in Dr. Bossie's discussion of some of the adverse events that it's really difficult to say that that's actually what's going on here. It's tough to reach that conclusion, based on the adverse event data alone.

So between the pharmacology and everything else -- and I will say that it's also difficult to reconcile this idea that there might be some patients who are experiencing this U-shaped curve and having these off-target effects, and either dropping out or experiencing adverse events, while at the same time describing that the patients who stayed in the study continued to do well, or to look at the data in the 114 study and see that that doesn't really fit the U-shaped curve hypothesis.

There was --

DR. SHAPLEY: But --

DR. FARCHIONE: Sorry, go ahead.

DR. SHAPLEY: You can see that the 114 study also was a factor of three smaller numbers, right? So one does have to wonder about --

DR. FARCHIONE: No, sure. I think by all

accounts, the 114 study was a proof-of-concept study, and we certainly can't take that as adequate and well controlled in order to support either efficacy or -- we might be able to get some safety information from it. It was promising. It did give us some suggestion that maybe this would be an effective treatment, but when we try to compare apples and apples and look at the 9.6-milligram group at 2 weeks in the phase 3 study, that is also still contradictory.

So given all of these different pieces that just aren't quite lining up, it's really hard to pin this explanation on a U-shaped curve.

DR. SHAPLEY: So the 9.6-milligram dose did show improvement, which is not as statistically significant in the phase 3 study as in the phase 2 study.

Then the other thing I'd say is that in the public comments, one of the letters that I wrote was from someone named Larry Young, who was an expert in oxytocin studies, and he actually provided some references about why one might expect

a better response for the 3.2-milligram dose than the 9.6-milligram dose. I have it in front of me. There are some journal references; that it's not just being offered qualitatively, but there's actually literature that would back up such an idea.

DR. FARCHIONE: Right. But in the absence of actual -- I don't even know if a thing would exist, or whatever, that would actually show receptor agonists in these patients at the time. There are a number of factors to consider, and looking at the hypothesis that neatly fit the data after you have the data in hand, when there are a number of other potentially conflicting explanations, is difficult for us to do.

We're not saying that that's not a possibility; it's just one of many possible explanations for the data that we're seeing.

DR. SHAPLEY: Okay. Thank you.

DR. NARENDRAN: Thank you.

Our next question is from Dr. Iyengar.

DR. IYENGAR: This is Satish Iyengar from

Pittsburgh. My question is about the sample sizes in the long-term follow-up.

When I saw slide 56 from the applicant's presentation, the sample sizes at the end seemed quite healthy; of the 128 starting, 104 in week 52 and 103 in week 4. But then in the FDA briefing, I remember reading -- I'm reading here that sample size has decreased from 59 subjects at baseline to 31 in week 28 and one in week 64. Andrew Potter's slide 55, I think, also indicated a very small sample size near the end.

I'm confused. What exactly is going on there? Can someone help?

DR. FARCHIONE: This is Dr. Farchione again. I can start that. I believe, if I recall correctly, slide 55, Andrew, from your presentation is the one where we were only looking at the patients who crossed over from placebo. That's the one that's really small.

DR. POTTER: Yes. Could we get FDA slide 55 up, please?

DR. FARCHIONE: Well, even if we can't bring

that that up, that does explain the difference in that particular group. But the briefing numbers were from the original clinical study report in the --

Dr. Bossie, can you go over where those numbers came from so that we can try to reconcile the differences there?

DR. BOSSIE: Sure. Thank you for the question. The numbers in the briefing document came from the clinical study report with the original data cutoff.

So I'm not sure entirely which numbers from the applicant's presentation you're referring to, but I'm thinking that the difference may be that their numbers were coming from the most recent safety update cutoff, including actual patients remaining in the study, as opposed to the briefing document, which might have been referring to actual endpoint assessments that were available, because with the original NDA submission, because of the data cutoff dates, there were smaller numbers.

DR. FARCHIONE: Right. So we know where

ours came from. Perhaps the applicant can clarify where their number came from and why they have the different number.

DR. IYENGAR: I think I understand. Thank you. Thanks for the clarification.

DR. FARCHIONE: Okay. Thanks.

DR. NARENDRAN: Our next question is from Dr. Dunn.

DR. W. DUNN: This is Walter Dunn. I have a question regarding slide 11. This is from Dr. Bossie's presentation, although it is a statistical question, so maybe Dr. Potter can comment on it.

The one-sided alpha level 0.1 for the phase 2 study seems a bit high. I'm wondering is this common or was there some rationale for such a high alpha level?

DR. FARCHIONE: This is Dr. Farchione again. One-sided alpha 0.1, two-sided 0.05, I think that the important thing to remember here is that Study 114 was a proof-of-concept study. It was very small. They're looking for a signal to help

inform whether or not to go forward in development. This wasn't intended to be an adequate and well-controlled study to support a marketing application.

Oftentimes in these early proof-of-concept studies, you might see different thresholds, but as you saw in our analyses, we do dig in more deeply. And if it's being submitted in support of a marketing application, we're going to look at sensitivity analyses that will set an appropriate threshold for that purpose.

DR. W. DUNN: Okay. Great. That makes sense.

Then one other question. I think I wasn't understanding the difference between the long-term follow-up and the open-label extension. In Dr. Bossie's presentation, if I understand correctly, in the long-term follow-up, you still had two arms, 3.2 and the 9.6. But did I hear correctly that in the open label, everybody's being converted to 3.2?

DR. FARCHIONE: That's further down the

line.

Sorry. Go ahead, Dr. Bossie.

DR. BOSSIE: Thank you for the question, and I apologize for the CONSORT diagram. I tried to make it simpler.

Subjects were blinded to which dose they were on in the original plan, the long-term follow-up. As far as I know in the extension, what happened was, is after the applicant unblinded the data and did the analysis, and determined that 3.2 milligram looked more efficacious than 9.6, they told everyone in the 9.6 arm that they were going to be transitioning to 3.2. So at that point it became open label for everyone.

Does that answer your question?

DR. W. DUNN: Yes. It makes total sense. Thank you.

DR. BOSSIE: Sure. Thank you.

DR. NARENDRAN: The next question is from Dr. Krishna.

DR. KRISHNA: Hi. This is Sonia Krishna. Since the FDA has worked with this company for

years and had to adjust the trial and the protocols based on COVID, et cetera, did the FDA have any opinion on which dose or how to decide the doses? For example, why isn't there a 6.4 dose? Thank you.

DR. FARCHIONE: This is Dr. Farchione again. In terms of the design elements in choosing the 3.2-milligram dose, the second dose for dose exploration, we didn't have any particular concerns about choosing that dose one way or the other.

DR. KRISHNA: Thank you.

DR. NARENDRAN: Does that answer your question?

DR. KRISHNA: Yes. Thank you.

DR. NARENDRAN: Our next question is from Dr. Baker.

DR. BAKER: Thank you, Narendran.

This is Robert Baker, the industry rep. My question, I think, is for Dr. Potter, but possibly for Dr. Farchione.

Thank you. It was very helpful that you included in the preread the guidance around

substantial evidence, and I think a lot of the judgment here is going to come because of the orphan nature of the illness.

In the statistical considerations there, it talks about balancing expectations for, I guess, degree of evidence against harmful consequences of a false positive and the harmful consequences of a false negative. I don't know if you're permitted to give further guidance to us beyond what's written in that, but I was wondering that I would think of the harms in that being on the one hand the false positive probably related to toxicity or safety risks, and false negatives would have to do with are there other good treatments that are not available or would this be the one.

But can you guide us on how you would think about that, the balancing part of the risk of false positives and false negatives? Thank you.

DR. FARCHIONE: Sure. This is Dr. Farchione again. I'll start from the high-level perspective, and then if there is something more statistically specific that you would like to know, then I'll

pass it over to Dr. Potter.

In terms of how we balance that, we have a requirement, based on the Food, Drug, and Cosmetic Act, that when we approve a drug, it needs to demonstrate substantial evidence -- I mean, that's why we're here today; that's what we're talking about -- because we want to avoid any circumstances where inadequate, or flawed, or uncontrolled data could be used to support our regulatory decisions.

There are numerous examples where studies without prespecification, or studies that have undergone extensive post hoc analyses and purport to show a drug benefit, end up not panning out when you get to the phase 3 studies, the adequate and well-controlled studies. The results just aren't reproducible, and that's common in our randomized, double-blind trials.

We know that we need to be able to find useful beneficial therapies for patients with serious diseases. This is absolutely an unmet need, and as we noted, there's nothing available to treat hyperphagia in Prader-Willi syndrome. But

we're also aware of the dangers of approving an ineffective drug that gives false hope or could mislead them into using an ineffective drug and foregoing an opportunity to do something else or to enroll in a future trial of something else.

The difficult thing here is, again, we have this flexibility when it comes to rare diseases, but the other thing that we also need to balance is ensuring that we do still reach that substantial evidence threshold. It's not that there is a different requirement for rare diseases or that we require less evidence, it's that we just need to be more flexible in how we look at it.

So I think, really, the big question here is, considering the post hoc nature and all of these other things, do we have enough to be able to pin our hopes on that 3.2 milligrams or not? In terms of exercising flexibility, that's why we're here today, because it's not an easy question to answer and we do have to balance benefits and risks.

In terms of the safety evaluation of this

product, we don't really have any disagreements or anything like that with the applicant. That's why we didn't focus on safety very much in our presentation. Pretty much, our review is still ongoing in that regard, but we think that between information requests, and postmarketing requirements, or labeling, we can manage whatever safety issues there may be.

But when you're balancing benefit and risk, you have to start with benefit because, otherwise, there's no risk that's acceptable in the context of lack of benefits. So that's why we're focusing on that side of the equation today.

DR. BAKER: Thank you for answering the question. That's very helpful. I agree there's judgment, but I appreciate the way you laid that out.

DR. NARENDRAN: The next question is from Dr. Troendle.

DR. TROENDLE: Hi. This is James Troendle. My question I think is for Dr. Bossie, probably.

Is it true that in 2018, the agency

recommended a thorough dose-finding efficacy study -- is what I'm reading in the FDA write-up -- and I guess that would be a phase 2, but the applicant seems to have progressed directly into a phase 3 with multiple doses. And the talk of a U-shaped curve, had this been done in phase 2, could have been determined, and then validated or confirmed in a final phase 3 study.

I just wanted to make sure I'm correct in that understanding. Thank you.

DR. FARCHIONE: Dr. Bossie, do you want me to take that one since that was before you were assigned to the application?

DR. BOSSIE: Yes. I'd be relying on the minutes only, and you were actually here.

DR. FARCHIONE: Yes. Okay.

In terms of asking for dose finding, there were a couple of reasons there. One, we didn't want to pin all of our hopes of replication on a single dose. Two, we always want to be able to characterize whether there are dose-related adverse events, or whether increasing the dose increases

efficacy, or whether you can avoid certain adverse events with a lower dose. So that was the impetus for that request.

We didn't have an objection to exploring that dose response in the studies that were conducted. It's difficult in a rare disease population to do all of those individual separate studies that you might when you have more patients at your disposal. In this case, that more efficient trial design I think was fine. We didn't have an objection to that.

DR. TROENDLE: Okay. Thank you.

DR. FARCHIONE: You're right. If there had been a separate study, maybe we could have had more information about U-shaped or not. We could have potentially supported or contradicted that hypothesis further, but this is what we have.

DR. TROENDLE: Alright. Thank you. That's the end of my question.

DR. NARENDRAN: Thank you. Thank you, Dr. Troendle.

Our next question, another question from

Dr. Shapley.

DR. SHAPLEY: Thanks so much. This is Alice Shapley again. I have a question about safety. I think this is a question either for Dr. Bossie or Dr. Farchione, and it has to do with how the adverse events are counted.

It seems to me that one of the most promising aspects of carbetocin is how safe it is; that there aren't that many significant safety concerns. I'm just looking at some of the slides about the adverse events, and some of the ones that are included are scoliosis surgery. There's also one about pyrexia.

But specifically, I was wondering about scoliosis surgery. Presumably, there's no causal effect between carbetocin and scoliosis surgery, so I'm just wondering why events like that would be counted in the safety profile for carbetocin.

DR. BOSSIE: I can take that.

DR. FARCHIONE: Yes. This is Dr. Farchione. It's not that they're counted against them. We can agree with the applicant that that may have been a

preplanned surgery or whatever, but they are still captured in adverse event reports, so we're just presenting the data as it is. Whether or not it's related to the medication is something that we determined in our review.

DR. BOSSIE: I can add.

DR. FARCHIONE: Go ahead, Paul.

DR. BOSSIE: Thank you for the question, and I understand where it's coming from. I believe in some of those cases, those are counted as adverse events either because of the surgical procedure or the hospitalization for the procedure. So that sort of automatically counts as a serious adverse event even though, as you point out, there doesn't appear to be any causal relationship between carbetocin or an underlying condition in Prader-Willi syndrome.

Does that answer your question?

DR. SHAPLEY: Yes. Thank you. I was just wondering if you can confirm your impression that this does seem to be incredibly safe. I think Dr. Farchione was saying you have no concerns about

the safety profile.

Is that sort of where you're coming from as well, that there are no significant safety concerns?

DR. BOSSIE: At this point in the review, no. And as Dr. Farchione mentioned, any reviews ongoing and any issues that might occur would be something that we could address in other ways. We wanted to focus today on the efficacy question.

DR. SHAPLEY: Thank you.

DR. NARENDRAN: I don't see any more questions. We still have 9 minutes or more than 9 minutes.

Are there any other questions for the agency from the committee members?

(No response.)

DR. NARENDRAN: I don't see any raised hands. So if there are no further questions, I believe we should be able to break for lunch.

We will now break for lunch. We could reconvene at 1:30 p.m. Eastern Standard Time. Panel members, please remember that there should be

no chatting or discussion of the meeting topic with other panel members during the lunch break.

Additionally, there's a preference for everybody to please rejoin at around 1:15 p.m. to ensure that you're still connected before we reconvene at 1:30 p.m. Thank you.

So at 1:30 p.m., we'll see everybody back and start with the OPH.

(Whereupon, at 12:32 p.m., a lunch recess was taken.)

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

(1:30 p.m.)

Open Public Hearing

DR. NARENDRAN: We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that 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 the sponsor, its product, 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 participation in the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and the 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 for 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. Thank you for your cooperation.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce

yourself? Please state your name and any organization you are representing for the record.

MS. MATESEVAC: My name is Lisa Matesevac, and I'm a parent of a person with PWS. The FDA has expressed a desire to understand the patient experience, and I'm grateful for the opportunity to share with you today our son's experience with use of LV-101.

My name is Lisa Matesevac, and I'm the mother of a teenager with Prader-Willi syndrome. Upon diagnosis, a bleak outlook was painted, as we were told that his future behaviors would place him in grave danger and that he would have many limitations. But I think the hardest part was hearing that there was no treatment for the insatiable hunger that would dominate our future.

We eagerly began participating in research studies and clinical trials. I count myself fortunate to have had the resources to do this. To be clear, it is not simple or effortless. It is incredibly challenging for a person with PWS whose need for routine structure and reassurance of food

availability demand a carefully crafted plan at all times. It is a little like the game of Jenga, where at any moment if you move the wrong piece, the entire tower crumbles, and you are left with a person utterly unstable.

Despite the inherent challenges of the clinical trial, we made the choice to participate because we want a different life for our son. Before enrollment in the clinical trial, life with PWS held many challenges. Notably, his hunger drive dominated every action we took. Every moment of every day was planned to ensure food safety and security, not only because of PWS, but because he has the added danger of severe food allergies.

When he eats something to which he is allergic, he has anaphylaxis. He stops breathing. Before carbetocin, this happened to him twice because his biological drive to eat superseded all logic. All he cared about was that he was hungry and there was food.

Now, imagine sending him to school and hoping he doesn't gain access to food from a

backpack, from the lunch table, from the garbage can, and the infinite number of other places food is accessible, much of which could quite literally cause his death. I hope this paints a clear picture of the terror we lived with each and every day.

Additionally, his behaviors were difficult to manage. He frequently displayed explosive behavior outbursts resulting in breaking things, verbal arguments, refusal to comply, and difficulty transitioning. At school, he was not working up to his potential because his dominating obsession with food would prevent him from fully participating in learning. Teachers were fearful of him and his significant needs, and living with PWS was hard back then, especially in school.

Our lives changed when he began receiving the carbetocin. We see measurable improvements in behaviors. He is calmer and has more control over his emotions because the hyperphagia has markedly improved. Our previously anxious and overwrought son became peaceful. Use of this drug changed his

demeanor and allowed him to reach a potential he had not previously experienced because he is no longer perseverating about food.

One example of this change is a transition from a special education classroom setting to a general education setting, where he is earning all A's and B's. He is experiencing successes we didn't see for him before using carbetocin. He is able to work independently, and when frustrated, he is able to verbalize this rather than have a behavioral outburst.

His need for routine has diminished considerably. He tolerates uncertainty with ease. He is accepting of lengthier, unexpected delays in meals. Gone are the questions seeking reassurance about what, when, and where he will eat. Recently, for the first time ever, we allowed him to stay with family overnight without us present because we can finally feel safe knowing he will not food seek and he is not in danger.

On the way home from this visit when we stopped to eat, he told us he wasn't hungry.

Instead, he watched us eat while he chatted with us about all the fun things he did while visiting with family. He left his food untouched in front of him. He wasn't ill. He wasn't distracted by a video game. He simply wasn't hungry. Let me say that again. He wasn't hungry. He packed up his food for later, and we got back in the car to continue home.

I now see a hopeful way forward with this treatment and a path that can lead him to achieve things we didn't dare dream for him before carbetocin because he is unburdened by the hunger and the anxiety. It is meaningful for our son. It is life-altering. There's a safety now that we didn't have before this treatment.

I see carbetocin as a necessary tool that allows our son to shine through and for PWS to finally take a back seat. Currently, there are no approved treatments, but I urge you to approve carbetocin for PWS. It is safe, it is effective, and we need it, now. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. WILSON: My name is Deahl Wilson. First off, I just want to thank you for hearing my comments today. Like I said, my name is Deahl Wilson. I am the parent of Matthew Wilson, who's a preteen. He was born in 2009 with Prader-Willi syndrome.

After his diagnosis, my husband and I as his parents wanted more than anything to give Matthew every opportunity in life we could for him. Matthew was accepted into the carbetocin study back in November of 2018. We were very excited and hopeful about this opportunity. Our family desperately wanted this drug to deliver and promise helping Matthew get a step closer to a more normal life outside of Prader-Willi syndrome.

As months went on, on this drug, Matthew's behavior didn't show any improvement, and in fact, his behavior had become even worse. I was getting

constant calls of concern from his teachers at school due to defiant behavior that we hadn't seen in Matthew before; things such as dumping trash on his head; running from the school; and hitting his teachers.

He became obsessive with skin picking, nail-biting, even to the point his fingers would bleed. His anxiety was so extreme that at times we would have to tell him to just go to his room so that we could get a little bit of peace. He would get nosebleeds and nose sores, and even began developing breast tissue. And as you can imagine for a boy, this was quite traumatizing.

These were difficult experiences and were not the behaviors we had seen previously in Matthew, so being on carbetocin, my husband and I quickly felt a deeper burden having a child that had the special needs.

In addition to dealing with Matthew's behavior at home and at school, there were so many criteria that we had to follow exactly to keep the medicine as effective as possible. It quickly

became like another child needing special care. We had to keep the drug at a perfect temperature. We had to pick it up/drop it off every day at school. We had to remember to take the medication everywhere we went, still keeping it at the correct temperature. We had to remember to administer the drug before every meal.

But despite all of these efforts, we held out hope that carbetocin would do the one thing we truly needed it to do, which was lessen the effects of hyperphagia. Sadly, after months went on, carbetocin, we saw no change. In fact, after all this effort, we had to deal with the adverse side effects it had caused in Matthew and in our lives.

In addition to the negative side effects, carbetocin did not deliver any relief to his hunger, which was obviously the whole point of taking this drug. Our whole family was devastated that the carbetocin had not helped Matthew. We were so disappointed by the side effects and the lack of efficacy of this drug that we had hoped for, that would improve all of our lives, but it

absolutely did not help, but rather made matters worse for Matthew and our family, and our school situation. It did nothing to help the hyperphagia, which was the whole point of this drug, making it completely useless for us to continue the use of it.

So I ask, do we really want to waste our resources and provide false hope on a drug that doesn't produce the needed result, and in fact even adds negative results? Every Prader-Willi parent wants to find relief for that hunger and their Prader-Willi child in need. This drug does nothing that would prove to be effective in helping with the vital task of relieving the effects of hyperphagia.

This constant feeling of hunger is devastating, and we would do everything to help our child live a more comfortable life. I do want to thank you for your time for listening to a parent of Prader-Willi syndrome.

DR. NARENDRAN: Thank you.

Speaker number 3, your audio is connected

now. Please introduce yourself and state your name and organization you're representing for the record.

MS. SENESE: My name is Maggie Senese. I am a caregiver, and my daughter Bridget was born with PWS. I want to start by acknowledging that the concerns in the FDA briefing document are concerns that I have as well. Ultimately, carbetocin did not show statistical significance at 9.6 milligrams like it set out to do. I question the duration and the efficacy of the trial data for the reasons that are listed in the document. If carbetocin is approved there, there should at least be a confirmatory trial. It is important to ensure that only effective drugs are marketed.

Bridget is only four, so hyperphagia has yet to hit. Well, she was not a patient in the trial, I have researched and spoke to patient families. Like others, the hope of a treatment for hyperphagia has been alive since Bridget was born. I don't want just any treatment, but rather one that I'm confident is safe and effective for my

child.

While there are risks that I'm willing to take, it is important to me that those risks are taken with a treatment that has shown continued long-term efficacy. As was said earlier, there is no risk that is acceptable in lack of benefit.

At the PWSA conference, Elizabeth Roof stated that the primary analysis includes all patients who completed the baseline and at least one post baseline visit in week 2 or week 8 prior to March 1st. My interpretation is in some of these patients, the FDA would only review data for them up to a maximum of 2 weeks on the trial, and in some cases, only up to 8 weeks.

It's important to ensure that carbetocin will continue to be monitored and adverse effects will continue to be documented. Up to 2 weeks for some patients isn't long enough for a drug to be studied for long-term use. This isn't substantial evidence of effectiveness.

I learned Levo eventually transitioned all patients to the 3.2-milligram dose. We know the

lower dose outperformed the higher dose in trials, but no other doses were studied beyond them. What if even lower doses are more effective? What if fewer times a day is more effective? We just don't know. No other dosing schedules were studied. Has there been long-term data collection with all the patients once they all transitioned to the 3.2-milligram dose? These questions are all reasons why continuing the carbetocin is so important.

At the SPWR conference, Dr. Jay Cormier mentioned that at the higher 9.6-milligram dose, they saw off-target effects happening in individuals in the study. Some of those individuals ended up withdrawing from the study. He does add that at the 3.2-milligram dose, that they are able to avoid more of the off-target effects. I am concerned that he said able to avoid more and not able to avoid all of the off-target effects at the lower dose.

If these off-target effects led to some individuals withdrawing from the study, I'm not

sure this is a risk I'm comfortable exposing my daughter to. From reading the FDA's briefing document, I see that these could be psychiatric adverse effects, which correlates with the patient experience I heard, and an increased risk of psychiatric adverse effects is not a risk I am comfortable taking for my daughter. For some individuals with PWS, the rates of psychosis are higher. Is this a risk that would be worth it to them?

Levo has argued that the off-target effects were not evident in the phase 2 trial because of the shorter duration, and the impact of adverse effects came with a longer duration of exposure. How do we know the same won't eventually happen on the 3.2-milligram dose? Will the longer duration of exposure eventually cause off-target effects?

You are tasked with looking to approve a drug that could be used for a lifetime in a person living with PWS. Failure to follow up for the long term would be unethical. These are children's lives we're talking about.

If approved, I hope carbetocin continues to be studied. We know that it is not possible to predict all of the drug's effect during its clinical trial. A confirmatory trial would make sure that carbetocin is truly safe and effective for the long term, so it would not be a burden, but rather a practical solution.

Our community is excited about the prospect of a treatment and has shown great support for carbetocin. I do not believe that there would be barriers to a confirmatory study. The community support could translate the potential trial candidates for a follow-up study. Ultimately, Levo must provide substantial evidence of effectiveness, and this could help.

I understand the urgency of our community to have an option to try, and I want treatments for hyperphagia. But I need to know that they are safe and effective for the long term. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 4, your audio is connected now. Please introduce yourself and state your name

and organization for the record. Thank you.

MS. MOUREAU: Hi. I'm Katie Moureau. My 6-year-old Cade was born with PWS. Cade is not on carbetocin, as he's not in hyperphagia, nor has debilitating anxiety, but I know it's coming. I see all those with PWS eventually hit hyperphagia. This is a fear of mine. I fear of losing my child one day, as he cannot control his hunger and will eat himself to death.

With that said, I'm excited for the potential treatments for Cade and the PWS community, but he is my child, and I'm not comfortable with giving him a drug that has known psychiatric side effects. This is a risk that I am not willing to take, especially knowing carbetocin did not meet its primary endpoint with statistical significance.

We already know those with PWS are more likely to have psychiatric issues. Why would I want to try a drug that has known psychiatric side effects, such as increasing aggression and agitation? I would not. According to the FDA

briefing document, carbetocin has had patients dropped because of these psychiatric side effects.

In addition, the dosage submitted to the FDA for approval is 3.2 milligrams. How can we be sure this is the correct dosage for the entire PWS community for all ages without the flexibility to adjust? How can we be sure our loved ones won't have an overdosing side effect? On the other hand, how can we be sure that this is ultimately a high enough dose? As our loved ones stay on the drug long term, maybe it'll lose effectiveness and be too low to help with a debilitating anxiety and hunger for our children.

Now, I'd like to address the execution of this treatment. Is it feasible? It is a 3-times-a-day dosing with 2 sprays in each nostril with meals. Is this a reasonable expectation for families, at least during the school year? This would mean one treatment during the school day at school. Will schools be supportive in helping the parents with this, or will parents have to come in to distribute the medication each day?

Have other dosing schedules been examined to see if there is room for change in it to make it more accommodating for families? Are all families going to be able to correctly dose as directed? What happens if they can't?

We don't know the answer to these questions. Would you be able to easily give your child a nasal spray 3 times a day, with their meals, without ever missing a dose? I hope that more follow-up could be done to look at these questions to make sure that our loved ones are getting the full benefit and treatment.

Carbetocin also needs to stay frozen. We travel to see specialists all over the U.S. for Cade, and as we travel for family vacations. I don't know how we could easily travel with carbetocin while keeping it frozen on a road trip or cross-country flight. This is definitely a time when we would need it most because of changes in routine, diet, and schedule.

I'm afraid of having to keep it frozen will become a barrier to being able to travel with the

drug. Carbetocin does not seem like a medication that you can easily travel with. How would this be normal? Cade and either myself or my husband would be forced to skip and ruin a family vacation. If the treatment is able to go for a longer period without being frozen, that could help, but my understanding is that it wasn't trialed.

Further follow-up is needed here to ensure that carbetocin can remain safe and effective. These are some of the things we just don't know yet. Would not keeping carbetocin frozen be a possibility? Could dosing schedule be altered? What happens when doses are skipped? These were not tested. Addressing some of these variables in a clinical setting would give families like mine the reassurance that carbetocin will remain safe and effective if it's approved.

It is important that we continue to follow carbetocin with a confirmatory trial after approval. It is extremely important that the safety and efficacy of this drug continues to be monitored, and if the drug is on the market and

available to those with PWS, we don't know how this drug will affect those in the long term. PWS is rare, and with rare, they may have many unknown side effects, even the most common drugs. For the safety of our entire community, this drug needs to be studied longer term after approval.

Lastly, carbetocin has only been trialed in patients ages 7 to 18. What happens to those over 18? PWS will not just go away. The debilitating symptoms of PWS need to have the treatment beyond the ages of 18. This is the age where they're to become legal adults and hopefully be able to go off on their own.

In a typical kid, this is scary enough to think of, but when you add PWS and the added challenges, maybe carbetocin would help with that, but we won't know unless approval goes beyond the age of 18. If carbetocin works, and then it is stopped, will our nightmares return? Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 5, your audio is connected

now. Please introduce yourself and state your name and organization for the record.

DR. SCHWARTZ ROTH: Thank you. I have no financial relationship with the sponsor. My name is Lauren Schwartz, and I'm here today to speak about my experience as a mother of a young adult with Prader-Willi syndrome and as a clinical psychologist at the University of Washington.

My daughter participated in a 2014 phase 2 carbetocin trial when she was in middle school. At that time, there were constant struggles to manage her stressness, anxiousness, and food focus. During the trial, we noticed impactful, positive changes in her challenging PWS behaviors, and tended to decrease distress and decreased food focus. This gave us a glimmer of what life could be like if carbetocin was made available to our loved ones. Unfortunately, she could not participate in the phase 3 trial, as she was too old.

Now I'm going to put on my psychologist hat and talk a bit about the trial results from that

perspective. As you are aware, PWS has many challenging behavioral features such as hyperphagia and anxiousness, both of which were key outcomes of the LV-101 trial. Anxiety, as parents refer to as anxious behaviors, is highly significant in PWS and impacts daily function.

This very important feature in PWS was well captured in the LV-101 study by the PWS Anxiousness and Distress scale, or the PADQ, which was used as an endpoint in the LV-101 trial. The PADQ items are consistent with a recently published article from experts in the field on consensus definition of PWS behaviors, including the unique aspects of anxiousness in PWS. The qualitative interviews conducted with over a dozen PWS caregivers as part of the development of the PADQ confirmed that the items captured important behaviors individuals with PWS displayed when anxious.

As a PWS parent for 22 years, and as a psychologist for longer than that, I can confidently say that the behaviors the PADQ captures are very significant and represent the

essence of anxiousness and distress in our loved ones with Prader-Willi syndrome.

Treating hyperphagia and anxiety behaviors have also been identified as a top priority for the PWS community. Several published studies have been shown that caregivers identify hyperphagia and other PWS associated behaviors, such as anxiousness, as the most important symptoms that urgently need treatment. A recently published study involving individuals with Prader-Willi syndrome found that they also prioritize treatment that would reduce their anxiety, distress, as well as their hunger.

Given that there are no approved treatments for PWS associated hyperphagia anxiety, these studies highlight the profound unmet medical need. LV-101 offers to be an important and safe step towards addressing this unmet need for our community.

Lastly, as it's been mentioned, many families are using psychiatric drugs, other drugs, and over-the-counter supplements to try to manage

the difficult PWS associated behaviors already. These drugs and supplements have not been rigorously tested for safety or efficacy in the PWS population, and many are known to have negative side effects, but parents are desperate to try anything that might help.

One of the risks of not recommending approval for LV-101 is continued off-label use of drugs and supplements that could cause further harm to our loved ones with PWS. Additional risks of untreated hyperphagia also include, as you've heard, accidents, choking, and gastric rupture for our loved ones.

It is also important to consider that the burden of clinical trials in our population is tremendous. Additional evidence cannot be practically required for this drug by another large clinical trial. It would take years to complete an additional trial, putting people with PWS at risk for serious health issues, as well as deaths related to the challenge of untreated hyperphagia.

The stories from today and the written

submissions reflect that many parents have seen observable positive changes in hyperphagia and anxiousness in their loved ones who participated in the trial. Having a medication such as carbetocin, with even modest improvements in some individuals with Prader-Willi syndrome and the key challenging behaviors with a low risk of side effects, would be a crucial tool to allow individuals with PWS the potential to have greater independence and improve quality of life. LV-101 offers the possibility of effectively and safely managing some of the challenging aspects of PWS.

DR. NARENDRAN: Thank you.

Speaker number 6, your audio is connected now. Please introduce yourself and state your name and organization for the record.

MS. HEDSTROM: Thank you for this opportunity to speak in support of the approval of carbetocin for the treatment of PWS. My name is Susan Hedstrom, and I'm the executive director of the Foundation for Prader-Willi Research and mother to a 12-year-old son with PWS.

The FDA has asked for the patient perspective, and here it is. Our families need access to carbetocin. Currently, there is no effective treatment for PWS associated hyperphagia and anxiety, highlighting a significant unmet medical need. The improvements that have been seen with the treatment of carbetocin are meaningful to people with PWS and their families.

In the absence of a cure, we would welcome treatments that alleviate even just some symptoms of PWS. A beneficial effect in even a portion of people with PWS would be significant due to the lack of other effective treatments. For many, even a modest improvement in hyperphagia would be life-changing, allowing for more independence and improved health and quality of life.

The PWS community is tolerant to risk. In fact, families have indicated they are willing to accept considerable risk in exchange for modest improvement in hyperphagia. Risk is not new to our community. We live with risk every day. PWS is associated with increased mortality with a median

age of death of only 29.5 years. Common causes of death include complications of obesity and hyperphagia-related accidents, such as getting hit by a car when running away to get food, or choking while rushing to eat food, and gastric rupture due to excessive food intake.

In addition, many families are using psychiatric drugs, compounding oxytocin and buying supplements such as CBD off the internet to try to manage PWS associated behaviors. None of these drugs have been rigorously tested for safety or efficacy in the PWS population, and many are known to have significant side effects. Carbetocin offers the possibility of effectively managing some of the most challenging aspects of PWS with a lower risk of side effects compared to the medications that families currently employ.

We appreciate that the FDA needs to do what it can to ensure a drug is effective prior to approving it, but from our perspective, the potential for a type 2 error that is not approving a drug that ultimately turns out to be safe and

effective is just as important and requires equal consideration. In this case, we have a drug that has an excellent safety profile in PWS and has persuasive evidence of efficacy in domains that are critically important to our patient population and for which there are currently no effective treatments; zero.

Our PWS community urges you to consider the flexibility that the FDA is afforded in evaluating new treatments for life-threatening rare diseases with high unmet need. The guidance for industry on demonstrating substantial evidence of effectiveness specifies that for rare disease, FDA may interpret the substantial evidence standard flexibly, considering the harmful consequences of false negative results and, in fact, the FDA has a strong history of doing so for orphan products.

Finally, in an ideal world, we'd be able to quickly complete large additional trials to collect additional proof of efficacy, but our world is far from ideal. Participating in clinical trials is a tremendously difficult undertaking for our loved

ones with PWS who have significant behavioral issues, anxiety, and medical challenges. Many of our families are barely hanging on, and completing additional large studies for this drug is not realistic.

Our community got the CARE-PWS study done despite the rarity of condition, despite the challenges of PWS, and despite a global pandemic, which is still ongoing. It would be an undue burden to ask our rare community to undergo additional years of clinical trials when there are ways to continue to acquire data on effectiveness post-approval, while giving the community access to this important drug.

In this case, we believe the potential harm of not approving carbetocin far outweighs the current uncertainty of benefit. We have seen a great safety profile for carbetocin. Let us give this drug a chance. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 7, your audio is connected now.

MS. WOLFER: Thank you for giving me the opportunity to share our experiences with LV-101, or carbetocin as it is known in our family. My name is Roxanne Wolfer. My son, Trevor, now 17 years old, diagnosed with Prader-Willi syndrome at 3 weeks of age, has been participating in this clinical trial for 22 months. During this time while traveling extensively and with occasional missed doses, he has not had any adverse side effects while his hyperphagia and anxiety have decreased significantly.

When Trevor was a small child, I would read stories of other people with Prader-Willi syndrome who died because of gastric rupture. I wondered, "Would this be our story? In a moment of no one watching, is that how this would end? How would it feel to be so hungry that you would do anything to find a bit of comfort?"

We knew once hyperphagia began, it would never leave. Before carbetocin, that was an always present threat because no matter how much Trevor ate, not only was he unable to feel full, he still

felt hunger. He could never say that he had had enough, and what would happen if I wasn't watching that one time when he had the opportunity to eat enough to actually burst his stomach? Now, because of carbetocin, he has finally had the opportunity to know what being full for a moment feels like. He still loves to eat, but the threat of death is alleviated.

At the beginning of this clinical trial, I was asked to keep track of how often Trevor was asked about food in a day. It was so often that I couldn't keep track of the number and stay sane. Now with carbetocin, his anxiety and preoccupation around food has greatly improved.

Because of all the food everywhere in our society, we used to spend a lot of time coordinating care with others so he wouldn't be in danger whenever he was away from us as parents. At youth group, we would always ask someone to watch him and send us pictures of whatever food Trevor had. When I dropped him off at Spanish class at a private school, I would always watch to make sure

he didn't go through the lunch room unattended.

Carbetocin has given Trevor the ability to self-regulate his food intake at a safe level so that he can now be independent at youth group with his peers, and I no longer worry when I drop him off outside the school building for classes. Independence of any sort is an immeasurable treasure for our loved ones.

Before carbetocin, we kept food at home locked when we were not actively monitoring Trevor. The environmental controls that we had in place have been learned and employed for years. We have had a hard time changing or removing any of them because of the fears and stress we have been living under. However, after being on carbetocin, we gave Trevor some rice cakes that were his to eat whenever he wanted. He actually let them sit in the cupboard until they were inedible, and I threw them away.

As a homeschooling family, Trevor has plenty of time to spend with his four younger siblings. They see the greatest benefits of carbetocin in the

ways Trevor responds to changes, even the exciting and fun changes in our routines. The amount of unnecessary questions and need to control his environment is not so overwhelming because of the lower level of anxiety due to carbetocin. They can now enjoy going on field trips and outings with him instead of constantly being prepared for an outburst. I feel it has given us glimpses of who Trevor is without some of the limitations of Prader-Willi syndrome.

I asked Trevor what he would like me to share with you. He said that one of the greatest benefits to him personally is that with less anxiety in his life, it helps him reduce skin and nail picking. Skin picking in the PWS population is a self-soothing but dangerous reality because of the high level of anxiety. The self-injurious behavior results in open sores and wounds that can become infected and last for weeks or months, sometimes requiring medical attention.

Trevor says he also enjoys more independence during all social events where food is served. He

now goes through the food line at potlucks safely by himself. He feels much better as a 17 year old without having a parent always at his side.

Once again, I'd like to thank you for asking for our perspective on LV-101. Our families need you to approve carbetocin so we can enjoy the time we have with our children. Our loved ones with Prader-Willi syndrome need you to approve this treatment to save lives and increase independence. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 8, your audio is connected now.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Our non-profit think tank scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products.

My perspective today is based on my training in clinical psychology, epidemiology, and public health and as a former faculty member and

researcher at Yale and Harvard. I also have a brother born with a serious disability, so I have that perspective as well. In my current position, I frequently testify about the safety and effectiveness of medical products and have participated in more than a hundred FDA advisory committee meetings over the years.

Testimony from family members in the open public hearing has been compelling, and even those experiences do not consistently support approval. Unfortunately, the evidence provided by the sponsor today is among the worst I've ever seen and would set a terrible precedent that would compromise the reputation of the FDA and the public's confidence in FDA approval.

The sponsor and parents have done an excellent job of explaining why hyperphagia is a terrible condition, and families urgently need help to treat or manage it. But that's the point; the treatment needs to work and not make matters worse. It's not appropriate for the sponsor to try to make this panel or the FDA feel guilty for expecting an

appropriate level of the scientific evidence.

We can see in the FDA briefing document the many ways that the FDA clearly told the sponsor what type of data they needed to provide to merit approval, and that the sponsor repeatedly ignored that advice. The pandemic interfered with the study, but that's not the main problem. The studies had other serious inadequacies, and that's why they do not prove efficacy for this very serious chronic condition.

None of us are asking for a perfect study. We're asking for a good study of an adequate number of patients studied for a reasonable amount of time with clinically meaningful and statistically significant results, not one-sided at the 0.10 level, and not a study that doesn't control for type 1 error.

The phase 2 study was only 2 weeks and only administered the higher dose. Of the only 38 patients randomized, six had major protocol violations, including being given the wrong drug. All the patients were white, except one, and only

14 were boys, and that includes placebo patients. So this was really a small study.

The phase 3 study was only 8 weeks long for the placebo-controlled portion. Neither of the two primary endpoints showed a statistically significant improvement for the higher dose, and the open-label part of the study is not good science. For example, only one patient receiving the lower dose stayed in the study for a year. If the drug worked, wouldn't more patients have stayed in the study?

Adverse events leading to discontinuation were primarily psychiatric, as you've heard. For the phase 2 trial, one child discontinued due to agitation, increased aggression, increased hyperphagia, and a broken bone. And there were only 20 patients that got the drug in that study, so that's a 5 percent serious adverse event rate. In the phase 3 trial, once again, 5 percent of patients taking the higher dose discontinued during the placebo-controlled period, in that case, due to impulsive behavior and tachycardia.

In the real world, will these psychiatric adverse events be dealt with adequately? This morning, the sponsor also mentioned one child who started acting out sexually. That can be very serious. Psychiatric adverse events are a real concern given how desperate parents are to give the drug a chance to work, but if there is no proven benefit, these adverse events matter.

In conclusion, I agree with the FDA's criticisms of the evidence. Families urgently need help, but the company should spend a few more months to establish whether this drug is effective and safe for more than 8 weeks before FDA considers approving it. Meanwhile, to help those families who need it, we encourage the sponsor to facilitate free access to this experimental treatment through FDA's expanded access program, which is more appropriate than approval at this time. Thank you very much.

DR. NARENDRAN: Thank you.

Speaker number 9, your audio is connected now.

MS. FISCHER: Hello. My name is Rachael Fischer, and my husband and I enrolled our son in the LV-101 clinical trial in February 2019 when he was just 7 years old. I am not receiving any kickback or incentive to participate on this call today. Moreover, we have no issue administering carbetocin at school, home, or during travel, including international travel for the 2 years and 8 months since we have been in the trial.

To fully explain how LV-101 has impacted our lives, I want to briefly recount the reason we pursued treatment. Our son was diagnosed with PWS when he was around 2-and-a-half years old. As a spectrum disorder, we hoped his later diagnosis would indicate higher functioning. Unfortunately, we soon realized that timing of diagnosis is not correlated to onset or severity of symptoms.

One of the criteria for the clinical trial was having a child in hyperphagia. Prior to his diagnosis, we thought hyperphagia was only the unrelenting intense pursuit of food, however, when you have a 7 year old with hypertonia and speech

issues, hyperphagia looks a little bit different. For us, it included rigid routines to accommodate a consistent meal schedule; inability to enjoy basic life moments like travel, play dates, outings to the pool, the park, or the zoo, without the constant obsession over meals or stealing food.

Changes in routine would rise hyperphagia. He choked on multiple occasions due to the rapid ingestion of food, requiring the use of the Heimlich maneuver on countless occasions. In addition to hyperphagia, he was also severely anxious. He had OCD-like behaviors. He was hoarding. He had prolonged meltdowns and aggression.

As parents, we were desperate. We took sugar out of his diet. We engaged in weekly behavior therapy. We administered methylphenidate to help him with impulse control. We gave medical grade CBD oil for anxiety. We increased speech therapy to help him use his words over his hands. We locked our stairs, our fridge, our trash can, our pantry.

At the young age of 7, PWS was completely controlling our lives. It was at this point we decided to pursue enrollment into a clinical trial. The one we chose was LV-101, and we will forever be thankful. Jude is now a thriving 10-year-old boy. Removing hyperphagia unlocked potential in ways we never expected, and moreover, we experienced no side effects.

For most individuals with PWS, the symptoms of hunger, aggression, rigidity, and other adverse behaviors increase over time. PWS becomes the definition of their journey. With our son, at 10 years of age, he's thriving and loved by his peers, family, and educators alike. We recently sat in an annual IEP meeting where all seven of his providers expressed that Jude is their favorite, and I quote, "an absolute joy to work with." His previously 80-page IEP is now just 29 pages because he no longer requires a behavior intervention plan.

By reducing hyperphagia, our son has better self-regulation, better executive functioning, and can read social cues. He has a funny sense of

humor, and he now knows how to make and be a friend. Moreover, since the trial, we haven't had to utilize the Heimlich maneuver because he eats more slowly, he engages in conversation during meals, and he can walk away from the table when he's full. He also now has food preferences and will not eat something that is not appetizing.

We never experienced this before. Because of LV-101, he's now brave, courageous, confident, engaging, and is beginning to experience the joy of being a 10 year old who can be free of the constant unrelenting hunger that once shadowed every moment of his life.

Conquering hunger has allowed our son to dive into the depths of his natural interests and skill sets, helping him discover new untapped potential. We now see he's capable of building Lego kits, riding a bike, skiing, fishing, golfing, playing video games, and truly loving nature and science. He is inquisitive and can focus on learning opportunities that were previously lost on him.

Truly, carbetocin has been such a gift to our family and our community, and we urgently ask you to recommend approval of this treatment. Please, help us open the door for people living with PWS so all can find freedom from this cruel disorder. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 10, your audio is connected now.

MS. RIVARD: Good afternoon. My name is Paige Rivard. I am the CEO of the Prader-Willi Syndrome Association USA, but most importantly I'm mom to Jake Rivard, an 11 year old living with Prader-Willi syndrome. I'm honored to speak with you today in support of the approval of LV-101.

Prader-Willi syndrome has a devastating and life-threatening impact on families and individuals living with PWS. At PWSA USA, we speak with thousands of families each year, and many of them are in crisis. They are dealing with the effects of their child's constant state of hunger, anxiety, and behaviors associated with the syndrome for

which there are currently no treatments.

Hyperphagia and anxiety are by far the largest concerns for our families. These symptoms can limit PWS individuals' ability to engage in normal daily activities and live an independent life. Parents and caregivers are constantly monitoring, thinking about, and planning their days around food, hoping to deter any adverse behaviors, such as the meltdown in the grocery store and outbursts in the restaurant, or any number of other situations that may cause anxiety and distress.

School is also a very common place where hyperphagia can disrupt daily activities. Individuals must be monitored constantly to make sure that they are not obtaining food from peers, teachers, or even trash cans. Parents must seriously advocate for their school to not use food as rewards or manipulatives in the classroom. The constant state of hunger makes it difficult for children with PWS to focus and learn, and can lead to disruptive behaviors in the classroom.

All of this can cause families to feel

isolated. We have heard from parents who have had to leave their careers to take care of their children with PWS. The impact to the entire family, including siblings, is significant. Caregiver burden is a serious issue in our community, and the symptoms of PWS are relentless.

It is also important to note that with PWS, clinical trials are often difficult for our community. As a rare disorder, PWS has a small patient population. Trials often involve travel, which can be difficult due to the disruption of routine, additional access to food, and concern for increased behaviors.

Today, we are asking for a choice. We have heard numerous ways families and individuals with PWS are impacted. We are asking for the approval of LV-101 to give our loved ones a chance because today there are no other treatments that address these symptoms. Given the unmet need and safety profile, we believe even a modest improvement in these symptoms could be life-changing for individuals with PWS and their families.

From the entire PWS community, we thank you for your time and opportunity to speak with you today, and for your consideration and approval of LV-101. I will now turn it over to Rob Lutz.

Rob?

MR. LUTZ: Thank you, Paige.

I have a 21-year-old daughter with Prader-Willi syndrome. You have read and heard today about all the yucky stuff about PWS, and all of it is true. But what is harder to describe is all the good stuff.

I am incredibly proud of my daughter with PWS. She may not have graduated from high school with a high GPA, with AP class credits, or with varsity letters, but she did win an award, which is given to the student that, quote, "Best Exemplifies Strong Work Ethics, Be Respectful, and Has Overcome Adversity to Be an Inspiration to Others." My daughter is not unique when it comes to PWS. Many win awards for their effort, their dedication, and their spirit. What can make a parent more proud?

Every day in school was hard for Isabel,

much harder than for a typical child. Academics were hard, and friends were hard. Being surrounded by food was hard. She would come home exhausted from just trying too hard, and yet we as a society and as parents ask for more. "Can't you just not steal food? Can't you just not worry about the field trip tomorrow? Can't you just not cause a scene at dinner in public?"

So my hope and belief is that carbetocin and other potential treatments for Prader-Willi syndrome will give them a better chance to realize a payoff from their efforts, to allow their hearts and the good stuff to shine through.

I am not expecting a cure for PWS, but it would mean more than I can express in words if my daughter could have a chance. Could she, despite our horrible luck at conception, have the opportunity to be happier, and less anxious, and less distracted by food?

I hope I have helped put into context what carbetocin could mean, and what individuals with PWS deserve, a safe treatment option that offers

them the opportunity to be more successful when they try so hard. Don't you think they've earned it? Thank you.

DR. NARENDRAN: Thank you.

Speaker number 11, your audio is connected now.

MS. McGHEE: I'm asking for your approval of carbetocin as a treatment for PWS. My name is Kathryn McGhee. I'm a parent of an adult with PWS, and I have no financial relationship with the sponsor. My daughter Hannah has been in the CARE-PWS trial for 33 glorious months, and by glorious, I do mean glorious if I compare it to our life prior to carbetocin. Hannah has experienced zero side effects and she has never missed one single dose. It is far too important, so she would never allow us to forget.

Hannah is 20, the youngest of our four children, and she was diagnosed with PWS at 12 days. She has exhibited food-seeking behavior since she was only two. The first time we caught Hannah eating trash from the kitchen, we were

shocked. We learned to lock the trash in the pantry and throw away food in the disposal. I was horrified and disgusted after finding the garbage disposal part displaced every morning. The camera revealed Hannah was searching for food in the garbage disposal.

We've then made sure the disposal was always left empty, but that led her to early-morning visits to our back-alley trash bins. My neighbor's found her multiple times eating spoiled trash. Her hunger was so bad, she would eat anything to try and satisfy it. Some of the more disturbing things she consumed were 24 frozen waffles, 3 large cans of orange juice concentrate, and once at a park, she ate a cupcake that was completely covered in ants.

Hannah loved visiting her grandma, but it became too difficult to keep her safe. Despite sending locks and cameras, she would always gain weight. Once she gained 15 pounds during a two-week visit. She never got a break from the constant feeling of starvation, so she spent most

of her time thinking about how to get more food. It ran her life, and ours. Our family truly struggled under the burden of PWS.

When Hannah started carbetocin, everything changed. At the start of the trial, she was at her heaviest weight of 137 pounds. Shortly thereafter, her food-seeking behavior ceased. She slowly began losing weight, even getting too thin at 107 pounds. We actually had to add food to her diet, which is unheard of with PWS adults, who usually need more food restrictions, not less. She is steadily holding at 118 pounds.

Since starting the trial, Hannah has not once touched the garbage disposal. Her nightly visits to the fridge completely stopped, and she finally sleeps through the night. Her every thought no longer revolves around food, leaving her more relaxed and less anxious. She has more self-control and independence. She can transition better, adapt easier to change, and is really able to enjoy so much more of life, family, and friends. The old Hannah would eat each and every chip she

ever found in her brother's room. The new Hannah brings us the chips uneaten. She just wants a picture of holding the bag with a huge smile on her face, so we can shame that brother for leaving food out.

I used to worry about her future all the time, but now, yes, I still worry, but I no longer have the constant debilitating and terrifying fear that my daughter might eat herself to death, and we no longer have to supervise her 24/7. It's hard to describe as a mother what a relief and a blessing this has been. Hannah's anxiety has gone down several levels, and our whole family is in a much better place. It has lessened the burden and made all of our lives better. It is not perfect, but the improvements have been life-changing.

It would be devastating to Hannah and her family if carbetocin is not approved. "The new and improved version," says Hannah, "is infinitely better." We beg you to please approve carbetocin as treatment for the most debilitating symptoms of PWS. You have the opportunity to change and

possibly save an untold number of lives. Please take it. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 12, your audio is connected now.

MS. McDOUGALL: Good afternoon. My name is Amy McDougall, and I'm mother to Noelle, who is 19 and diagnosed with Prader-Willi syndrome. I'd like to thank you for the opportunity to share today about our family's experiences as we strive to meet the needs of our daughter.

As Noelle was considered failure to thrive as an infant, our primary concern was getting enough nutrition in her. But as you can see from our first slide, when her hyperphagia emerged, the traumatic change was difficult to process. The physical impact of the hyperphagia was unmistakable and places our children at extreme risk.

Our family's lifestyle changed in ways my husband and I never would have dreamed when we began having children. Noelle would cry and ask perseverative questions about when she could eat

and what she could have. She wouldn't sleep at night because she would be up at night seeking food. We put locks on our kitchen with keys in the lock box, and we had to change the codes every so often so she wouldn't figure them out. We installed cameras and motion sensors.

Noelle would cry and punch herself in the stomach and say things like, "Shut up, belly." She needed a one-to-one at school to keep her safe from stealing or taking food from the garbage. She was unable to participate in class parties because the presence of additional food was so stressful to her. One teacher shared about the fact that opening a cough drop across the room [indiscernible] to Noelle being so distracted that she missed 20 minutes of a lesson.

It was incredibly difficult to manage her need for routines around food in her food seeking to the point that it interfered with our ability to participate in family and community events. Despite our best efforts, Noelle found ways to circumvent our food security. She actually stole

one of my credit cards, set up a Door Dash account, and instructed the provider to park at a place out of sight of the cameras.

When people would ask me about Noelle's needs, I would often just shrug and be like, "Well, that's what we do." I'm a school psychologist by profession, and I thought that I was well equipped to do what our family needed. A defining moment came for me one weekend, where I realized the extreme amount of daily stress the hyperphagia created for our family.

At a hockey tournament, I realized I didn't know where Noelle was, and I started to have a panic attack as I cycled through all the dangerous possibilities that Noelle's hyperphagia could lead her to. I could only start to breathe again when my husband reminded me that we hadn't brought Noelle with us that weekend. We had left her with a family member.

The emotional and physical toll that hyperphagia takes on, not only the affected individual, but on families, is immense. With no

effective treatment on the horizon, our hopes were limited. In contrast, carbetocin has given our family a whole new perspective. Noelle's ability to attend school had improved. She started showing stronger academic growth. Her grades were better. She actually graduated from high school with a Regents diploma last June, which is the highest awarded in New York. She felt comfortable enough to enjoy attending events such as her prom, even though there would be food there.

Her anxiety has decreased to the point that she can actually enjoy family gatherings and events. This summer, we were actually able to go on vacation with our full family, and Noelle was able to go with the flow enough that she could enjoy what was going on with a minimal amount of redirection. My husband and I paused at one point and said that we knew that we wouldn't have been able to even stay out that week if we didn't have the carbetocin. We would have probably had to go home, given the amount of stress that she would be under.

For me, however, what's even more meaningful than my own reduced stress is the fact that my daughter is actively advocating to remain on carbetocin. She speaks about her reduced stress, her ability to enjoy activities, and the successes that she's experiencing. While she still needs external structures to keep her safe, she's talking about possibilities for her future that she wasn't able to focus on previously.

She is anxiously awaiting the results of this hearing, as she desperately does not want to return to the hunger and anxiety-dominated life that she suffered before carbetocin. Thank you so much for your time.

DR. NARENDRAN: Thank you.

Speaker number 13, your audio is connected now.

MS. TWEEL: Good afternoon. My name is Sasha Tweel. I am mom to Sophia Tweel who has Prader-Willi syndrome, and I have no financial affiliation with anyone. I'm here speaking on behalf of my daughter.

I'd like you to pretend with me for just a moment. Pretend that you're the hungriest you've ever been. Maybe you were on a diet, maybe you were fasting for a medical procedure or religious reason, or maybe you simply didn't have enough money to access food. How did it make you feel? What were you thinking when you were unable to eat?

I'm willing to guess that it was difficult to think of anything but your next meal. If you're anything like me, you fantasized about exactly what you were going to eat and how wonderful it would be to finally feel satiated, to finally feel full.

Now imagine for just a moment that you were never able to achieve that relief, that you would never feel full. What must that feel like to never have those thoughts, that natural drive to eat to fullness, fulfilled? I wonder about this a lot, as I know that it is my daughter Sophia's reality. How heartbreaking it has been as a parent to not be able to make this better.

January 2, 2019, Sophia and I traveled to Nashville to begin her participation in a

carbetocin clinical trial. During that visit, Sophia was very anxious. She had many repetitive questions for the team mostly around timing of the process, but the underlying current always being, "When am I going to eat next?"

One of the biggest challenges for families with a loved one with PWS is deviating from any normal schedule, as anxiety skyrockets, and unexpected departures from a plan often lead to uncontrollable meltdowns, as the person with PWS is simply too overwhelmed to deal with the unknown.

Looking back, that first visit was painful because I could see clearly what we were up against. The initial questionnaire showed me how much of her behavior was ruled by her fear and anxiety. While I was still hopeful, I felt a bit taken aback considering the scope of what I was hoping would change. And after that beginning, we returned to Nashville every few weeks to check in, and at first I didn't noticed much change. The visits got easier, but I attributed that to becoming a new routine, and Sophia becoming more

accustomed to the process.

But then things started shifting, slowly, but there were differences. When there were shifts in the plan, her adjustment to the new plan was less difficult. Always ruled by a very rigid timetable because of her hunger, Sophia stopped asking what time it was all the time. She would forget to ask for a snack. She could play with her friends and not need to be right next to me at 5 p.m., asking when dinner would be ready. In fact, one night when we were at a barbecue, there was food everywhere, and she didn't ask for anything to eat until after 8 p.m. This was unheard of before she began taking carbetocin. It felt like a miracle.

In early December 2019, our family took a week-long vacation to Disney World. We had been there once before, and it was a total disaster. There was such a focus on food and when everything would happen, that it was impossible to enjoy the delights all around us. I had wondered if it was truly the most magical place on earth. We were so

miserable, and no number of princesses could fight the monster that was my daughter's insatiable hunger.

But this time it was different. It was different because we had carbetocin. Sophia was wondering when we would eat, but it didn't rule our days. We were able to make our plans and enjoy all the things we were there to see. Princesses, and characters, and swimming, and shows were equally as important as where we would be eating dinner. And sometimes we lost ourselves so fully to the experiences, that it was easy to forget that we were different than the other families all around us. That was true magic, a vacation that could be enjoyed, not ruled by food, anxiety, and fear.

When I asked Sophia what she might like me to tell you about her experience with carbetocin, she said she wanted you to know that she feels better. "I'm not so hungry all the time." In Sophia's case, the hunger has not disappeared, but it has significantly diminished. She still asks for food, and what will be served, and when, and

makes her plans around it. But if things change or we don't know the answer to that question, it's ok. That is such an improvement that we cannot imagine going backwards to when things felt so frightening and out of control.

There is no other treatment available to help my daughter manage these unmanageable feelings. We ask that you please help us to help our daughter, and all of the other individuals who struggle with PWS, and approve carbetocin for this use. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 14, your audio is connected now.

DR. DYKENS: Thank you. My name is Dr. Elizabeth Dykens. I'm a clinical psychologist and professor in Vanderbilt University's Department of Psychology. I have no financial relationship with Levo, although Vanderbilt was a site for the LV-101 trial.

My publications have focused on the behavioral features and trajectories of persons

with Prader-Willi syndrome. Today, I want to address two issues, the development of the HQ-CT and the course of hyperphagia and behavior problems in PWS.

First, my colleagues and I developed the Hyperphagia Questionnaire because previous efforts to measure hyperphagia were not successful. Two of these five failed efforts included, first, giving people with PWS unlimited access to food and measuring your food intake, which was deemed unethical and too risky by all of my university IRBs; and second, using self-reports of food-related behavior, which is unreliable, as individuals with PWS often lie about their food consumption in order to avoid getting in trouble for sneaking food.

As such, we developed the Hyperphagia Questionnaire, using FDA guidelines for patient-reported outcomes. Based on our extensive clinical experiences of PWS, we generated a bank of pertinent items, administered it to parents, and solicited their feedback, including behaviors that

we may have missed. We used this feedback to revise the questionnaire, administered it to another large cohort of parents, and conducted psychometric and factor analyses of their responses. With input from the FDA, the Hyperphagia Questionnaire was subsequently adapted for use in clinical trials by only including items that tapped observable behaviors.

The HQ-CT has now been successfully used as a primary endpoint in multiple PWS clinical trials. In addition, preliminary studies find that the HQ-CT relates to biomarker indices of hyperphagia, specifically with eye-tracking measures of food versus other stimuli in visual exploration tasks and visual event-related potentials of food stimuli.

A second issue relates to the possible attenuation of hyperphagia with advancing age. Our lab at Vanderbilt has evaluated 350 people with PWS, age 4 to 66 years. We find that despite some fluctuations in hyperphagia due to stressful life events or changes in food security, that once

hyperphagia onsets in childhood, individuals remain hyperphagic throughout the life course. None of our 350 participants show reduced hyperphagia, consistent with a proposed and very rare PWS nutritional phase 4.

Indeed, our recent interview study of adults with Prader-Willi syndrome, referenced earlier by Dr. Schwartz, overwhelmingly indicate that their hunger is unrelenting. One young man stated, "The food around me, I gotta have it, but it's like a poisonous drug that kills me." Another offered, "I'm surrounded everywhere by fast food I shouldn't eat. I struggle so hard." And from a young woman, "Food, it just calls out to me. I can't do or think of anything else until I eat it."

These reflections are supported by HQ-CT longitudinal data that were presented earlier today, as well as follow-up analyses of only those individuals assessed two or more times. These analyses showed an increase in hyperphagia in adolescents and young adults and relative stability than high HQ-CT scores among older adults.

Relatedly, our longitudinal data revealed an escalation of psychiatric, behavioral, and emotional problems with advancing age in PWS, which complicates the reporting of psychiatric AEs as related to carbetocin.

In brief, HQ-CT was developed with FDA guidance, filled the gap left by previous failed efforts, and has performed quite well in clinical trials. As well, the improved hyperphagia and related symptoms in PWS reported by Levo are best attributed to treatment effects of intranasal carbetocin and not to the natural history of this life-threatening disorder. Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 15, you're our last speaker. Your audio is connected now.

MS. ROOF: Hi. I'm Elizabeth Roof. I was a subinvestigator on both carbetocin trials, both 114 and 301. I'm a PWS researcher from Vanderbilt University, working with more than 350 people with PWS, doing seven clinical trials in PWS over my

27-year career.

I've talked with so many parents who've told me about how PWS affects their lives. The most important common symptom of PWS, hyperphagia, emerges when their children are quite young, and it's incredibly difficult for families to manage.

Hyperphagia can kill. That's not an overstatement, as I've had 6 patients die from hyperphagia, not from obesity or related comorbid conditions, but hyperphagia itself. One young man stands out to me, a tall, thin 21 year old with a bright smile and beautiful blue eyes. Growth hormone made him tall, and his mom kept him thin and healthy, making sure his food was secure, and he was always supervised.

One day while attending a holiday party, the usual staff monitoring him was gone for 5 minutes. This young man went home, didn't want to eat dinner, and was complaining of stomach pain. His parents drove him to the local ER. This healthy young man who kept saying that he had not eaten any extra food died of a gastric rupture the very next

day. His family will always grieve the loss of this amazing young man with such a tragic end.

PWS puts such a burden on these families. Hyperphagia is such a tremendously stressful thing to manage, as it's life-threatening and there are no currently FDA-approved treatments. Even though hyperphagia itself can be difficult to manage, that makes it no less real or deadly.

The Hyperphagia Questionnaire we developed is a snapshot of hyperphagia and food-related behaviors. Just like snapshots, it doesn't show us everything, but we get a glimpse of what parents see and manage every day. The decrease in HQ-CT scores in those with PWS highlights the real and meaningful and measurable changes that parents reported when their children took carbetocin. We personally saw changes in talking and asking less about food. We saw less arguing and negotiating about when and what they would eat. We saw less food stealing, fewer meltdowns, and more flexibility about when meals were served. At visits, we saw visible easing of stress for

patients and their families.

We noticed that kids went from asking constantly about breakfast to being able to have conversations about school, their pets, favorite sport teams, and even which Marvel hero was the coolest. It was amazing to see how things changed, and I had a front-row seat with the countless hours I spent with these families every week.

Finally, I have something to offer PWS patients besides a grim future based on what I've seen in the past. Carbetocin offers substantial benefit, the substantial benefit of real symptom relief of hyperphagia and even related to stress and anxiety. Hope for a better future with carbetocin turns down the blinding glare of hyperphagia like a dimmer switch, a place where children with PWS can learn, hang out with friends, and maybe be able to spend some time without their parents having to monitor every morsel that goes in their mouth.

Parents get to see a glimpse of normal life when they don't have to institutionalize their

children at home just to keep them safe from the deadly effects of hyperphagia. Parents aren't asking for much here, just hyperphagia managed so that their children can thrive, maybe even survive until adulthood. Asking parents to do another trial is such a disservice to all of our families who've sacrificed so much in the three years. Families did the heavy lifting here, the traveling, the scheduling, 3-times-a-day dosing, the time away from work, school, and family.

Would so many people do that for three years during a pandemic for a medicine that doesn't work? No, because carbetocin works, and the effects are durable as we follow still more than 20 patients currently. No drug is going to work for every person, but we want the FDA to meet us halfway and realize that another trial is not going to prove anything different than we've already demonstrated with our stories, that carbetocin provides substantial benefit.

Dr. Farchione eloquently pointed out that the FDA understood, but it's difficult to do a

dose-finding study in these rare populations and that the FDA didn't want to pin all of our hopes on one dose. Well, the PWS community doesn't have that luxury. We have to pin all of our hopes on that one 3.2-milligram dose of carbetocin because it may be the very thing standing between life and death for our kids, and we don't have any FDA-approved treatments for hyperphagia.

As we've shown substantial evidence here today for carbetocin, I urge you to approve this drug. Thank you so much for your time.

Questions to the Committee and Discussion

DR. NARENDRAN: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will proceed with the question to the committee and panel discussions. I would like to remind public observers that while this meeting is

open for public observation, public attendees may not participate except at the specific request of the panel.

After I read the question, we will pause for any questions or comments concerning its wording; then we will open the question to discussion. I will read the first question, which is a voting question.

Question number 1, has the applicant provided substantial evidence of effectiveness for carbetocin nasal spray, LV-101, in the treatment of hyperphagia associated with Prader-Willi syndrome?

Are there any questions about the question, panel members?

(No response.)

DR. FRIMPONG: Good afternoon. This is the designated federal officer, Joyce Frimpong. I will provide instructions for the voting.

Our question is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the

record, and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you're a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There'll be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you only need to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the roster and each voting

member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

Are there any questions about the voting process before we begin?

(No response.)

DR. NARENDRAN: Thank you.

I'll read the question again.

Has the applicant provided substantial evidence of effectiveness for carbetocin nasal spray in the treatment of hyperphagia associated with Prader-Willi syndrome?

Are there any questions about the question from the panel members? If you do, please raise your hand.

(No response.)

DR. NARENDRAN: I see no questions or comments concerning the wording of the question. If that's the case, we will now begin the voting on question number 1.

DR. FRIMPONG: We will now move voting members to the voting breakout room to vote only.

There will be no discussion in the voting breakout room.

(Voting.)

DR. FRIMPONG: The voting has closed and is now complete. Once the vote results display, I will read the vote result into the record.

(Pause.)

DR. FRIMPONG: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

There is 1 yes, 12 noes, and no abstentions.

DR. NARENDRAN: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote, if you wish.

We'll start with Dr. Dunn.

DR. W. DUNN: This is Walter Dunn, and my vote was no. This was based on a narrow

interpretation of the question with the focus on the phrase "substantial evidence." However, if the question posed were, is their modest evidence of effectiveness, then I perhaps would have to reconsider my vote. But my vote for this question was no.

The foremost question in my mind in arriving at the conclusion was were the findings from the 3.2-milligram dose real; that is, were those results simply by chance? The lack of replication and the absence of a clear pathway to formally evaluate the p-value of that 3.2-milligram group suggest that any interpretation of finding should be conducted with extreme caution.

The next question in my mind was, is that proposed U-shaped response curve a plausible explanation for the nature of the results? I think based on the oxytocin literature, this is certainly believable, but with the data at hand, with the carbetocin data at hand, I do not see convincing, or really even credible evidence, that off-target effects of aggression were responsible for the

negative results for that 9.6-milligram dose.

So ultimately, we're left with no good explanation as to the lack of replication. This is not to say that U-shaped response curves are not possible in the absence of an exploratory model. We have certainly seen this in recently approved antipsychotic medications.

I'll conclude by saying that the term "unmet medical need" is often liberally used portraying use in proposed treatment, but I believe that carbetocin is a sincere attempt to address a true and severe unmet medical need for patients with Prader-Willi syndrome and their families. Ultimately, this will only be one of many considerations that the FDA will be contemplating in their final decision. Thank you.

DR. NARENDRAN: Thank you.

Next is Dr. Keller.

(No response.)

DR. NARENDRAN: Dr. Keller, you might be muted.

DR. KELLER: Yes. This is Dr. William

Keller, and I voted no. I don't have anything further to add.

DR. NARENDRAN: Thank you.

Dr. Troendle?

DR. TROENDLE: Hello. This is James Troendle. I voted no. I think that the wording is critical, as Dr. Dunn's already mentioned, but I don't think that it even met even a low bar for evidence, let alone substantial evidence. It's far from that.

The FDA's analysis shows that even the 3.2 milligram, even if you ignore the multiplicity issues, which are abundant, is not really a robust analysis. That does not even show that it passes the lowest bar possible. I do think it's interesting that this is worded this way because it doesn't talk at all about any possible risk-benefit trade-off. There are just [inaudible – audio gap] benefits, whatsoever.

DR. NARENDRAN: Thank you.

Dr. Thomas?

DR. THOMAS: Hello. This is Patrick Thomas,

and I voted no for some of the similar concerns previously stated.

DR. NARENDRAN: Dr. Jeffrey?

DR. JEFFREY: Hi there. Jessica Jeffrey from UCLA. Given that there are no current therapies approved to treat hyperphagia associated with PWS, I would like to have seen substantial evidence for LV-101. But unfortunately, I just don't believe substantial evidence of effectiveness has been provided by the applicant today, and my detailed reasoning is similar to Dr. Dunn.

DR. NARENDRAN: Thank you, Dr. Jeffrey.

Next is Dr. Shapley.

DR. SHAPLEY: Hi. This is Alice Shapley. I voted yes. I believe that substantial evidence was presented for the efficacy of carbetocin with a liberal view of the term "substantial evidence." But in particular, I think in light of the promising safety profile of carbetocin, I'm convinced of the high ratio of benefit to risk for this treatment for the PWS community. Thank you.

DR. NARENDRAN: Thank you.

Next is Dr. Billington.

DR. BILLINGTON: This is Charles Billington. I voted no as well. I was very moved by the compelling stories of family members who find effectiveness of the drug, but as my colleagues have said, given the question that we've been asked, is there substantial evidence, I'm afraid the answer must be no. It's hard to find any evidence of a signal at all. Thank you.

DR. NARENDRAN: Thank you, Dr. Billington.

This is Raj Narendran. I voted no. I also struggled with this notion that it seemed it was not very clear to really figure out whether this is a by-chance finding with the 3.2 milligram, especially with the statistical issues that were involved with the prespecified endpoint not being met.

With that, I'll pass it on to Dr. Fiedorowicz.

DR. FIEDOROWICZ: Yes. Hello. This is Jess Fiedorowicz from the University of Ottawa and the Ottawa Hospital. I voted no. The testimonies of

those affected by Prader-Willi syndrome are compelling, at times heartbreaking, and the unmet medical need is unquestionable.

I think it seems everyone on this committee recognizes that the question is related to whether there's substantial evidence of effectiveness of carbetocin for Prader-Willi syndrome, and on this question, I agree with the overall conclusions of the FDA.

There are suggestions of an efficacy signal for the lower 3.2-milligram dose that should encourage further study, but neither study provides substantial evidence of efficacy by the statutory standard, even granting the deserved exception to at least two adequate and well-controlled clinical investigations.

In CARE-PWS, the primary endpoints were definitively negative. Secondary endpoints were encouraging, but questionable, and not even statistically significant when appropriately analyzed. I'm sorry to report to patients and families that carbetocin does not have substantive

evidence of effectiveness for Prader-Willi syndrome at this time. Thank you.

DR. NARENDRAN: Thank you.

Dr. Iyengar?

DR. IYENGAR: This is Satish Iyengar from Pittsburgh. I also voted no. I heard the phrase "two studies" several times during the course of the day, but the focus here is on the 3.2 dose, and for that we only have one study, which, first of all, doesn't meet the regulatory requirements.

The FDA identified a number of statistical issues/problems with their study, and the thing that stuck out to me most was that the 9.6-dose study did not replicate. And given the fact that the 3.2-dose study didn't really hold up strongly to the sensitivity analysis that they did, I just have no confidence. I have little confidence that it will replicate. I'm done.

DR. NARENDRAN: Thank you.

Dr. McGough?

DR. McGOUGH: It's Dr. McGough. I voted no. I would have loved to be able to vote yes. This is

an orphan condition with dire consequences. I think the safety profile of this drug sounds very favorable, but in terms of the evidence of actually effect, I think there's significant evidence of bias in the study design, at least in the analytic plan used.

I'm worried about type 1 error. I think the story around the U-shaped response mechanism of action is speculative at best, and what we heard today just doesn't meet the threshold of substantial evidence supporting efficacy. So my vote's no.

DR. NARENDRAN: Thank you.

Dr. Krishna?

DR. KRISHNA: Hi. This is Dr. Sonia Krishna. I voted no. I was incredibly moved by these serious stories and descriptions, and appreciate the photos of your family members, and unfortunately I don't think the data matches at this point. Thank you.

DR. NARENDRAN: Thank you.

Ms. Witczak?

MS. WITCZAK: Yes. Kim Witczak. I voted no. I think that the wording "substantial evidence" needing two studies, the original goal it looks like it was trying to replicate the 9.6, and it didn't. I don't know about that 3.2, and if that is the ideal dose, there are a lot of questions. I, too, would love to see something like this for all the people that were there, and truly believe that this is an unmet need.

I would like to -- and maybe this is more something that the FDA can answer or let us know if it is something. The idea of expanded access is possibly an option for the families that do want it. I would encourage the company to continue studying it, and maybe it's 3.2 and some other doses and seeing if it replicates. Thank you.

DR. NARENDRAN: Thank you.

In summary, everybody on the panel agrees there's a great unmet need for hyperphagia in Prader-Willi syndrome. This is a really heartbreaking problem, and it would be great to have a drug. However, the panel members felt that

carbetocin, as tested, didn't really meet the goals for the higher dose.

For the lower dose, it was a little bit exploratory. There are concerns about lack of replication, of whether that would hold up. There are also statistical issues related to interpreting it that people felt diminished it, and it didn't meet the substantial efficacy standard.

Some people felt there was maybe some moderate efficacy possibly, and it's worth exploring further. Maybe it meets the threshold for a liberal definition of substantial effectiveness. But overall, it seems there is good congruence that people were concerned enough that they didn't feel it meets the definition for substantial effectiveness for hyperphagia in Prader-Willi syndrome. And there was also a lot of concerns about whether the U-shaped curve in itself explains the lack of efficacy for the higher dose as well.

So that's my summary. Are there any other closing comments from the agency about thoughts to

the panel? I'll turn it over to the agency.

DR. FARCHIONE: Thanks, Raj.

This is Dr. Farchione again. Again, I just want to take this opportunity to thank everyone for their time today and for their consideration of the presentations. I particularly want to thank the folks who took the time to provide comments during the open public hearing. Those experiences are always very valuable to us as we consider the state of the application and as we think about how we're going to complete the review as we move forward at this point.

So again, it's really been very valuable, all of the feedback, and the questions, and the information that was presented today, so thank you all so much.

Adjournment

DR. NARENDRAN: Thank you.

I do want to thank members of the public, once again, for coming forward and providing the testimony. I do also want to thank the FDA staff and Levo Therapeutics, and the division, for their

efforts in conducting this online through the pandemic.

With that, we'll now adjourn the meeting. Thank you.

(Whereupon, at 3:05 p.m., the meeting was adjourned.)