FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE (PCNS) MEETING

Thursday, April 19, 2018

8:00 a.m. to 11:45 a.m.

FDA White Oak Campus

Building 31 Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

G. Caleb Alexander, MD, MS

(Chairperson)

Associate Professor of Epidemiology and Medicine

Johns Hopkins Bloomberg School of Public Health

Center for Drug Safety and Effectiveness

Baltimore, Maryland

Mark W. Green, MD, FAAN

Professor of Neurology, Anesthesiology, and Rehabilitation Medicine

Director of Headache and Pain Medicine

Vice Chair of Neurology for Professional Development and Alumni Relations

Icahn School of Medicine at Mt Sinai

New York, New York

David S. Knopman, MD

Professor of Neurology

Mayo Clinic

Rochester, Minnesota

Richard J. Kryscio, PhD

Professor, Statistics and Biostatistics

University of Kentucky

Sanders-Brown Center on Aging

Lexington, Kentucky

Chiadi U. Onyike, MD, MHS

Associate Professor of Psychiatry and Behavioral Sciences

Division of Geriatric Psychiatry and Neuropsychiatry

Department of Psychiatry and Behavioral Sciences

The Johns Hopkins University School of Medicine

Baltimore, Maryland

Joel S. Perlmutter, MD

Elliot Stein Family Professor of Neurology

Professor of Radiology, Neuroscience, Physical Therapy & Occupational Therapy

Washington University School of Medicine

St. Louis, Missouri

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE MEMBER (Non-Voting)

Mark Forrest Gordon, MD

Senior Director

Clinical Development, Neurology and Psychiatry

Teva Pharmaceuticals

Malvern, Pennsylvania

TEMPORARY MEMBERS (Voting)

Jane B. Acri, PhD

Chief, Medication Discovery & Toxicology Branch

Division of Therapeutics and Medical Consequences,

National Institute on Drug Abuse

National Institutes of Health (NIH)

Bethesda, Maryland

Danielle Boyce, MPH

(Patient Representative)

Senior Research Data Analyst

Johns Hopkins University

Baltimore, Maryland

José E. Cavazos, MD, PhD

Professor of Neurology, Neuroscience, and Physiology

Assistant Dean & Director, MD/PhD Program

University of Texas Health San Antonio

San Antonio, Texas

Harriet de Wit, PhD

Professor

Department of Psychiatry and Behavioral Neuroscience

University of Chicago

Chicago, Illinois

Richard P. Hoffman, PharmD

(Acting Consumer Representative)

Pharmacist/Medical Writer

Hernando, Florida

John Mendelson, MD

Senior Research Scientist, Friends Research Institute Founder and Chief Medical Officer
Ria Health
San Francisco, California

Eluen Ann Yeh, MA, MD, FRCPC, Dip ABPN

Associate Professor, Faculty of Medicine
University of Toronto
Director, Pediatric MS and Demyelinating Disorders Program
Associate Scientist, Neurosciences and Mental Health, SickKids Research Institute
Staff Physician, Division of Neurology
The Hospital for Sick Children,
Toronto, Ontario, Canada

FDA PARTICIPANTS (Non-Voting)

Ellis Unger, MD

Director, Office of Drug Evaluation I (ODE-I)

Office of New Drugs (OND), CDER, FDA

Robert Temple, MD

Deputy Director

ODE-I, OND, CDER, FDA

Billy Dunn, MD

Director, Division of Neurology Products (DNP)

ODE-I, OND, CDER, FDA

Eric Bastings, MD

Deputy Director

DNP, ODE-I, OND, CDER, FDA

Teresa Buracchio, MD

Clinical Team Leader

DNP, ODE-I, OND, CDER, FDA

Dominic Chiapperino, PhD

Acting Director, Controlled Substance Staff

Office of the Center Director, CDER, FDA

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

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. ALEXANDER: Good morning. I think we'll get started. My name is Caleb Alexander, and I'm chairing the committee and would like to welcome all of you, sponsor, FDA participants here, and members of the advisory committee, and those of you that have joined us as guests.

I'd like to remind everyone to first silence your cell phones, smartphones, and any other devices that you've not already done so. And I'd also like to identify the press contact, Sandy Walsh and Michael Felberbaum. If you're present, can you please stand? Thank you.

Once again, I'm Caleb Alexander. I'm the chair of the Peripheral and Central Nervous System Drugs Advisory Committee, and I'll be chairing this meeting. I'll now call the meeting to order. We'll start by going around the table and introducing ourselves, and we'll start with the FDA

to my left and go around the table. Before we do so, I just want to let everyone know that these meetings are always informative and educational, and I'd like to remind people that all of us are smarter than any of us, so I'm looking forward to a really good discussion.

One point of order that I want to mention also with respect to the agenda is that following the presentations from the FDA and the sponsor, there's an opportunity for brief clarifying questions. And I've learned from experience that it's helpful if -- these moments really are moments for clarifying questions for the party that's just presented, so I'd like to avoid a lot of back and forth during that period of questions, or back and forth between the FDA and the sponsor, or using the FDA's time to answer questions after the sponsor's presentation or vice versa.

So thank you, and once again, let's begin with introductions, and we can start with the FDA to my left.

DR. UNGER: Good morning. I'm Ellis Unger.

I'm director of the Office of Drug Evaluation I in the Office of New Drugs, Center for Drug Evaluation and Research, FDA.

DR. DUNN: Good morning. Billy Dunn, director of neurology.

DR. BASTINGS: Eric Bastings, deputy director, neurology.

DR. BURACCHIO: Teresa Buracchio, clinical team lead neurology.

DR. CHIAPPERINO: Good morning. Dominic Chiapperino. I'm the acting director in the control substance staff.

DR. CAVAZOS: Good morning. Jose Cavazos. I'm professor and assistant dean at University of Texas Health, San Antonio. I'm a clinician scientist in epilepsy.

DR. PERLMUTTER: I'm Jose Perlmutter, a professor of neurology, neuroscience, radiology, at Washington University, School of Medicine in St. Louis.

DR. KNOPMAN: I'm Dave Knopman. I am a professor of neurology at the Mayo Clinic in

Rochester, Minnesota.

DR. CHOI: Moon Hee Choi, designated federal officer.

DR. ALEXANDER: Caleb Alexander. I'm an associate professor of epidemiology and medicine at Johns Hopkins.

DR. GREEN: Mark Green, anesthesiology and rehabilitation medicine, and director of headache medicine at [inaudible - mic fades].

[Inaudible - mic off].

DR. YEH: Ann Yeh. I'm an associate professor of child neurology at the University of Toronto.

DR. KRYSCIO: Good morning. Richard Kryscio, professor of statistics and biostatistics, University of Kentucky.

DR. MENDELSON: John Mendelson. I'm a professor at UCSF, but mainly I'm a chief medical officer for Ria Health and a senior research scientist at Friends Research Institute.

DR. ACRI: I'm Jane Acri. I'm chief of the medication discovery and toxicology branch at the

National Institute on Drug Abuse.

DR. de WIT: My name is Harriet de Wit. I'm a professor in the Department of Psychiatry and Behavioral Science at the University of Chicago.

DR. BOYCE: I'm Danielle Boyce. I'm a senior research data analyst at Johns Hopkins, but more importantly, I'm the patient representative. I have a little boy with severe epilepsy.

DR. HOFFMANN: I'm Richard Hoffmann. I'm a medical writer and pharmacist, and I'm the consumer representative today.

DR. GORDON: Good morning. My name is Mark Gordon. I'm senior director in clinical development at Teva Pharmaceuticals.

DR. ALEXANDER: Great. Thank you.

Dr. Temple, do you want to introduce yourself?

DR. TEMPLE: Hi. Bob Temple. I'm deputy director of ODE I.

DR. ALEXANDER: Terrific.

For topics such as those being discussed at today's meeting, there are often a variety of

opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will only be allowed to speak on the record if recognized by me. 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 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.

Now I'll pass to Moon Hee Choi, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants at 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 USC Section 208, Congress has authorized FDA to grant waivers to special

government employees or 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 their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 USC 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, NDA 210365, cannabidiol oral

solution, sponsored by GW Pharmaceuticals, for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.

This is a particular matters meeting during which specific matters related to GW Pharmaceuticals NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

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

Teva Pharmaceuticals.

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 other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. ALEXANDER: Thank you. We'll now proceed with the FDA's introductory remarks from Dr. Billy Dunn.

FDA Opening Remarks - Billy Dunn

DR. DUNN: Thank you very much, Dr. Alexander.

Good morning to you all. Welcome to all our committee members, guests who have traveled here, and all the folks who are joining us by electronic means for this important meeting. I want to thank

the committee for all your willingness to be here, your eagerness to consider the important topics we will discuss today, and your forthrightness in sharing with us your perspectives on the application under consideration.

I want to especially thank the public attendees, both in person here with us today and those that are joining us by audio or video broadcast, for their commitment to developing safe and effective treatments for Dravet syndrome and Lennox-Gastaut syndrome. I particularly want to note and thank those affected by Dravet syndrome or Lennox-Gastaut syndrome who are joining us today.

For those of you who have requested an opportunity to address the committee or who have provided written comments for the committee, we look forward to and are deeply appreciative of your input. Your efforts to be here are invaluable and tremendously appreciated. Thank you.

We are here today to discuss cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. There is a

significant unmet medical need for new treatments for these conditions. Although there are six drugs approved specifically for the treatment of seizures in patients with Lennox-Gastaut syndrome, there are no drugs approved specifically for the treatment of seizures in Dravet syndrome.

Both syndromes are characterized by elevated mortality rates, developmental impairment, episodes of status epilepticus, and multiple seizure types that are generally refractory to many of the drugs typically used for the treatment of seizures. We are highly sensitive to the urgent need for the development of new treatments for both of these severe epilepsy syndromes.

Before briefly describing some of the issues we will ask you to discuss today, I want to stress that we have not made any final decisions on the approvability of this application. With that said, as you have seen in the background materials for this meeting, we have largely concluded the primary portion of our review process and have not identified any obstacles to approval. The reason

we are here today is to gain your input into some of the issues we have confronted during our review process so that we may incorporate it into our ultimate decision on approvability.

As will be discussed in detail today during the presentations you will hear, cannabidiol is a cannabinoid prepared from the Cannabis sativa plant. It is structurally unrelated to other drugs approved for the treatment of seizures. Cannabidiol is currently a Schedule I drug based on its derivation from Cannabis sativa. The exact mechanism of the anticonvulsant effect of cannabidiol is unknown, but does not appear to involve an interaction with cannabinoid receptors.

The applicant provides effectiveness and safety data from three adequate and well-controlled studies of conventional design and additional safety data from other studies conducted during the development program, along with an extensive expanded access program that the sponsor has supported.

The applicant also conducted focused

nonclinical and clinical studies to assess the abuse potential of cannabidiol. These studies have been reviewed in great detail by our staff, and key points will be presented to you today by several members of our primary review staff: Dr. Natalie Getzoff, a clinical reviewer in the Division of Neurology Products, who will discuss efficacy and safety findings; Dr. Lara Dimick-Santos, a clinical reviewer in the Division of Gastroenterology and Inborn Errors Products, who will discuss our review of liver safety; and Dr. Katherine Bonson, a reviewer from the controlled substances staff who will discuss the abuse potential assessment of cannabidiol.

These presentations will highlight a number of issues, including our conclusion that the effectiveness of cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome has been demonstrated and that the safety profile associated with cannabidiol treatment appears acceptable for its intended use; our detailed consideration of the liver toxicity

observed during clinical development, including its association with concomitant use of valproate; and our extensive assessment of the abuse-related data that supports our finding that cannabidiol has negligible abuse potential.

In addition to an opportunity to ask clarifying questions following the presentations, there will be time for additional committee discussion before we ask you to cast a vote indicating your impression of the benefit-risk profile of cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome.

Again, no final decision has been made on approvability, and we very much look forward to the insights you will provide. We have convened this committee because we feel that a final decision requires your input and advice.

Thank you for the substantial efforts that you have made in preparing for and attending this meeting, and thank you for the important work that you will do today.

Dr. Alexander, thank you very much for the time to offer my comments to the committee. I return the proceedings to you.

DR. ALEXANDER: Great. Thank you very much.

We will now move to applicant presentations.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, the 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 that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest 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.

We will now proceed with GW Pharmaceutical's presentations.

Applicant Presentation - Alice Mead

MS. MEAD: Good morning. Mr. Chairman, members of the advisory committee, and the FDA, I'm Alice Mead, head of U.S. public policy and public affairs at GW Pharmaceuticals. Thank you for the opportunity to present our data on cannabidiol oral solution, or CBD-OS, for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, or LGS, and Dravet syndrome, or DS.

Cannabidiol, or CBD, is one of more than a hundred cannabinoid molecules derived from the cannabis plant. Each molecule has its own pharmacology, and therefore potentially its own therapeutic action. CBD and THC are the most commonly derived cannabinoids, however, unlike THC, CBD does not engage the cannabinoid CB1 receptors.

Therefore, unlike THC, CBD doesn't provide the high that recreational users commonly seek from the THC-containing cannabis plant.

Cannabidiol oral solution is comprised of crystalline CBD, which has been purified from a cannabis extract. The purity and potency are assured through a quality management system that includes adherence to the rigorous and exacting good manufacturing practices applicable to pharmaceutical products. All GMP manufacturing processes are subject to preapproval inspection by the FDA.

I'd like to describe the regulatory history of CBD-OS. First, the active pharmaceutical ingredient of CBD-OS demonstrated consistent anticonvulsant effects in preclinical models of generalized and partial seizures. Soon after, physicians treating children with drug-resistant epilepsy began requesting access to CBD-OS.

In 2013, the FDA responded by authorizing a number of physician-initiated expanded or compassionate access programs, or EAPs. In 2014,

we opened an IND to conduct clinical studies. The FDA granted fast-track designation to CBD-OS in 2014 and rare pediatric designations in 2017. These designations were based on the recognition that patients with LGS and DS suffer a significant and disabling seizure burden, which persists even when patients are taking many antiepileptic drugs or AEDs.

We have now completed four controlled clinical studies consisting of two pivotal studies in LGS and a dose-ranging safety study in Dravet followed by a pivotal study. As we'll show you, adjunctive CBD-OS therapy met the primary endpoint of reduction in seizure frequency in patients with drug-resistant LGS and DS in all three consecutive pivotal studies.

The data demonstrate that CBD-OS improves seizure control in patients taking concomitant AEDs. Overall, the benefit-risk profile of CBD-OS is positive. The safety and tolerability are consistent across studies and the risks can be managed through the label and the medication guide.

Therefore, we propose the following indications: CBD-OS for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients age 2 years and older. Our proposed dosing schedule is to titrate CBD-OS to an initial target dose of 10 milligrams per kilogram per day with further dose adjustments determined by clinical response and tolerability up to 20 milligrams per kilogram per day.

Turning now to the agenda for the rest of our presentation, first Dr. Elizabeth Thiele will discuss the unmet need for additional antiepileptic medications for patients with LGS and DS. Dr. Kevan VanLandingham will then review the design of our clinical studies and efficacy results. Dr. Stephen Wright will review the safety data. Dr. Orrin Devinsky will conclude the presentation with his clinical perspective on the utility of CBD-OS for his patients with LGS and DS, and Dr. Volker Knappertz will moderate the Q&A session. We also have additional experts to help answer questions. All external experts have been

compensated for their time and travel.

Thank you. Now I would like to invite Dr. Thiele to the lectern.

Applicant Presentation - Elizabeth Thiele

DR. THIELE: Thank you and good morning. I'm Dr. Elizabeth Thiele, and I'm director of the pediatric epilepsy program at the Massachusetts General Hospital, where I take care of more than 1200 children, most with highly drug-resistant epilepsy. I appreciate the opportunity to speak with you today about the significant unmet need for effective and well tolerated treatment options for patients with Lennox-Gastaut syndrome and Dravet syndrome.

These are two of our most difficult to treat epilepsy syndromes. Although they are distinct syndromes, LGS and Dravet share many similarities. LGS and Dravet are both lifelong, highly drug-resistant forms of epilepsy with poor long-term prognosis due to repeated exposure to seizures over time. Both syndromes are characterized by multiple seizure types with tonic,

generalized tonic-clonic, and atypical absence seizures occurring in both.

The typical patient takes a combination of multiple antiepileptic drugs as well as non-pharmacologic therapies. Unfortunately, even with the available treatment options, it is estimated that more than 90 percent of these patients continue to have numerous, uncontrolled seizures every day.

There are a few characteristics that distinguish the two syndromes. In LGS, onset is typically in children between the ages of 3 and 5 years of age and due to many different etiologies. These children have multiple seizure types, including drop seizures, which are associated with the greatest clinical impact. Drop seizures frequently lead to falls and injuries, which can be severe and typically include atonic, tonic, and tonic-clonic seizures. In fact, most of these patients wear helmets or use wheelchairs to minimize trauma from these seizures.

In Dravet syndrome, onset is in the first

year of life in otherwise healthy infants, typically around 6 months into life with the first seizure in the setting of a febrile illness. Dravet is a genetic epilepsy caused by a mutation in the SCN1A sodium channel gene. During the second year of life, there is onset of mixed seizure and cognitive plateauing or regression. In these patients, convulsive seizures have the greatest impact. These include clonic, tonic, and tonic-clonic seizures. These also can lead to falls and injuries.

In both syndromes, uncontrolled seizures put patients at great risk for morbidity and mortality. The majority of these patients also have severe intellectual impairment. Studies in patients with Lennox-Gastaut show that at least 75 percent experience cognitive impairment within 5 years of onset. Behavioral and psychiatric comorbidities are also common in these patients, including attention deficit hyperactivity disorder, aggressive behavior, psychosis, and depression. These can result from the seizures, the underlying

etiologies, as well as side effects of the medications.

Most importantly, these patients also face an increased risk of death compared to others with epilepsy. Death can occur from a number of causes ranging from drowning during a seizure, to status epilepticus or prolonged seizures, to sudden unexplained death in epilepsy or SUDEP. Because of the multiple uncontrolled seizures, patients with LGS and Dravet usually require full-time and often lifelong support. At any moment of any day, a patient could collapse or fall from an unexpected seizure. Most families dedicate their lives to providing 24-hour vigilance 7 days a week.

Parents feel they can never leave their young child or adult son or daughter with LGS or Drave unattended. This means that a parent won't even take a shower until someone is there to keep watch, and this vigilance continues after the child goes to sleep. A recent study revealed that 82 percent of parents of children with Dravet sleep with their child for fear of missing the convulsive

seizures, which frequently occur during sleep.

This does not stop when the patient reaches adulthood. About 90 percent of patients require some type of assistance in adulthood often beyond what their families are able to provide. Many end up in an assisted living facility or a nursing home. And that is why the goals of therapy are to reduce the frequency and severity of the seizures these patients experience; minimize treatment related side effects; improve the patient condition; and improve daily functioning.

However, most of my patients are not achieving these goals with currently available therapies. This results in a considerable unmet need for new treatment options in LGS and Dravet. The reality is that most of my patients are taking between 3 and 6 antiepileptic drugs every day. These agents rarely provide sufficient seizure control and are often accompanied by intolerable side effects. While there are six options approved for LGS, there are no drugs specifically approved to treat Dravet syndrome. Therefore, we need new

classes of antiepileptic drugs that work differently from our current options.

To conclude my presentation, in LGS and Dravet, seizure burden remains high despite treatment with multiple antiepileptic drugs. Parents and caregivers live in constant fear of the next seizure, which could cause serious injury or even death. Thus, parents are desperate for new ways to try to get control of their child's seizures. As a physician, I want to be able to provide a treatment that I know is not only effective but also safe and well tolerated.

Thank you. I'll now turn the presentation over to Dr. VanLandingham

Applicant Presentation - Kevan VanLandingham

DR. VanLANDINGHAM: Thank you, Dr. Thiele.

I'm Dr. Kevan VanLandingham, senior medical director at GW. I'm a trained neurologist, an epileptologist, and I served as medical monitor for these studies. I will share the efficacy data with you.

The efficacy evidence comes from three

consecutive, positive, randomized, double-blind, placebo-controlled studies. All three demonstrate that CBD-OS added to other AED therapy met the primary endpoint of reduction in seizure frequency in patients with inadequately controlled seizures in Lennox-Gastaut syndrome and Dravet syndrome.

All three studies examined CBD-OS dosed 20 milligrams per kilogram per day compared to placebo. The LGS study seen on the left, study 1414, also evaluated the 10-milligram per kilogram per day dose. All three studies used the same 14-week design, where CBD-OS or placebo was added to current AED therapy similar to the design used for other AED approvals.

Following screening, patients were observed for 4 weeks to establish their baseline 4-week seizure rate. Patients meeting the protocol specified seizure count thresholds were then equally randomized to receive CBD-OS or placebo added to the patient's baseline regimen of AEDs.

Patients were titrated to the target dose during the first 2 weeks and then maintained on

that dose for 12 weeks. Thus, the overall treatment period was 14 weeks, including the 12-week maintenance period. Following completion, patients could enter the open-label extension study.

All three pivotal studies used well established epilepsy endpoints to evaluate efficacy. The primary endpoint was the percent reduction in drop seizures for LGS and convulsive seizures for DS during the 14-week treatment period compared to the 4-week baseline period. These endpoints were chosen as they are associated with the greatest clinical impact.

The key secondary endpoints followed the same hierarchy for both LGS studies. The first was a responder analysis in patients with a 50 percent or greater reduction in drop seizures. The second was percent reduction from baseline in total seizure frequency. The third was an assessment of Subject/Caregiver Global Impression of Change. The DS study had only one key secondary endpoint, 50 percent or greater reduction in convulsive

seizures.

Now let's review the enrollment criteria. Patients with LGS had to be 2 to 55 years old, uncontrolled on current therapy, having at least 8 drop seizures over a 4-week span, and at least 2 drop seizures every week. Patients with DS needed to be 2 to 18 years old, uncontrolled on current therapy with at least 4 convulsive seizures during the 4-week baseline.

First, I'd like to take you through the Lennox-Gastaut data. Baseline demographics for enrolled patients with LGS were balanced, mean age was 15 to 16 years, most patients were Caucasian, and about three-quarters were enrolled in the USA. Disease characteristics and treatment were also generally balanced and representative of this population with inadequately controlled seizures.

These patients had a large number of drop seizures, around 80 during the 4-week baseline period. That's 2 to 3 drop seizures every day. Total seizures ranged from 145 to 181 seizures during the 4-week baseline period. That's more

than 5 total seizures every day. In each study, patients were taking a median of 3 AEDs.

Turning now to the efficacy results for our two LGS studies, both studies and both doses in the 1414 LGS study met the primary endpoint, providing a statistically significant and clinically meaningful reduction in drop seizures during the treatment period. Three secondary endpoints were prespecified and tested using a hierarchical gate-keeping procedure.

The first was a 50 percent or greater responder rate, which demonstrated a statistically significant improvement for both studies and in the LGS study 1414 at both doses. The next endpoint in the hierarchy showed statistically significant reductions in the frequency of total seizures for both doses. This gives us confidence that there was not an increased frequency of total seizures while reducing drop seizures.

Finally, let's look at the Global Impression of Change. The Subject/Caregiver Global Impression of Change was used at the last study visit where

changes in overall condition were graded on a 7-point Likert scale. In each of the LGS studies, the proportion of patients achieving an improvement, or a score of 5, 6, or 7 on the Likert scale as shown in the yellow highlighted box, was in favor of CBD-OS over placebo. This difference was statistically significant.

To further evaluate the consistency of the treatment effect, other secondary endpoints were also assessed. Seizure reduction thresholds of 25 percent and 75 percent were improved by the addition of CBD-OS. Remember that these patients face multiple seizures on a daily basis, and a 25 percent reduction in drop seizures is clinically meaningful.

Twenty to 25 percent of patients on the 20-milligram per kilogram per day dose achieved a 75 percent or greater reduction, more than double the placebo rate. While there were no complete responders during the treatment period, which includes the titration phase, a small proportion of patients on CBD-OS were seizure free during the

maintenance period.

Now I'd like to share the clinical results from our study in children with DS. Study 1332 patients were younger than the LGS patients, as would be expected based on disease onset in the age inclusion criteria of 2 to 18 years. Most were Caucasian and enrolled in the USA. Baseline disease characteristics and treatment were also generally balanced and representative of this inadequately controlled population.

In line with the known pathology, the median frequencies of convulsive and total seizures were lower than in the LGS studies. These children had a median of 12 to 15 convulsive seizures during the 4-week baseline period, which is about 1 every other day. Median total seizures were 42 for placebo and 24 for CBD-OS during the 4-week baseline period or 1 to 2 seizures per day. The median number of baseline AEDs was 3.

Turning now to the efficacy results, study 1332B also met its primary endpoint with a statistically significant reduction in convulsive

seizures during the treatment period. As shown on the right, you can see the results for the 12-week maintenance period, which represents the efficacy once the target dose has been achieved.

Now let's review the key secondary endpoint for this study, the 50 percent responder rate. We observed a numerical improvement in the prespecified 50 percent responder rate with a p-value of 0.08, which did not meet statistical significance. However, we did consistently see greater achievement in seizure reduction thresholds of 25 and 75 percent. In fact, some of the children in the CBD-OS arm became convulsive seizure free during the treatment period compared to none in the placebo arm. Study 1332B demonstrated a reduction in total seizures during the treatment period compared to placebo.

Finally, let's review the Global Impression of Change. As expected, based on the clinical results, more caregivers reported improvement in global impression of change if their child was on CBD-OS. Almost two-thirds of CBD-OS patients

improved compared to only one-third on placebo.

These three positive studies allow us to conclude that CBD-OS added to other AED therapy reduces seizure frequency in patients with LGS and DS. The seizure reductions achieved in these studies are very important to patients, their families, and physicians.

All three pivotal studies met their primary endpoints. All three are supported by their prespecified sensitivity analyses and secondary endpoints. CBD-OS provided clinically meaningful reductions in seizure frequency over placebo. In these LGS and DS studies, about 40 percent of patients had a 50 percent or greater reduction in the number of drop or convulsive seizures when adding CBD-OS.

Thank you. I now invite Dr. Wright to the lectern.

Applicant Presentation - Stephen Wright

DR. WRIGHT: Good morning. I'm Stephen Wright, senior medical advisor at GW. I have been closely involved at all stages of the planning,

execution, and analysis of these CBD-OS studies. I will review the safety and tolerability profile of CBD-OS for these patients with drug-resistant epilepsy. The data I will present demonstrate that the identified risks are manageable through labeling and the medication guide.

Overall, the safety database includes more than 600 patients in GW-sponsored studies with 391 patients treated for at least one year. The open-label extension trial represents patients who continued from the randomized controlled trials into long-term use. Approximately 97 percent of patients from all controlled studies chose to receive CBD-OS in this extension.

The expanded access program on the right-hand side of the slide provides an additional 684 patients with drug-resistant epilepsy to the safety database. This expanded access program is a physician-led program where patients with no or very few therapeutic options were treated with CBD-OS in a clinical practice setting. Given the rarity of these syndromes, this is a substantial

safety database.

This slide shows the similar overall safety of CBD-OS in the two indications of Lennox-Gastaut syndrome and Dravet syndrome. Given the similarities, we will present the safety data for both indications. As the all CBD-OS group combined, we refer to this as pooled LGS/DS. Looking at the all CBD-OS group, we see a higher incidence of overall adverse events compared with the placebo groups, and here are shown the most common adverse events.

Those showing a clear difference between drug and placebo, were somnolence, decreased appetite, diarrhea, and fatigue.

Most adverse events were mild to moderate in intensity. The incidence of several adverse events was 13 percent in the all CBD-OS group and 5 percent in the placebo group. The most common severe adverse events in the all CBD-OS group compared with placebo were somnolence and pneumonia.

Let's now look at serious adverse events.

The incidence of serious adverse events was higher in the CBD-OS group than in the placebo group. The most common serious adverse event in the all CBD-OS was status epilepticus, pneumonia, increased transaminases, convulsion, and somnolence.

Looking now at adverse events leading to discontinuation, these were more common in patients taking CBD-OS than in the placebo group, with 9 percent discontinuing CBD-OS therapy. The most common adverse events leading to withdrawal were raised hepatic transaminases, ALT and AST, and somnolence.

Now looking at adverse events leading to death, it's a tragedy for any parent or caregiver when their child or patient dies, and as we've heard from Dr. Thiele, patients with these drug-resistant epilepsies have a relatively high mortality rate. Recent studies suggest that the overall death rate in this situation is approximately 20 per 1,000 patient-years. The mortality rate appears to be greater in patients with multiple seizures and multiple comorbidities.

In the randomized controlled trials in the open-label extension, there are 716 patient-years of data, and in the expanded access program, another 690 years, so regressively, we would anticipate a number of fatal events in the patients included in our clinical trials. Overall, 20 fatal adverse events were observed in approximately 1400 patient-years.

In the LGS and DS controlled studies, a 17-year-old man with a history of status epilepticus and aspiration pneumonia experienced a fatal event of acute respiratory distress syndrome in the all CBD group. In the open-label extension trial, 7 patients of the 644 over a prolonged exposure had a fatal adverse event. There were 2 cases of sudden unexpected death in epilepsy, and the other 5 were various event terms.

In the expanded access program, 12 patients had a fatal adverse event, and the fatal adverse events represent a variety of individual preferred terms, including 2 SUDEP and 1 status epilepticus. These 20 fatalities are no greater than what would

be expected in this high-risk patient population, and none of the fatal adverse events were considered related to treatment.

Next, I'd like to review elevated transaminases. The incidence of raised ALT was higher in the CBD-OS groups compared with the placebo group. This imbalance was observed at 3 times, 5 times, and 8 times the upper limit of normal as shown here. An elevated transaminase of greater than 8 times the upper limit of normal was one of the discontinuation criteria agreed with FDA. Importantly, no patient met Hy's law criteria in the development program.

Looking more closely at patients with a clinically important 5 times increase of ALT, we've identified two key risk factors for transaminase elevations, concomitant use of valproic acid and the CBD-OS 20-milligram per kilogram per day dose. Overall, 13 percent of patients on concomitant valproic acid and CBD-OS 20-mgs per kg per day experienced a transaminase elevation of greater than 5 times the upper limit of normal.

In addition, any elevation of baseline ALT was associated with a 2-times higher likelihood of a subsequent 5 times the upper limit of normal increase of transaminases. Importantly, these elevations occur predominantly during the first 30 days of exposure. Overall, the elevations were transient and typically resolved quickly within 14 days. Discontinuing CBD-OS or valproic acid, adjusting treatment, or most commonly treating through appeared to resolve the elevations.

We believe the data demonstrate that the safety and tolerability of CBD-OS are acceptable in this patient population. Somnolence was the most common adverse event reported, however, most were mild or moderate, and few patients had to discontinue CBD-OS.

To date, liver enzyme elevations have not resulted in any severe liver injury, and the risk of hepatotoxicity is manageable through labeling and the medication guide. Monitoring of liver function is recommended at baseline and periodically during treatment to help minimize this

risk. And postmarketing enhanced pharmacovigilance surveillance will further characterize the risk. Finally, the long-term safety data from the open-label extension and the expanded access program is consistent with what we have seen in the controlled clinical studies.

Now, turning to the question of abuse liability, GW has investigated the abuse liability of CBD-OS according to published FDA guidelines and in discussion with FDA and the controlled substances staff. In preclinical studies, CBD has limited reinforcing effects and limited evidence of self-administration, although it has not been possible to exclude some abuse potential. In the clinical trials program, 2 cases of potential abuse or diversion were noted.

We've also conducted a human abuse liability study comparing CBD-OS to placebo and to two products, dronabinol and alprazolam, that are known to have abuse liability. This study showed that CBD-OS differentiated from both these active comparators. I'm going to show these results

briefly.

The human abuse liability study was designed in consultation with FDA. This was a randomized, double-blind, double-dummy placebo and active control crossover study in healthy recreational polydrug users. The primary endpoint was mean drug liking. The 3 doses of CBD-OS was 750, 1500, and 4500 milligrams, representing for an average person a 10-milligram per kilogram, 20-milligram per kilogram, and a 60-milligram per kilogram dose. Ten milligrams and 30 milligrams of dronabinol, a synthetic THC, and alprazolam 2 milligrams were also included as active control arms.

Let me walk you through the primary endpoint supporting a low abuse liability for CBD-OS. The vertical axis describes how much the blinded study drug was liked, where a score of 50 is neutral on either liked nor disliked this drug, and anything above 50 means the drug is liked.

The assessments were made over a 12-hour period and are compared to placebo, which you can see is at or around 50, representing neutrality.

You can see by the blue lines representing the 3 doses of CBD-OS, drug liking was slightly greater for the two higher doses of CBD-OS compared with placebo, but drug liking for CBD-OS was clearly lower than for alprazolam and for both doses of THC, indicating a lower potential for abuse compared with these products. Although not shown, these results were similar for all of the secondary endpoints in this study.

Thank you. I'd like to invite Dr. Devinsky to the lectern to present his clinical perspective on these data.

Applicant Presentation - Orrin Devinsky

DR. DEVINSKY: Thank you. I'm the director of the epilepsy center at NYU, and I appreciate the opportunity to talk about my experience with CBD-OS.

Over the last 30 years, I've treated more than 25,000 adults and children with epilepsy and have been involved in a number of clinical studies. Many of my patients have drug-resistant epilepsies, including Dravet syndrome and Lennox-Gastaut

syndrome. I was one of the original investigators in the CBD-OS expanded access program and the lead investigator in two of the three pivotal studies we're discussing today.

I would like to emphasis that Lennox-Gastaut syndrome and Dravet syndrome are two of the most severe and relentless epilepsies. Both are associated with very high rates of morbidity and mortality. Approximately 20 percent of Dravet patients will die before age 20, mostly from SUDEP and status epilepticus. In LGS, the numbers are not as well defined but are likely comparable.

In general, the greater the seizure burden and severity, the greater the degree of intellectual disability, psychiatric morbidity, and the higher the frequency of accidental injury, drowning, and other causes of death. It is impossible to imagine the lives of these patients and families. Parents live with the relentless fear that at any moment their child may fall down in a convulsive seizure, injure themselves severely, have a prolonged seizure, or die in their

sleep. There is no respite from these fears. As a medical community, we owe it to these patients and families to identify new therapies and make them available.

Data from the CBD-OS trials reveal that this medication can reduce seizures and improve quality of life for many of my LGS and DS patients and their families. In LGS, those patients had drop seizures reduced by 40 to 49 percent in the maintenance period, a clinically robust reduction that is statistically significant in the frequency of these seizures when compared to placebo. In Dravet, there was a 41 percent reduction in convulsive seizures, again, a very clinically and statistically significant reduction for these children and young adults compared to placebo.

As a clinician and researcher, these results are enormously meaningful in patients who are often on three, four, or five additional drugs at a time, drugs that have failed to sufficiently control their seizures and drugs that have debilitating physical, behavioral, and cognitive toxicities.

Here, looking across the three studies, roughly a quarter of patients had their most disabling seizures reduced by 75 percent or more. The two studies on the left show the dramatic reductions in drop seizures in LGS, and on the right, the Dravet study shows the same potentially life-altering reduction in convulsive seizures. Many of my open-label treated patients were able to lower concomitant antiepileptic drugs. Reduced seizures and reduced medication and burden has greatly improved the quality of life for many of my patients.

The sponsor's proposed dose titration schedule will allow us to manage patient response on an individual level. Similar to current clinical practice, patients will be dosed to an initial target dose of 10 milligrams per kilogram per day and then assessed for clinical efficacy, safety, and tolerability. From there, we will have the option to titrate up to 20 milligrams per kilogram per day if clinically appropriate.

The safety profile of CBD-OS is quite

consistent across the LGS and DS trials. The drug is generally well tolerated, side effects are overall mild to moderate, and they're mostly CNS and GI related, very similar to other antiepileptic drugs, and they are usually transient. The majority resolve by the end of the trial, and unlike other currently available antiepileptic drugs, behavioral and cognitive side effects were very infrequent.

There is a potential for elevated hepatic transaminases, which was more common among individuals taking CBD-OS 20 milligrams per kilogram per day as well as those taking concomitant valproic acid. Most of these elevations resolved within 14 days and most who continued treatment returned to baseline over the course of the study.

The safety profile of CBD-OS compared favorably with many other medications I frequently use in these children. Its management is consistent with what I already do when I initiate patients on a new antiepileptic agent. We

routinely check multiple lab parameters, including liver function, and we repeat those measures at appropriate intervals and when we make significant adjustments to co-medication or increase the dose of a new medication.

I'm very comfortable managing the transaminase elevations since I see this all the time with other antiepileptic drugs. The fact that most of these elevations occur within 30 days and almost all within 90 days reassures me that we will capture and be able to manage the risk of hepatotoxicity with routine clinical practice. Therefore, the safety and tolerability profile of CBD-OS will fit well into my practice and that of my colleagues who routinely treat patients with Lennox-Gastaut and Dravet syndromes.

In conclusion, there is a great need for CBD-OS for patients with Lennox-Gastaut syndrome and Dravet syndrome. These are incurable conditions today. We palliate these patients. We try to make their lives better. We do the best we can to balance seizure control, and side effects,

and quality of life. And while CBD-OS won't work for every patient, in my experience, it offers clear benefits when considered in isolation, and the benefits are even greater when considered against the efficacy and side effect profile of other antiepileptic drugs and when considered in the context of these horrific and life-claiming disorders.

Thank you for your attention. I will turn the lectern over to Dr. Knappertz, the chief medical officer of GW Pharma, to take questions.

Clarifying Questions

DR. ALEXANDER: Thank you. We'll now have time for clarifying questions for the sponsor. Once again, these are for the sponsor, not the FDA. Please remember to state your name for the record before you speak. And if you can, please direct your questions to the specific presenter.

We're now joined also by our final advisory committee member. If you'd like to just introduce yourself briefly, please.

DR. ONYIKE: Yes. Forgive me for my

tardiness. My name is Chiadi Onyike from Johns Hopkins University. I'm a neuropsychiatrist.

DR. ALEXANDER: Great. Thank you.

Questions for the sponsor? Richard Hoffmann?

DR. HOFFMANN: I'm not sure who to direct this question to, but there seems to be a significant drug interaction between cannabidiol and clobazam. The active demethylation metabolite of clobazam along with cannabidiol is increased by 300 to 500 percent. So my question is, in these three studies, did you notice any difference in efficacy between patients who were receiving clobazam along with cannabidiol and those that were not?

DR. KNAPPERTZ: We did not see any important interaction on the efficacy side in our clinical trial program. The inhibition is the CYP2C19 inhibition, which metabolizes the N-desmethylclobazam, and then that becomes enriched. What's important, we believe, is that the exact efficacy of N-clobazam, the N-desmethyl

metabolite of clobazam, is unknown. It's purported to be 20 percent of the effect of the parent, and there is indeed, as you mentioned, a 3-fold increase in the co-administration with CBD-OS.

We did not measure the metabolites in our clinical trial program, but I believe Dr. Thiele from Massachusetts General Hospital did measure those and did look at the efficacy as it was related, and the safety as it was related to her patients in the expanded access program.

Elizabeth, please?

DR. THIELE: Hi. Elizabeth Thiele, Mass General Hospital. As said, we did, through our expanded access program, look at the interaction between clobazam and CBD initially from a safety perspective because when we started titrating the patients up on CBD, we noticed that many of them were becoming somnelent and lethargic. And we saw that this definitely correlated with an increase in desmethylclobazam levels. By reducing the clobazam dose in all situations resulted in improvement in the somnolence.

We also were very interested in looking at was there an efficacy relationship with the desmethylclobazam level. We presented these results last year at the American Epilepsy Society, and we did not find a significant correlation between efficacy and desmethylclobazam levels.

DR. ALEXANDER: Great. Dr. Green?

DR. GREEN: I have two questions. The first one, it was mentioned that there was no significant affinity to CB1 receptor. Is there affinity for the CB2 receptor?

DR. KNAPPERTZ: There's no significant affinity to the CB2 receptor either. So neither CB1 nor CB2 receptors are significantly bound by the concentrations that we've studied and even by supratherapeutic concentrations that we studied in animal models.

DR. GREEN: My second one -- and I guess it's probably unanswerable because of the few patients -- was there a reduction in SUDEP related deaths in the open-label trials?

DR. KNAPPERTZ: We did not see a reduction

in SUDEP related deaths.

DR. ALEXANDER: Great. I have a question about the interaction with valproic acid, and I'm just curious the mechanism for that. Maybe you alluded to it, but I missed it. And I'm just wondering what can one learn from that about the likelihood of other potential drug-drug interactions that haven't been identified.

I'm also interested, there was a comment I think from Dr. Thiele that a lot of these patients take non-pharmacologic treatments as well. So I'm just wondering if you can speak a little further to both how valproic acid may interact with this and increase the risk of hepatotoxicity, but what we can learn about this that would be relevant to other potential DDIs.

DR. KNAPPERTZ: So with regards to the drug-drug interaction on the additive effect on transaminase elevation observed in our clinical trials with CBD-OS, we did not observe a pharmacokinetic interaction; that is we did not see in our phase 1 studies, where we looked at VPA and

CBD-OS, an increase in the level of VPA.

I would like to ask Dr. Paul Watkins to talk about his impression from some in vitro work that was conducted on the potential mechanism of drug-drug interaction, although caveating this, this is in vitro work that is not easily translatable to the in vivo or human situation.

DR. WATKINS: Yes, good morning. I'm Paul Watkins, and I'm a clinically trained hepatologist at University of North Carolina Chapel Hill, with a longstanding interest in drug-induced liver injury. I am compensated to be here today, but I have no other interest, I believe, that are affected by the outcome here.

The company has tried hard to find mechanisms underlying the transaminase elevations. And in terms of the valproate interaction, it is likely that the effect is at the level of oxidated phosphorylation. Both the parent CBD and the major metabolite are known to inhibit enzymes in the electronic transport chain. This is a reversible inhibition; this is not damaging to the

mitochondria. Valproate is also known to interfere with oxidated phosphorylation, so the most plausible explanation is that both are affected, oxidated phosphorylation.

Now, what other conditions or drugs might also be an issue here is really under investigation, but that is in my mind the most likely mechanism.

DR. ALEXANDER: Thank you. Ms. Boyce?

MS. BOYCE: Hi. I'm the patient representative, and I have a child with drug-resistant epilepsy that we're talking about. I first want to say thank you for capturing the caregiver burden. I thought you did a terrific job. Just this morning, I didn't exhale until I received a text from my husband back in Philadelphia that my child didn't die from SUDEP overnight, and this is my every day, so thank you for mentioning and addressing that.

My question is about valproic acid. I know thousands of families who their kids take that. It's very common practice, particularly for that

drug, to have your liver levels checked on a regular basis, even more so than others. So I just wanted to ask the neurologists if that's common practice or just what I've observed because I think that might address some of the concerns about the hepatic concerns.

DR. KNAPPERTZ: I'm going to ask Dr. Devinsky to address the question.

DR. DEVINSKY: Thank you. Orrin Devinsky from NYU. That is a very common issue in epilepsy care. Valproic acid is the anti-seizure medication perhaps together with felbamate that has the highest risk of hepatotoxicity. So traditionally when we start patients on valproic acid, we try to get baseline liver function tests, platelet levels, and other measures, and then repeat them at some intervals. It varies by practice. Our European and Canadian colleagues do it much less frequently than American neurologists, but typically a month after starting and then perhaps 3 months and 6 months afterwards is a somewhat common routine.

I think from the presentations, it would be

clear if CBD is initiated, and especially in a child on valproic acid, and especially at higher doses, that liver tests should be obtained at baseline before adding CBD-OS perhaps a month later. I personally would advise colleagues if the liver test elevation was present but modest, to observe it and repeat it in 3 or 4 weeks later. And that's what I did as a clinician on the expanded access trial, where I had many patients in the double-blind and open-label studies because most of those in the vast majority of cases came back to baseline to what they were before CBD-OS was added.

So this is really a standard part of epilepsy care. I feel very comfortable with it. I think my colleagues like Dr. Thiele do similar things in their practice every day with many patients. This is not unanticipated and unexpected.

DR. ALEXANDER: Thank you. Dr. Cavazos?

DR. CAVAZOS: Yes. I have two questions that have to do with the effect of this medication

in populations that are different than just the 78, 82 percent Caucasians. One has to do with the potential mechanism of effect that has to do with the GPR55 and what do we know about polymorphisms of this in different populations?

I do know, just looking at the literature, that there are some differences in some Japanese populations, for example. Has the company examined the effect? And it could be also in [indiscernible] channels. That's the other potential mechanism to change excitability.

DR. KNAPPERTZ: To answer the question directly, I am almost certain we have not examined the effects on polymorphisms of GPR55, but I'm not certain whether Professor Whalley has something to add at this point. I'm going to ask Professor Whalley to the microphone, our head of nonclinical pharmacology and research.

DR. WHALLEY: Thank you. Ben Whalley, director of research, GW Pharmaceuticals. It's an excellent question. As two very novel and emerging molecular targets, you're correct about the

presence of polymorphisms. However, the physiological consequence of those and the physiological consequence of the interaction of CBD with those targets at this stage remains unknown.

DR. CAVAZOS: Is there any understanding about chronic effects and sensitization and other classic pharmacological changes with chronic use?

The last portion has to do with dosing. Dosing or dispensaries and other formulations that are out there have been done out of label in doses that are dramatically different, much lower in terms of 100-fold differences.

What do we know about the effects of your medication at lower doses given the fact that many neurologists are convinced that there is an effect with formulations that are much lower?

DR. KNAPPERTZ: So we studied three doses, 5, 10, and 20 milligrams per kilogram per day. The 5-milligram dose was not assessed for efficacy but assessed for safety, and the determination and the choice for the doses for the pivotal trial came from a data monitoring committee recommendation

after the dose-finding study based on safety was completed.

So we do not have much efficacy data on doses below 10 milligram. We do see encouraging dose response in the 75 percent responders, and I would like to show that data to be able to show you the dose response that we find is important to remember.

For those patients who have this highly clinically significant response of over 75 percent drop-seizure reduction in the 1414 2-dose study, we show a nominally significant difference of 25 percent of the CBD-OS 20-milligram patients attaining this and only 11 percent in the 10-milligram where there's only 3 percent in placebo attaining this large reduction in seizure frequency. So there is evidence for dose response.

We also have some evidence that during the titration phase of all three studies, at stages 8 days into the titration, where barely the 10-milligram dose was reached, there is significant reduction in seizure frequency, and I'm going to

show you that data as well at day 8. So they just have reached the 10-milligram dose, and there is a notable reduction in seizure frequency.

So we do have some evidence that the onset of action is early and happens at lower doses. However, we do see the dose response that I pointed out between the 10- and the 20-milligram arm, and we believe that the 10-milligram dose is the appropriate dose to titrate to at first, then to hold at that dose and evaluate for efficacy, safety, and tolerability at that time.

DR. ALEXANDER: Great. Thank you. We just have a few more minutes. I heard one other question there, which was do we know anything about sensitization also or differences in responsiveness to the product over time, which I think was the question getting at long-term efficacy if I heard correctly.

DR. KNAPPERTZ: Yes. We have systematic data from the open-label extension study, and in that open-label extension study, as I'm showing you on this screen now, we have observed the patients

up to 48 weeks. And you can see that the effect is robustly retained, albeit it's an open label, so there's durability of effect. There's no indication for tachyphylaxis.

At the far right side of the screen, we show you the last 12 weeks because not all people in this analysis had completed the 48-week period. So even where you look at all 364 patients, you can see that there is a retention of the reduction from baseline and no indication for tachyphylaxis of the effect.

DR. ALEXANDER: Mr. Hoffmann, if I could just allow Dr. Mendelson a question because I don't think we've heard from him, and then we may have to move on. But we will have time for other questions for the presentations.

DR. MENDELSON: Hi. Your abuse liability study suggests a very low abuse liability, yet you report two possible cases of abuse or diversion. Maybe we should hear a little more about those. Are they actually concerning or is it just someone lost their medication? I would hate to see this

drug scheduled based on two case reports versus a good abuse liability study.

DR. KNAPPERTZ: You're right. These are based on a missing investigational product with no adequate explanation. So we had an adjudication committee that dealt with cases of potential abuse or diversion, and this committee adjudicated these two cases for us. The first case was likely a therapeutic error resulting in an accidental overdose without medical consequences. There was one case which then was labeled a potential abuse, and the second case has multiple instances of lost IMP, which was ascribed by the committee as potential abuse resulting from diversion.

DR. ALEXANDER: We'll keep going just for a few more minutes. Mr. Hoffman, briefly, and then I think Dr. Yeh.

DR. HOFFMANN: I had a brief question. If somebody from the company could give a brief overview of how this drug is manufactured, where is the plant cultivated, is hemp the plant that's used, and how do you extract the CBD and purify it?

Just briefly and without any trade secrets.

DR. KNAPPERTZ: We are growing the plants in glasshouses and greenhouses that are computer controlled, the temperature, humidity, and lighting controlled. The plants are enriched for CBD and decreased in THC through Mendelian breeding. Our growth medium is controlled. It is devoid of heavy metals and other contaminants. There are no pesticides and no fungicides that are being used. And there's dedicated quality control personnel and oversight. Manufacturing is in accordance to good manufacturing practices and consists of multiple steps that then leads to the API.

DR. HOFFMANN: Is it the hemp that's used, which is the variety of cannabis that has the highest amount of CBD and the very lowest amount of THC?

DR. KNAPPERTZ: It is a proprietary strain of the cannabis sativa plant that we have created through Mendelian breeding --

DR. HOFFMANN: And it's manufactured on your site or at a university?

DR. KNAPPERTZ: We have done this in house for 20 years.

DR. HOFFMANN: Okay. Thank you.

DR. ALEXANDER: I overlooked Dr. Perlmutter. My apologies.

DR. PERLMUTTER: This would be directed, I believe, to Dr. Wright and is a question about treating through elevations of ALT. How long does it take for the ALT to come back down, and is it dependent upon concomitant to other antiepileptic drugs?

DR. WRIGHT: Stephen Wright, senior medical advisor at GW. Perhaps I should start by saying there are certain rules governing what happens to patients who have an elevated transaminase. If it goes above 8 times upper limit of normal, they should be removed from the study. In those cases, those patients all resolve. In patients who go above 5 times upper limit of normal, they're observed, and if it remains above 5X, then they should be removed from the study. In those patients, all have resolved.

In those that go above 5X, perhaps I can show you the slide which demonstrates this most adequately I think. These are whose ALT was elevated above the clinically important 5 times upper limit of normal throughout the development program. There are 38 dots on the slide.

You can see if you look along the horizontal axis that the great majority of those resolve within 14 days, and that resolution is independent of the peak of the ALT. It's independent whether they were taking valproic acid or not. And I think that probably gives a quite reasonable answer to your question, that resolution.

DR. PERLMUTTER: And how would the risk of elevated ALT compare to adding valproic acid, for example, which is the one we commonly check for?

DR. WRIGHT: The risk of getting an elevated ALT on versus off is approximately 6-fold. If we look at that on -- [inaudible - mic fades]. You can see on the 20-milligram/kilogram dose, patients on valproic acid, 13.2 percent rate of elevation. On 10 milligrams per kilogram per day, 4.3, which I

think gives a good answer to the dose response, the dose relationship of the transaminase elevation compared with 1 percent on placebo, and the off VPA rates are much lower. In fact on the 10-milligram per kilogram dose, no patient got this elevation of transaminases off valproate.

DR. ALEXANDER: Okay. We'll just do two more hopefully brief questions and responses. Dr. Yeh and Dr. de Wit, and then we'll move on.

DR. YEH: My question is actually very brief. You had a certain percentage of patients that withdrew from the drug. When you discontinued the therapy, were there challenges with withdrawal seizures or any catastrophic ICU stays or anything like that?

DR. KNAPPERTZ: I am sorry. If I understand your question correctly, this is about patients who are withdrawing from the study and what happens to them subsequently?

DR. YEH: No. Actually withdrawal of the drug. In some patients that I've taken care of who have withdrawn the drug due to lack of access,

there have been withdrawal seizures, so I'm just asking a labeling question.

DR. KNAPPERTZ: All patients who withdraw have subsequent safety follow-up, and there has been no observation of increased seizure frequency associated with withdrawal of CBD-OS.

DR. ALEXANDER: Dr. de Wit?

DR. de WIT: Could you comment on the mechanism of action of the therapeutic effect?

DR. KNAPPERTZ: I'm going to ask Professor Whalley to address the question of mechanism of action, which he has studied in his laboratory at Reading University extensively over the last 8 to 10 years.

DR. WHALLEY: Thank you. Ben Whalley, director of research, GW Pharmaceuticals. This could be a long story, but I'll give you the headline summary in the interest of time. We believe it's a multimodal mechanism of action through our work in animal models and in vitro models primarily involving the targets GPR55, TRPV1, and ENT1, which is the endo

nucleotide transporter for adenosine. So it's a multiple molecular target only to reduce neuronal excitability.

Obviously, as we said at the beginning -- Billy Dunn said at the beginning -- the exact contribution of these molecular targets to the effects in humans, for the antiepileptic effect of CBD, remains to be fully determined.

DR. ALEXANDER: Great. Thank you very much to the sponsor and to the advisory committee for those thoughtful queries. We'll now move to the FDA presentations.

FDA Presentation - Natalie Getzoff

DR. GETZOFF: Good morning. My name is Natalie Getzoff. I'm a medical officer and neurologist in the Division of Neurology Products, and I will be presenting an overview of the efficacy and safety of cannabidiol in patients with Lennox-Gastaut syndrome and Dravet syndrome.

I will begin with a summary of the efficacy results. The application contained efficacy and

safety data from three adequate and well-controlled trials, two in Lennox-Gastaut syndrome, studies 1414 and 1423, and one in Dravet syndrome, study 1332B. Additional safety data came from three other sources, study 1332A, which was a 3-week, randomized, double-blind, placebo-controlled dose-finding study in patients with Dravet syndrome. This study was separate from study 1332B; and study 1415, which is an open-label extension study in patients with Lennox-Gastaut syndrome and Dravet syndrome, and the expanded access program, which consists of a number of small investigational studies in refractory epilepsy patients.

Here are the efficacy results of the trials described in the applicant's earlier presentation. FDA independently analyzed the efficacy data and confirmed the study results that the applicant reported earlier. As you can see from the table, the median reduction in drop seizures or convulsive seizures was significantly greater in the cannabidiol groups when compared to placebo in all

three trials.

The differences between cannabidiol at both doses and placebo were statistically significant all favoring cannabidiol and demonstrating efficacy. Sensitivity analyses yielded similar results to the primary analysis in all three trials.

Now I will present a brief summary of FDA's analysis of safety data from the cannabidiol development program primarily from the controlled trials. As noted earlier, safety data was derived from the controlled trials as well as from patients enrolled in the open-label extension study and the expanded access program. There was adequate exposure to allow for the assessment of safety.

There was one death during the controlled trials in a patient taking cannabidiol 20 milligrams per kilogram. This patient died from acute respiratory distress syndrome, and the death was not considered to be treatment related. Nineteen deaths occurred in patients in the open-label extension study or in the expanded

access program.

The most common cause of death in the uncontrolled studies was sudden unexplained death in epilepsy or SUDEP, which occurred in 4 patients. Five patients had other seizure related deaths, including one patient who had status epilepticus. Overall, the causes of death were varied and not unexpected for this patient population. None of the deaths was clearly associated with the drug. As expected in trials of an effective drug for treatment of seizures, the rate of study discontinuation associated with adverse events was higher in patients taking cannabidiol than in patients taking placebo.

This table presents the most common treatment-emergent serious adverse events from the controlled trials in Lennox-Gastaut and Dravet syndromes. As the table indicates, serious treatment-emergent adverse events, notably somnolence and lethargy as well as infections, occurred more frequently in patients taking cannabidiol than in patients taking placebo.

Drug-induced liver injury occurred more frequently in cannabidiol treated patients. This manifested primarily as transaminase elevations without concomitant bilirubin elevations. There were no cases of liver failure, Hy's law, or death due to liver injury. Although there were two serious adverse events reported as hepatic failure, a review showed that neither of these patients met accepted criteria for liver failure because neither had hyperbilirubinemia or elevated INRs. Dr. Dimick-Santos will provide a more detailed discussion of the liver findings in her presentation.

This table includes a selection of treatment-emergent adverse events that were frequently seen in the controlled studies. Hepatic, gastrointestinal, and central nervous system adverse events particularly occurred at higher incidences in patients taking cannabidiol than in patients taking placebo. Infections and rash were also more commonly seen in the cannabidiol treated patients. The incidence of

seizures as adverse events in the cannabidiol and placebo groups were similar.

There's an apparent dose response with some adverse events such as transaminase elevations, diarrhea, somnolence, and rash, but a dose response was not seen for all adverse events. Overall, the adverse event profile appears acceptable and manageable with labeling and monitoring.

In conclusion, the results of the three pivotal studies provided substantial evidence of the effectiveness of cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. The general safety profile appears acceptable, and identified risks can be managed with labeling and monitoring. At this point in our review, we have not identified any obstacles to approval.

Thank you. I'll now turn the presentation over to Dr. Dimick-Santos who will discuss the agency's analysis of the liver findings.

FDA Presentation - Lara Dimick-Santos

DR. DIMICK-SANTOS: Hello. I'm Lara Dimick

from the Division of Gastroenterology and Inborn Errors Products at the FDA. I'll be reviewing the data from the liver safety report that the sponsor submitted, and this review has been done in collaboration with Dr. Mark Avigan from the Office of Pharmacovigilance and Epidemiology.

I will not re-review the design of the clinical trials, the demographics, baseline characteristics, or exposures, as this data has already been presented. This presentation will focus on the signal of liver injury seen with cannabidiol. First, I want to go over some of the baseline data.

As you can see here, normal liver biochemistries were not required at baseline, and in fact, transaminases could be elevated up to 5 times upper limits of normal. However, exclusion of patients with significant elevations in total bilirubin or INR excluded any patients with significant underlying liver disease, and therefore it is unknown how these patients would react to this drug.

This next slide is just to remind you of the modest size and duration of the placebo-controlled trial data with only 540 patients exposed, however, it is reasonable secondary to the rarity of these diseases. Some liver safety data information was also derived from other groups from the phase 1 studies and the expanded access program.

This table shows the frequency of the biochemical monitoring during the placebo-controlled trials. Similar monitoring was included in the expanded access trials and the long-term extension trials, and this frequency of monitoring appeared to be appropriate to detect the signal of liver injury in these patients.

There were protocol-defined withdrawal criteria, as was discussed a little earlier, and this was very similar to the entry criteria except for the fact that the 5 times upper limits of normal was an entry criteria, but here for a withdrawal criteria, it had to last for more than 2 weeks.

This slide is just a little busy, but it's

just to show that about 20 percent of the patients at baseline had mild elevations in their transaminases with very few patients -- and again, I don't really have a pointer to show it to you, but very few patients having ALT elevations greater than the 3 times upper limits of normal at baseline.

Again, as has also been mentioned by several presenters, most of these patients were on multiple antiepileptic drugs at baseline with over 50 percent of patients on clobazam and over 40 percent of patients on valproic acid, both of which have been known to cause acute elevations in liver biochemistries and liver injury. But remember, these drugs were in the background and used continuously before the patients were randomized.

Now I'll move on to the results of the controlled trials. I will only briefly touch on data from the expanded access program, however, that was reviewed extensively in the sponsor's liver safety data report.

As you can see, there was a clear CBD related effect that caused ALT and AST elevations across a range of strata above upper limits of normal. The frequency of these aminotransferase elevations was dose related. And if you focus on the 20-milligram per kilogram group in the third column over and the placebo group, you can see the significance of significant ALT elevations above 3 times upper limits of normal, and the CBD 10-milligram group is 1.5, and the 20-milligram group is 16 percent, and then the placebo group less than 1 percent. However, as you go up to higher elevations in ALT, 10 and 20 times, you see that there are really no significant elevations greater than 20 times, except one outlier in the placebo group.

For those of you who are not familiar with an eDISH plot, this is a tool that's designed to show evidence of significant liver injury in data sets from clinical trials. This graph shows the peak values for each study subject in the pivotal randomized trials with total bilirubin on the Y-

axis and ALT on the X-axis. Those treated with CBD are marked by blue-colored stars and those on placebo are by red diamonds.

The right upper quadrant is called the Hy's law area and designates an area where total bilirubin would be greater than 2 times upper limits of normal and ALT greater than 3 times upper limits of normal. This is the area we look at for evidence of significant liver injury. As you can see, there were no patients in this pooled DS/LGS study and, not shown on this slide, there were also none in the expanded access programs. There are patients in the right-lower quadrant here, and these are patients with elevations in ALT but without significant elevations in total bilirubin over 2 times upper limits of normal.

Next, I want to show you two cases, and this first case is from a 12-year-old female with Lennox-Gastaut syndrome in trial GEWP1414, and then rolled over to the open-label extension. Her baseline labs were normal, and in her background treatment, she was taking concomitant clobazam,

valproic acid, ethosuximide, Keppra, and multivitamins.

As you can see here, she was started on placebo in the controlled trials. Then after 3 months here, she was started on cannabidiol. It was tapered up to a 26-milligram per kilogram per day dose, however, at about day 20 to 30 she became symptomatic, she developed altered mental status, and was hospitalized. That is right about here when this peaks. And as you can see, here's total bilirubin in the turquoise, ALT and AST in the red and the blue. Her transaminases elevated all the way up to an AST of 14 to 15 times upper limits of normal and ALT about 10 times upper limits of normal. And there was a slight increase in her total bilirubin. It didn't reach that threshold of 2 times the upper limits of normal, but there is definitely a bump.

Valproic acid levels were also high, and it was stopped, at right about the peak, right there, that second block, and the patient recovered. CBD dose was adjusted down. It was tapered down.

However, it was never discontinued, and then as she recovered, it was titrated back up. She continued on the CBD and did not have any evidence of recurrent liver injury. This case is adjudicated by the sponsor as likely related to CBD and demonstrates the multiple approaches that were taken in the trial in response to the CBD-related liver injury.

I want to show you one more case, and it shows you a 28-year-old with Lennox-Gastaut syndrome and mental retardation who was at baseline on Topamax, valproic acid, clobazam, Dilantin, and diazepam. Baseline liver chemistries were normal except for a mildly elevated GGT. So this is the run-in period and this is when drug is started, and this is when it gets to its 20-milligram day dose. But within about 2 weeks, the patient experienced lethargy, elevations in the transaminases, and right here at about the peak up at the top, on day 29, and then again on day 30, the clobazam dose was decreased. However, on day 31, the patient abruptly discontinued his CBD, his liver injury

symptoms resolved, and he went on -- and this case was adjudicated by the sponsor as to be likely related.

This next slide is to show time to onset of liver injury. In general, most of the cases of liver injury occurred early in the treatment course within 30 days and the majority within 3 months. There were hardly any new cases beyond one year. The use of concomitant valproate influenced both the incidence and the time to onset of the drug-induced liver injury. The top line of this graph, as you can see, shows people on concomitant valproate at the 20-milligram per kilogram per day dose, and you can see at 30 days the number of cases, 60 days, and 90 days. But a few of these cases did occur after that 90-day time point.

Here we're showing discontinuations of the 540 CBD patients in the controlled trials. Thirty-seven patients had ALT elevations greater than 5 times the upper limits of normal, which is what we consider evidence of a clinically significant liver injury. Eighteen patients discontinued from drug.

On behalf of the sponsor, Dr. Watkins, a hepatology expert who you met earlier, conducted an unblinded review of the individual narratives of all 37 patients, and he assessed that CBD contributed to the ALT elevations in 35 of the 37 cases, and it was also possible for the remaining two cases. We agree with this assessment, and we will discuss what happened to the other patients next.

Of those 37 patients from the controlled trials with ALT greater than 5, 17 patients recovered without or prior to stopping CBD; 12 patients recovered without any dose reduction; and 5 patients recovered after dose reduction or during taper. Eleven patients were rechallenged with CBD after experiencing ALT or AST greater than 3 times the upper limits of normal, which resulted in CBD discontinuation for more than 2 days. Of these, 4 patients experienced recurrence of ALT/AST elevations greater than 3 times normal; however, the nature and characteristics of the recurrence was not significantly different from the initial

elevations in terms of magnitude, time to onset, or the continued absence of any significant hepatic functional impairment. Seven patients did not experience a recurrence in ALT elevation.

This is, again, a little bit of a busy slide, and it's showing you the upper limits of normal, and then valproic acid, yes/no, yes/no, yes/no. And if you look here, there's a clear association between valproate and CBD with an increased frequency of ALT elevations. Patients who were not taking concomitant valproic acid exhibited ALT elevations greater than 5 times upper limits of normal at zero percent in the 10-milligram per kilogram per day group and 2.5 percent in the 20-milligram per day group. Only patients who were taking valproic acid in combination with CBD experienced ALT elevations greater than 8 times upper limits of normal. That's in the pooled control trials.

Other contributing factors, felbamate and clobazam potentially had some contributing factors because they both are known to be associated with

elevations in liver chemistries and liver injury, however, it was not clear from the control trial data whether these were clinically significant. Baseline elevations in liver chemistries however were associated with subsequent increased elevations in transaminases during the trials. With the limited data, there was no significant influence of age, underlying seizure, etiology on the transaminase elevations.

Then just briefly, in the expanded access programs, it was notable that the protocol CBD stopping rules were inconsistently adhered to by practitioners managing the patients. Several of the patients had reduction in doses of other concomitant medicines, especially valproate, however, 30 patients had ALTs greater than 5, and of these, 24 recovered prior to stopping CBD.

Conclusions. Our conclusion is that there is a casual association with the use of CBD and ALT elevations consistent with hepatocellular, drug-induced liver injury. However, there were no cases of severe liver injury, and no cases meaning

Hy's law criteria, and no deaths associated with liver injury. There is a dose-response relationship with higher frequency of liver elevations and the 20 milligram per kilogram group.

No patients with baseline underlying significant liver injury have been studied, therefore, it remains unknown how these patients might respond. The majority of patients with ALT elevations greater than 8 times upper limits of normal were discontinued from drug, therefore, it is not known whether these patients may have adapted or gone on to develop a worsening liver injury.

Concomitant valproic acid was the most frequently associated risk factor for CBD associated drug-induced liver injury, and there is a potential unknown for chronic liver injury. There's not enough patients at this time exposed for years to this drug to know whether some patients might have a smoldering inflammatory response that could potentially -- and I can only say potentially -- cause a problem for them down

the line.

I want to acknowledge again Dr. Mark Avigan's contribution to this review and the presentation. Thank you very much. I am to introduce the next person, who is Katherine Bonson, and she will be discussing from the controlled substances staff.

FDA Presentation - Katherine Bonson

DR. BONSON: Good morning. I'm Katherine Bonson, the pharmacologist in the controlled substance staff, and I'm going to be talking to you today about the abuse potential assessment that we did for cannabidiol CBD.

Under the FDA guidance from 2017 called the Assessment of Abuse Potential of Drugs, all CNS active drugs need to undergo an abuse potential evaluation during drug development. CBD is controlled under the Controlled Substances Act as a Schedule I substance because it is a constituent of a cannabis plant.

Under the current NDA, CBD is proposed for the treatment of a CNS disorder. Thus, it was

necessary to conduct an abuse potential assessment for CBD. During drug development, CSS, my group, provided feedback to the sponsor regarding which abuse-related studies in animals and humans would be required as well as feedback on their appropriate design.

So these are the studies that were done. We asked about receptor binding, where the drug acts neurochemically. We looked at behavioral studies, and these were all done using animal doses that produce plasma levels equivalent to or greater than human therapeutic plasma levels, and these were general behavior; the Irwin test; open-field test; and rotorod test; the Tetrad test that evaluates cannabinoid effects; drug discrimination that asks does a test drug produce similar sensations to a known drug of abuse; and self-administration, which asks does a test drug produce rewarding properties that produce reinforcement. We also looked at the clinical studies in terms of the adverse events in the clinical safety studies and a human abuse potential study, a HAP study.

For the receptor-binding studies, there was no significant affinity of CBD for either of the cannabinoid receptors CB1 or CB2, and this is unlike what happens with THC, which is the main psychoactive constituent of cannabis. There was also no significant affinity for other abuse-related sites, including opioids, GABA, dopamine, serotonin, NMDA, ion channels, or transporters.

For the general behavioral studies, these are conducted as safety studies for all drugs under development, and in the Irwin test of general behavior in mice, CBD produced a slight alteration in gait and a decrease in pain response relative to vehicle, but these were transient. In rats, there were no changes in behavior.

In the open-field test of locomotion in mice and in rats, CBD reduced locomotor activity at moderate and high doses relative to vehicle, and in the rotorod test of motor activity in rats, CBD produced no changes in latency to fall off a slowly rotating rod relative to vehicle.

The data from these general behavioral studies show that CBD produces some CNS activity, but only at relatively high doses. However, in order to determine whether CBD produces abuse-related CNS effects in animals, additional preclinical studies were required that specifically address abuse potential, and these are the Tetrad test, drug discrimination, and self-administration.

The Tetrad test is a screening test that measures changes in four behaviors that are known to be produced by CBD, and these are a decrease in locomotor activity, immobility, hypothermia, and antinociception. CBD did not alter locomotor activity, immobility, or antinociception, but it produced a little hypothermia at the highest dose. THC produced a decrease in locomotion as well as an increase in hypothermia and antinociception, but little immobility. This test shows that CBD does not produce an overt behavioral profile associated with a cannabinoid.

Then we had them do drug discrimination, and drug discrimination is an experimental method of

determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Test drugs that produce a response similar to a training drug with known abuse potential are also likely to be abused by humans.

In rats trained to discriminate THC from vehicle, CBD produced less than 46 percent generalization to the THC queue and full generalization is 80 percent. In rats trained to discriminate midazolam from vehicle, CBD produced less than 11 percent generalization to the midazolam queue. These data suggests that CBD has not produced sensation similar to THC or to a benzodiazepine.

We then had them do self-administration, and self-administration is a method that assesses whether a test drug produces rewarding effects that increase the likelihood of behavioral responses in order to obtain additional drug. That's called positive reinforcement. Drugs that are self-administered by animals are likely to produce

rewarding effects in humans, and the ability of a test drug to produce self-administration is indicative that the drug has abuse potential.

In the study they conducted, animals were trained to lever press for a rewarding substance. Rats were trained with intravenous cocaine or heroin in two separate studies, while monkeys were trained with midazolam. After self-administration of the training drug was stable, animals were allowed intravenous access to the following substances, which then produced varying degrees of self-administration in terms of infusions per session.

Cocaine produced the most. It was around 45 infusions in a session compared to CBD over a range of doses that produced less than 10 infusions. In midazolam trained animals, midazolam produced around 13 infusions compared to CBD over a range of doses, which was less than 1 infusion.

In heroin-trained animals, heroin produced around 18 infusions compared to CBD over a range of doses that was less than 7, and vehicle for all of

the three studies produced less than 5 infusions per session. These data suggest that CBD produces insufficiently rewarding properties to sustain positive reinforcement.

As described in our guidance, following completion of preclinical abuse-related studies, the resulting data are evaluated to determine if there are sufficient abuse-related signals to justify the need for a human abuse potential, HAP, study. Based on the preclinical studies evaluating receptor binding, general behavior, similarity to THC, and ability to produce rewarding effect, CBD did not produce meaningful abuse-related signals in rats and in monkeys.

The next step in an abuse assessment is to examine the adverse event profile in clinical studies to see if there's an abuse-related signal. In the phase 1 clinical studies with CBD -- and these evaluated pharmacokinetics -- patients who were hepatically and renally impaired in studies looking at the impact on sleep, there were no reports of euphoria-related AEs. And this is the

primary way that we determine whether a drug might get you high. No other abuse-related AEs were reported in any of these studies, so the AE data from phase 1 studies, which in this case does not include the HAP study, do not show that CBD produces signals of abuse.

The phase 2/3 studies are not really useful for evaluating abuse signals related to CBD because of the underlying neurological impairment in patients and the presence of confounding drugs. So specifically, the children in the studies are too ill or too young to volunteer accurate information regarding psychiatric of neurological AEs that are indicative of abuse, and the children in all three of the efficacy studies remained on their current antiepileptic drugs.

Based on the assessment of abuse potential of drugs, our guidance, a human abuse potential study is not typically conducted when there is a lack of a strong preclinical abuse-related signal and when there is a lack of euphoria-related AEs from clinical safety studies. However, given that

CBD is a Schedule I substance and that it can produce sedative effects, FDA required that the sponsor conduct a HAP study to provide additional experimental evidence of whether CBD has meaningful abuse potential in humans.

The HAP study. HAP studies evaluate the ability of a test drug to produce positive subjective responses in subjects compared to a known drug of abuse and to placebo. Subjects in HAP studies are individuals with a history of recreational drug use but who are not drug dependent. When the test drug produces consistently large responses on positive subjective scales that are far outside the acceptable placebo range, it is likely that the test drug has abuse potential.

The HAP study that was conducted with CBD evaluated the oral abuse potential of 3 doses of CBD, 750, 1500, and 45 [sic - 4500] milligrams, and these represent the 2 therapeutic doses 10 and 20 milligrams scaled up for a 75-kilogram adult and a supratherapeutic dose that represents 3 to 6-fold

greater than the therapeutic doses.

We also looked at dronabinol, which is synthetic THC for humans, at 10 and 30 milligrams; alprazolam at 2 milligrams; and placebo. This study used a randomized, double-blind, placebo-controlled, crossover design in healthy recreational polydrug users with a history of cannabis and benzodiazepine abuse, and there were 35 completers.

On the primary measure of the visual analog scale of drug liking, which is a bipolar scale of 0 to 100 with 50 as neutral, dronabinol and alprazolam produced statistically significantly higher drug liking scores: 74, 87, and 79, respectively, compared to placebo, which validates the study.

CBD at the lower therapeutic dose of 750 milligrams produced a mean drug-liking score of around 57, which did not differentiate statistically from placebo on drug liking and was within the acceptable placebo range of 40 to 60. CBD at the two higher doses produced very small

increases in mean drug-liking scores that were statistically significant from placebo, but these scores, 61 and 64, are barely outside of the placebo range.

On other positive subjective measures such as the visual analog scale for take drug again, good drug effects, high, and stoned, dronabinol and alprazolam produced statistically significant increases in mean scores ranging from 37 to 85 out of 100 on unipolar scales, where 0 to 20 is the acceptable placebo range in comparison to placebo.

CBD at 750 milligrams produced mean scores of 10 to 22 that were not significant on these measures. At the two higher doses of CBD, there were small but significant increases in mean scores 14 to 42 compared to placebo on the visual analog scales for take drug again, good drug effects, high, and stoned. All of the subjective responses to CBD, both the primary measure drug liking and all of these secondary measures, were statistically significantly less than those produced by either of the positive controls.

After each session, subjects were asked how much the test drug felt like any of the list of drug classes. This was done on a scale of 0, not like this drug class, to 100, very much like this drug class. The means score show that, as expected, dronabinol at both doses was identified as THC, 58 and 91 out of a 100; alprazolam as expected was identified as benzodiazepine 88 out of 100; and placebo as expected was identified as placebo, 71 out of 100.

CBD at the two lower doses was not identified as THC or any substance except for possibly like placebo with 54 and 52 out of 100. CBD at the highest dose was not identified as THC or any substance at all less than 36 out of 100 for any of the drug classes or placebo. It's interesting because the lack of humans being able to identify CBD as THC parallels the animal drug discrimination study where animals did not indicate that CBD produces THC-like sensations.

Then we turned to the abuse-related adverse events in the HAP study, and dronabinol produced

high levels of euphoria, 31 to 63 percent; alprazolam produced a low level of euphoria, around 8 percent; and CBD produces a similarly low rate of euphoria, around 5 to 8 percent. Placebo produced no euphoria. There were no other abuse-related adverse events reported for any of the drug treatments.

So the question that we wanted to ask was, though, was the euphoria signal from CBD, which ranged from 5 to 8 percent, indicative of abuse? And when an individual analysis was done on these subjects -- and remember, this is only 2 or 3 subjects out of 35 who completed -- out of the subjects who had a euphoria-related AE following administration of CBD, it turns out that euphoria-related AEs did not predict a high score on any of the positive subjective measures, and conversely, a high score on positive subjective measures for any subject did not predict a report of a euphoria-related AE.

So our concern regarding euphoria-related AEs does not appear to be valid since they were not

predictive of concurrent positive subjective responses in the same subjects.

Our conclusions from the HAP study are that CBD at the lower dose does not produce positive subjective responses indicative of abuse, and CBD at the two higher doses, which is the highest therapeutic dose and the supratherapeutic dose, produced some statistically significant increases in positive subjective responses, but these are statistically significantly less than the increased produced by alprazolam or dronabinol, and they were often very close to the acceptable placebo range. These two higher doses also produced much lower levels of euphoria compared to dronabinol, and they were either identified as placebo or no drug class at all.

Our overall conclusions then about the abuse potential of CBD is that the preclinical data do not provide signals that CBD has abuse potential. There were no abuse-related AEs in the phase 1 clinical study population outside of the HAP study. The HAP study showed that the higher therapeutic

dose of 1500 milligrams and the supratherapeutic of 4500 milligrams produce marginal signals of abuse potential from subjective measures and AEs. So we see very little evidence that CBD has meaningful abuse potential even at supratherapeutic doses in adults. Thank you.

Clarifying Questions

DR. ALEXANDER: Thank you very much. I think that concludes the FDA's presentations. And if that's the case, we'll move for clarifying questions for the FDA. These are for the FDA.

Mr. Hoffmann?

DR. HOFFMANN: I'd just would like the FDA to clarify if this product is approved as a prescription drug product, what will happen to the status and the enforcement of regulations for all the multitude of CBD products that are available over the counter?

DR. CHIAPPERINO: We can't address that in this committee meeting. Obviously, there will need to be a scheduling action of some sort because cannabidiol is currently controlled in Schedule I

and cannot remain there if it's going to be a marketed drug product and prescribed. But these considerations go up the chain. For the substance cannabidiol, the decision is going to be going up through FDA management and to the Department of Health and Human Services and to DEA for some other considerations in order for them to form any decision about cannabidiol's control under the CSA.

DR. HOFFMANN: Just as a follow-up, currently what are these products classified as? They're not dietary supplements. They're not dietary foods of any kind. What are they?

DR. CHIAPPERINO: I don't think that we can address that here. They're not approved drug products; that we can say. There are some marketed as dietary supplements, and FDA remains vigilant about considering products that require some enforcement activities under the FDC&A.

DR. DUNN: And I would just like to add in response to that question that the process that was just described that would involve sister agencies and such is a standard process for the scheduling

of drugs. It will be going through that normal process as many drugs do.

DR. ALEXANDER: I have a question about the transaminitis. As a general internist, it makes me a little nervous thinking about treating through. On the other hand, we saw data that was very helpful and reassuring, I think, especially that no patients, if I understood correctly, either fulfilled criteria for Hy's law, experienced liver failure, or died from liver failure. There was a suggestion about or mention of we don't know if people could have, quote/unquote, "smoldering inflammatory response."

So the question is, what do we know about other products, the history of other products that the FDA has regulated, therapeutics? Products that have transaminase elevation, what pans out with these over many longer years of study with respect to whether or not they ultimately turned out to be benign or not so benign with respect to the impact on the liver?

DR. AVIGAN: Hi. I'm Mark Avigan. I'm a

hepatologist, and it's an excellent question. Generally, there's not a long-term problem. In other words, with most of these hepatotoxic drugs with patients who have adaptation, they resolve, and the liver recovers, and then there is no long-term consequence of continued maintenance. There are of course some drugs that give a different profile of injury such as methotrexate, which would be a great example, where the effect, over time of accumulation of exposure, actually can potentially be fibrogenic.

I think in this case that's very unlikely because we see a lot of patients with adaptation, where they were treated through and there was resolution, but there were some for whom the drug was stopped. So this is more of a check box question, that in long -- this is not a red flag; it's just a check-box question, that in the long run, patients on long-term treatment will just have to be assessed from the point of view of the drug development program. But I don't think it will end up being an issue. It's more of the question of

what you do with an acute event and which patients need to be stopped, what would be the stop rules and so on.

DR. ALEXANDER: Thank you. Dr. Green?

DR. GREEN: We haven't spoken very much about drug interactions, and cytochrome P450 3A4 is pretty pervasive, and I understand this is metabolized that way. And I also understand it's a fairly potent peak-like or protein pump -- I don't know if it's an inhibitor or a substrate, and that's pretty pervasive.

Would there be any consideration in listing these as potential drug interactions?

DR. AVIGAN: I think Dr. Watkins, who really is an expert on many of these kinds of questions, answered the issue quite well, which is that they're potential mechanisms of toxicity where there could be conceptually drug-drug interactions. But we don't have an exact account for where the intersections would be. Clearly, a finding of the mitochondrial effect of the 7-carboxy metabolite of CBD is important to know about because so many of

these patients are also on valproic acid with a fluorine metabolite potentially intersecting.

So that would be, again, something of concern, but I think that we have to be somewhat open-minded about where these drug interactions could be. And we would learn more about them as we follow patients empirically by monitoring and making clinical decisions about dose reductions or stopping drugs when we get at a certain level of threshold.

DR. ALEXANDER: Dr. Mendelson?

DR. MENDELSON: Yes. Hi. A wonderful presentation on the abuse liability. I live in California, and you can now go buy CBD at a store, and the numbers, the amount projected in sales, are up to a billion dollars by 2022. What are people buying CBD for? I don't think they all have seizures. What's the abuse -- does the FDA have any signal, and should there be any concern about monitoring not necessarily abuse liability of CBD but other sales and other channels for safety?

DR. ALEXANDER: Is there a way to sharpen

that with respect to this application or the question at hand for us?

DR. MENDELSON: I think it's more -- once this product becomes available and it's sold, it's going to compete with over-the-counter versions and will maybe make the sale more likely or less likely. It's unclear to me. It's actually fascinating that many people are using this already in huge numbers.

DR. CHIAPPERINO: I think that these committee proceedings are to discuss the safety and efficacy of this proposed product. Obviously, there is a lot of interest in what's going on with CBD in the states. These products are marketed for a variety of things, and the FDA has issued warning letters. And in several cases, many companies have received some enforcement letters from FDA, but we can't really consider the future and what might happen.

DR. MENDELSON: I don't disagree with that, but it's worth noting that there's so little abuse liability in this population and informal abuse

liability studies.

DR. DUNN: Dr. Alexander, I'd also like to point out that using the term "cannabidiol" loosely like that might cause unfair comparisons or even equivalence determinations with a pharmaceutical product that is under our application review right now, but presumably would be produced and marketed if approved according to many manufacturing regulations and quality assurance issues. So cannabidiol here at this committee meeting today is referring to pharmaceutical grade cannabidiol as proposed by the applicant, which could be very different than the undetermined things that you're referring to that are out there.

DR. ALEXANDER: Okay. Thank you. It looks like things have picked up a bit. We have Dr. Cavazos, Dr. Acri, Dr. Onyike, and Dr. Yeh, among others.

DR. CAVAZOS: I want to push this a little forwarder because dosing is still an issue, and we do not understand what doses are about. I mean, people are sending in dispensaries. I'm in Texas.

It is a very highly regulated state process for that with a very limited indication, even though there is not an indication from the FDA to seizures. But still the issue is a 100-fold difference, and I want to make sure that the public understands and is protected about these issues given this pharmaceutical grade product.

DR. ALEXANDER: I appreciate that, and we will have opportunity for general discussion. Is there a particular question for the FDA about the doses that were studied?

DR. CAVAZOS: Were they evaluated in both toxicity, safety, and efficacy from their review at different doses beyond the three studies that were shown at 10 and 20 milligrams per kilogram?

DR. ALEXANDER: Can the FDA speak to the dose, the determination of doses, the dose finding study, the reasonableness of the doses that were studied rather than alternative doses higher or lower?

DR. DUNN: I don't think we can comment as to the sponsor's strategy in terms of what doses

they chose to pursue, but we've presented the information that we analyzed with regard to efficacy and safety of the doses that were studied.

DR. ALEXANDER: Okay. And we could hear from the sponsor subsequently later this morning about that if that's helpful.

Dr. Acri?

DR. ACRI: Kit, that was a really nice presentation on abuse liability. In the briefing materials, you discuss the possibility that there were trace amounts of THC in the product that might have accounted for the weak signal of euphoria, but then the plasma levels were inconsistent with that possibility. But I'm wondering -- and maybe this isn't a question for you but for the company -- what the trace amounts of THC in the final product actually are and whether they might contribute.

DR. BONSON: We have two backup slides. If you can go to my first backup slide, please. I think it's around 26.

So we asked could the low level of positive

subjective responses from CBD be due to residual THC. And the quantity of the residual THC contained in the CBD drug substance batch used for the human abuse potential study was around 0.03 to 0.06 percent weight per weight, and this is less than the product spec limit of 0.15 percent. So when you look at the doses that were used in the HAP study, the THC could range from 0.3 at the lowest percent in the lowest dose, up to 2.7 milligrams of THC in the highest dose that was used. And since the lowest marketed dose of Marinol, which contained synthetic dronabinol THC is 2.5 milligrams, the 2.7-milligram of residual THC in CBD might be of concern.

Next slide. So the residual THC in the CBD solution did not appear to produce meaningful Cmax plasma concentrations of THC. So 750 milligrams -- and again that was a very low range of THC -- produced only 0.27 nanograms per milliliter of THC, and when you went up 6 times higher, the levels of THC barely moved. It only went up to 0.40 nanograms per milliliter.

These plasma levels of THC after CBD administration are much lower than the THC levels after administration of actual dronabinol in clinical studies so that 5 milligrams of dronabinol produced 4.7 nanograms per milliliter of THC, and 10 milligrams produce about double that, 7.9 nanograms per milliliter. You can see this is one-tenth to one-twentieth of what you find with even the highest dose of CBD. So it's our conclusion that it appears unlikely that any positive subjective responses after CBD were the result of residual THC.

Does that answer your question, Dr. Acri?

DR. ACRI: Yes, it does. And I'm assuming that the manufacturing controls are such that there will never be higher than 0.05 mgs of THC in the final product.

DR. BONSON: I think that's a question for the sponsor.

DR. ALEXANDER: I'd like to wait if that's okay, but let's put a pin in that one also for the sponsor to address when they next speak or during

the discussion period around the question.

Dr. Onyike, we just have a minute or two, and then we'll move to a brief break.

DR. ONYIKE: So far we've heard about the human abuse potential from the perspective of the compound, but what I'm interested in as well is what is likely to be the behavior of the population that this medication targets. I'm predicting that it will be very low likelihood that they would misuse it. But I would like to know what is the likelihood -- or what is known of misuse or diversion of clonazepam in populations with LGS or DS, or any other serious epilepsies.

DR. ALEXANDER: Can you just link that to this study product?

DR. ONYIKE: Yes. Well, I'm linking it in terms of the target population. What is known of the behavior of people who have LDS -- sorry, LGS, DS, or other serious epileptic syndromes who are prescribed clonazepam.

DR. ALEXANDER: Does anyone at the FDA want to tackle that?

DR. CHIAPPERINO: I don't think we can tackle an epidemiology related question about a substance that is not before us right now for consideration. It's an interesting question. I think clonazepam is controlled as a Schedule IV drug. We have not reviewed data recently to know what is happening from epidemiology studies.

DR. ALEXANDER: Thank you. One final question from Dr. Yeh, and then we'll have a brief break.

DR. YEH: Mine is a quick question related to the self-administration studies. Thank you very much for that nice presentation. In the comparisons between cocaine and CBD and the other substances and CBD, you reported that there was a range of doses. Did you find a dose effect in the self-administration?

DR. BONSON: No, no. It was always less than the very low levels that were already shown, so I don't think even if there were slight differences like 5 to 6 to 7 at the various doses, that those were meaningfully different.

DR. YEH: So those are meaningless, then --

DR. BONSON: I believe so.

DR. YEH: -- even though they're higher than placebo.

DR. BONSON: If they were, yes.

DR. YEH: Yes. Okay. Thanks.

DR. ALEXANDER: Thank you. We'll take a 10 -- 15; okay. It's going to be 15 minutes. It won't be shortened if necessary. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume in 15 minutes.

(Whereupon, at 10:18 a.m., a recess was taken.)

Open Public Hearing

DR. ALEXANDER: We'll now reconvene the advisory committee meeting. And just one point of order, we'll have an opportunity for brief responses and clarifications from both the sponsor as well as the FDA before the question that's posed to the committee and the committee discussion. So

I just wanted to let both the FDA and the sponsor know about that opportunity.

We'll now begin the open public hearing portion of the meeting.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it's important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral 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 payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at this 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 this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this 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 me. Thank you for your cooperation.

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

MS. NUSSENBAUM: I'm Evelyn Nussenbaum, and

I am here representing myself.

DR. ALEXANDER: Thank you. Please proceed.

MS. NUSSENBAUM: Thank you. Good morning. My son, Sam Vogelstein, was the first person to try Epidiolex, and our family helped set in motion its launch and path to the United States. I want to briefly tell you how we found our way to it because it underscores how important it is to have scientists and the government involved in the development of pharmaceuticals made from cannabis and how gratified I am to see you all here.

Sam started Epidiolex in May of 2013. He's been completely seizure free two and a half years. He has or had epilepsy with myoclonic absence that caused him to have as many as a hundred seizures a day that looked like this.

(Gestures.)

MS. NUSSENBAUM: They started when he was 4, got worse when he was 6, and nothing could stop them, not 2 dozen medications, the ketogenic diet, and corticosteroids that gave him moonface like a cancer patient. By the time we found our way to

Epidiolex, he'd had uncontrolled epilepsy for eight years.

Sam does not have Lennox-Gastaut or Dravet, which I know are the symptoms under official consideration today, but Epidiolex didn't even have a name when he tried it five years ago. It was just a pile of pharmaceutical grade cannabidiol that GW Pharmaceuticals was studying. I learned about CBD in the British medical journal, Seizure, which had a paper about how it worked as a anticonvulsant in rodents. It was a ridiculously thin thread to hang my hopes on. But in 2012, we had no other options, no medications, and Sam was not a surgery candidate.

First, we tried CBD tinctures we bought locally in Berkeley, California, but when we had them lab tested, they all had less CBD than their labels claimed and some had none at all. We bought pot with a scientist friend who also had an epileptic child. Two chemists extracted the CBD for us, gave us what we estimated was about 2 weeks worth. Both kids responded immediately, but the

2 weeks went fast, and the chemists could not risk helping us again. Then I read about GW. Epilepsy was not their focus then, but they had greenhouses, plant stock, labs, and they were extracting cannabidiol and other cannabis compounds regularly and systematically.

While some people love to hate evil drug companies, I'm not pro or con. I admire GW, and I paid my own way here. But they're good at something crucial, quality control. Every dose of medicine a drug company makes is the same, batch to batch, bottle to bottle, and dose to dose. When you're trying to treat a serious disease, you don't think about how important that is until you can't rely on it.

I never aspired to treat Sam with cannabis. I cringe when people congratulate me on treating my child with a so-called natural substance. I'm relieved doctors are overseeing the administration of this plant compound isolated from the other compounds with which it normally occurs. Honestly, if I'd found good science that a motor oil extract

could help seizures, I would have pursued that, but I pursued Dr. Jeffrey Guy instead. And when I finally got through to GW's chairman in the fall of 2012, I didn't surprise him. He had been reading the same studies that I had, certainly more since he actually had a medical degree; I'm a journalist.

After learning that Sam had responded to lab-extracted CBD, he was open to letting us try GW's but not here. Anti-cannabis sentiment was too strong. It was legal for us to try in London under a doctor's supervision, so we went during Sam's Christmas vacation, and it worked. The day before Sam started GW CBD extract, he had 68 myoclonic absence seizures. After 3 days, he had one in 1 day. We stayed two weeks most entirely seizure free. Once home, we submitted applications to the DEA and the FDA to make Sam his own one-boy trial. We got approval in the middle of 2003. He remains on it today. And now I'm going to go really fast.

One other thing, Epidiolex is not the only AED Sam takes. Sixteen months after starting it, 99 percent seizure free, he had a tonic-clonic

seizure and another. This is typical in adolescence for his system. We upped his Epidiolex, but it didn't help. But when we added a tiny amount of Depakote, a drug he had failed twice before, everything stopped. The same thing has happened to another boy with Sam's seizures.

I would like to suggest that there's a synergistic mechanism between CBD and Depakote in very low doses. I know that in one study when kids already on large doses added Epidiolex, liver enzymes increased. But this is different, so I'm hoping someone will look.

Thank you for considering giving our kids access to this drug. Thank you to GW for making a safe and consistent and quantifiable medication. And thank you for letting me talk.

DR. ALEXANDER: Thank you very much. Will speaker number 2 please step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. VOGELSTEIN: Hi. My name is Sam Vogelstein. I am 16 years old. I live in

Berkeley, California. I had seizures for 10 years. My parents tell me that there were times where I used to have more than 100 seizures a day. Then I went to London with my Mom to try the medication you are considering for approval. I was the first person to try it for epilepsy, and it helped get rid of my seizures. I've been seizure free for more than two years now.

Now I can understand what goes on at school, and I can have adventures that never would have been possible before. I just went to South Africa for two weeks without my parents on a school trip. I had a bar mitzvah 18 months ago. I'd like to be a neurologist and help people with epilepsy someday. I wouldn't have been able to do any of that if I hadn't tried this medication. It changed my life. I want it to help other people, too. I want people to be able to get this medication at pharmacies, and I hope this will bring us closer to getting rid of epilepsy. Thank you for letting me speak.

(Applause.)

DR. ALEXANDER: Thank you very much. Will speaker number 3 please step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. PRIVITERA: Michael Privitera. I'm a professor of neurology. I direct the epilepsy center at the University of Cincinnati, but I'm here representing myself. I was a site investigator for the 1414 study, but I did not get any sponsorship from the company to be here today.

I want to start by saying that this is a historic moment, and I want to congratulate GW, Greenwich. I want to congratulate the investigators involved in this study. I also want to congratulate the patients and families who were brave enough to participate in these studies, and I do want to congratulate the FDA. I think this is a remarkable time.

I want to make just three quick points. First, I think something that everybody in this room understands is that we absolutely really need new treatments for people with epilepsy. I've been

in this field for 35 years. We've had lots of new drugs approved, and I still have hundreds, if not thousands, of people in my practice that continue to have seizures despite optimal doses of medications.

Second, I think the data that we saw this morning is remarkable in terms of the rigor that was applied to the study of this compound both in terms of efficacy and safety and also the abuse potential data that I think was really excellent.

Third, I'm very excited because I think this compound will open new doors. We don't really understand exactly how it's working to stop seizures, but it's very different than any other drug that we've seen, and I really am excited about the potential future.

These studies were really the most rigorous scientific studies done. They were placebo controlled, careful monitoring of compliance, blood levels, adverse effects, drug-drug interactions as you've seen. No cannabis related product has ever been through rigorous studies like that. This will

be more reliable than the dispensary marijuana that's available in many states, including my own state. We know that there will -- we'll know about impurities, THC content, dose-to-dose variability, and expiration dates. These are things that no one in any dispensary will be able to tell you about the compounds that are there. I think this is extremely important. As somebody previously said, these are the kinds of things that we rely on with all our drugs or even when we buy Tylenol at the pharmacy. And until you don't have those things, you don't realize what you're missing.

Again, I feel like this is just the beginning. We're just starting to learn about how this drug works, how we dose it, what the drug-drug interactions will be, and I'm very excited for additional breakthroughs in neurology. I hope that this compound will be available or it will be useful in other neurologic disorders. And I think most importantly, I've talked to many people in different therapeutic areas who've said, you can't do the research because it's Schedule I. And I

think what we've proven today is that when you have the desire and the willingness to do it, you can do these studies. We can look at this carefully, and I'm really excited about the future of epilepsy. Thank you.

DR. ALEXANDER: Thank you very much. Will speaker number 4 please step up to the podium? Please introduce yourself and state your name and any organization you are representing for the record.

MS. VILLAS: Are there slides? There should be slides for this. Put those on the screen.

DR. ALEXANDER: Do we have any slides for speaker number 4? Shall we go to speaker number 5, and we'll come back. Please, give us a few minutes.

Will speaker number 5 please step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. CARLIN: Yes. My name is Stephen Carlin, and I'm speaking on behalf of my daughter,

Zora Carlin. Also I have slides as well.

DR. ALEXANDER: Okay, speaker 5, yes. Please continue.

MR. CARLIN: I'm not being compensated to testify at today's hearing. My travel is being supported by GW. Speaking on behalf of my daughter, Zora, she has a severe form of epilepsy called Dravet syndrome. It's very hard to treat as well as to control the seizures. She's at a very high risk of SUDEP, and it's even at a higher risk when her seizures are not controlled.

At 6 months old, she was diagnosed with Dravet syndrome, and that's when she began taking very powerful antiseizure medications that had stolen her smile, happiness, and ability to communicate effectively. This is when mayhem showed up at our door.

Upon taking and failing up to 15 different powerful drugs, her seizures only became worse. She got to a point where she was having 40 to 50 seizures a day, taking 30 to 40 milligrams of valium to try to stop them. Nothing work. She

just had seizure, after seizure, after seizure. The short ones probably lasted her 5 minutes, and the long ones went 30 minutes and beyond.

Her life consisted of sleeping and seizing, not to mention the side effects that the medications -- they were horrible. One medication caused her to physically rip her skin off and bang her head purposely against things in the house. She was having such a hard time walking without falling or bumping into things. She lost her ability to smile or do anything fun, live normally like most kids.

She couldn't go outside. She couldn't do anything the other kids could do. She couldn't ride her bike. She couldn't swim. She couldn't swing on the swings. She couldn't do anything outside. She tried to, but would always start having seizures and wind up back in the house sleeping. I haven't even mentioned all the school that she missed. She was missing school constantly and with the seizures and the medications, it would erase her memory, and that's what made school

important. And most of all again, she couldn't smile. My whole family couldn't do anything. Her big sister Eva, she couldn't do anything either. She was basically succumbed to the home because of Zora's seizures.

Long story short, her dad found out there was something out there called cannabidiol or CBD. He stopped everything and worked long and hard at the North Carolina General Assembly to get it accepted. Even our neurologist agreed that it would be a good option to help save her smile. All his hard work paid off. He was able to get started in a clinical trial taking Epidiolex, where we were sure that this would work and slow her seizures and bring her beautiful smile back.

On January 13th, her dad was thrilled to give her the first dose of Epidiolex while under the care and control of our neurologist. Little did we know how much our lives were about to change. Within a few days, her seizure activity greatly decreased. Over the following months, she was able to both reduce and stop taking medications

that stole her smile.

Her seizures went from 40 to 50 a day to only a few or none per week. She can now go outside in the summer, ride her bike, swim, swing on the swings, do all the things that all of her friends do. No longer does she miss going to school, and she's learning and speaking amazingly. Most of all, she can finally maintain her smile.

This has changed our whole family's life, and we're pleading with you today to please approve her smile by approving this medicine. I want to thank you for giving me the opportunity to speak. This is just a small fraction of our story, and I hope it made you smile. And thank you, GW, for giving us our family back. Thank you.

DR. ALEXANDER: Thank you very much for your presentation. We will return to speaker number 4, but I'd like to continue on for the time being.

Is speaker number 6 here?

(No response.)

DR. ALEXANDER: Okay. We'll go to speaker number 7. Will speaker number 7 please step up to

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

DR. BEBIN: Good morning. My name is Martina Bebin, and I'm professor of pediatric neurology at the University of Alabama at Birmingham and the Children's Hospital of Alabama. I have been involved in antiepileptic drug development for over 20 years. I am here at my own expense but have served as a consultant for GW in the past. Currently, I'm also involved in another GW clinical trial for tuberous sclerosis complex.

For the past three years, I have served as the principal investigator for a large pediatric expanded access program for Epidiolex. The UAB CBD program was established to evaluate the safety and tolerability of cannabidiol for the management of treatment-resistant epilepsy. Eighty children have been treated in this program, and support was provided by the state of Alabama General Fund, and Greenwich Biosciences provided Epidiolex at no cost to the patients.

As PI of the CBD program, I've had a unique opportunity to treat a wide array of different types of debilitating epilepsy and epilepsy syndromes with Epidiolex. All of the participants in the program had failed multiple antiepileptic drugs and carried a heavy seizure burden. The parents of these children were all committed and enthusiastic to have access to Epidiolex through the expanded access program and realized the safety and tolerability information collected was valuable to further understand the potential role of Epidiolex in the treatment of epilepsy.

Over the past three years, the program has been able to follow each participant's change in seizure frequency, severity, use of seizure rescue medication, side effects, potential drug-drug interactions, and overall change in quality of life and cognitive function. I would like to share some of the insights I've gained as my role as PI.

The overall response to Epidiolex in the UAB pediatric EAP program is impressive. At least 70 percent of patients had a 25 percent reduction

or more in seizures, and approximately 63 percent had a 50 percent or more reduction, and approximately 30 percent had a 75 percent reduction or more in seizures at one year participation in the program.

I learned there was no way to predict who would be a responder and non-responder to Epidiolex. It requires careful consistent monitoring of the child's seizure counts, change in seizure severity, use of rescue medication for prolonged seizures, reports of side effects, and overall changes in quality of life. It became clear there is an optimal dose range for responders, and it can vary between 5 to 15 milligrams per kilogram per day. This is why knowing the seizure type the child is having and having the parents maintain seizure diaries is an invaluable resource.

The side effects of Epidiolex are manageable and the drug-drug interactions can be minimized and often avoided with close monitoring of liver function tests and AED levels. For a small

percentage of patients who have become seizure free, it has been remarkable. It is rewarding to see and hear the sense of relief from the parents and children.

For the adolescents who have become seizure free, Epidiolex has provided the first opportunity to drive, change their outlook in school, and aspirations for the future. For the younger children, it has meant a greater ability to participate in peer group activities, attend school field trips without their parent, spend a night at a friend's house, and sleep in their own bed for the first time in years.

Given my experience for the past three years, it is my opinion that Epidiolex has the potential to make a significant impact in improving the seizure control and quality of life for so many children suffering from intractable epilepsy. The U.S. expanded access program has provided important information on safety and tolerability of Epidiolex and has helped laid the foundation of our understanding of Epidiolex and its role in the

treatment of epilepsy. Thank you.

DR. ALEXANDER: Thank you very much. Will speaker number 8 please step up to the podium? Please introduce yourself, state your name and any organization you are representing for the record.

MS. TREADAWAY: Hi. I'm Katherine, and this is my husband Tim, and we came here from Dallas, Texas to give testimony on behalf of our daughter, Riley, who was diagnosed with Lennox-Gastaut syndrome. GW did support our travel, but they are not compensating our time here today. We wanted so much to be here to share Riley's story and are very grateful for this opportunity.

A Brazilian poet wrote so eloquently, "Nothing we endure makes sense if we don't touch people's hearts." I hope Riley will touch your heart today and convince you of the need for more therapy options for children with intractable seizures.

It has not been an easy life for Riley. Her first seizure was at 4 months old, and she was started on antiepileptic medication. This was just

the beginning of a whirlwind of craziness and hospitalizations. She began to have infantile spasms at 6 months, requiring more medications, which we could not even purchase in the U.S. at the time.

Riley is now 13 but cognitively she's about the same she was at 1. We do everything for Riley. We diaper her, bathe her, dress her, feed her. She's unable to communicate in any way and is completely nonverbal. No matter what we have tried over the last 13 years, nothing has controlled her seizures. I feel like they have stolen her happiness and childhood. She has about 5 seizures a day and some are violent. She throws up after some of them. She has to go to sleep immediately after some. One seizure resulted in her arm being broken and another needing stitches on her face.

She has been on so many medications over the years. Some have pushed her development back even to the point that she began to aspirate food and liquids requiring a feeding tube to be placed, another heartbreaking and difficult loss. Another

made her like a zombie incapable of even rendering us a smile. She has had a temporal lobe resection. She's been on the ketogenic diet. She has a vagal nerve stimulator. None of these have stopped her seizures and given her an opportunity to learn and just be a regular kid.

The dreams that I've had for Riley have slowly drifted away over the years because of unstoppable seizures. The hope and possibility of a new treatment can't come fast enough. If this therapy could save families the heartache and horror and fear of seeing their child convulsing with violent seizures and give them a chance of living a regular kid's life, I would not hesitate for one second in urging your approval of this new therapy.

MR. CHAPMAN: This is the best advocate for Riley God could have given that little girl. I'm going to go off script a little bit because seeing and hearing some of these other stories are real close to home. It's hard to watch every day. You know they can't learn when their brain activity is

not right. We don't trust any of the available resources for what we think she needs. We trust what GW's doing. She's only 13, and time is of the essence. It's getting worse. We think it will help, and we think a lot of these kids deserve a shot at being help.

Thanks for your time. I respect your professional opinion, and I'm grateful that you're here to help us provide these opportunities for all these children.

MS. TREADAWAY: Thanks so much.

DR. ALEXANDER: Thank you very much. We'll return to speaker number 4. Will speaker 4 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. VILLAS: I'm back. My name is Nicole Villas and I am representing the Dravet Syndrome Foundation who is dedicating to funding research and supporting families. The sponsor did not pay for my travel to be here today, but they do sponsor other community-wide events. I'm going to do this

without the slides. We're not sure why they're not going through, so bear with me. This will be a little bit different than I planned.

By now you guys know that Dravet syndrome is one of the most severe forms of epilepsy, that the seizures are not just one-dimension [indiscernible], self-resolving occurrences that are done after they finish. They can be long, they can be medical emergencies, and they can require very extensive recovery times for our children. These kids and adults with Dravet syndrome are not your average epilepsy patients. They've been through a lot, and if they're more than a year into this mess, they've probably run through all of the FDA-approved treatments available to them, none of which are indicated for Dravet. They've tried the ketogenic diet, brain surgeries, implants, supplements, dietary things; everything you can think of, they've tried, and they're still seizing.

But of course we know it's not just about the seizures. We did a recent survey of our community and found that in 13 areas that we

surveyed, our patients had at least one issue in each of them. The areas would range from sleep issues, to behavioral issues, to cognition and speech impairment. And in those 13 areas, almost all of our patients had at least one issue going on. A lot of the traditional anticonvulsants out there have side effects that affect those issues, and when you add medication after medication in this rational polytherapy, you can quickly arrive at a risk-benefit analysis that doesn't make sense for our kids.

In recent years, the FDA has pledged to take the patient's voice into account in reviewing new drug applications, and luckily for you, we've compiled this data. You can find it; it's published. But our caregivers' top concerns are speech and communication, sibling issues, cognition and development, behavior, and others. Epidiolex has a chance to affect a lot of those areas. The caregivers' global impression overall had significant benefit, and that overall score affects a lot of the issues that our caregivers rank as top

concerns.

One of the issues was sleep, and although the sleep measures didn't show statistically significant benefit, you might think that that's not a benefit of Epidiolex for our kids. But when you remember they're on a whole bunch of other medications that often do interrupt sleep, having the option of introducing a med that doesn't affect sleep is actually a really positive thing for our community. So it's those little intricacies of the well tolerated side effect profile that this drug offers that really is attractive to our patients.

In the same survey, the community voiced their preference for treatments that reduce seizures without the heavy side effects. This liver enzyme issue that we've heard about this morning is not a top concern for caregivers. We've dealt with that in other medications. We know how to handle that. We don't like the side effects that dull cognition and create aggressive behaviors that a lot of these other anticonvulsants do, which brings us to our last point.

If you followed our community for the past six years, you've seen the documentaries. You know that families are experimenting and it's happening a lot. Up until now, neurologists have been innocent, frustrated bystanders whose hands are tied. They can't advise or prescribe on cannabidiol, but they don't have anything else to offer us either. This is your chance to arm them with a well-researched, consistently-manufactured monitored product that they can offer as a medication.

These patients have been through so much. They've overcome so much. They can do so much. As you see in the pictures, they're capable. And everyone in this room, the regulators, the clinicians, the parents, we owe it to them to not hold them back and reduce seizures with minimal side effects.

The Dravet Syndrome Foundation, who's dedicated to research, applauds the rigorous clinical trials that have brought CBD before this regulatory committee, and we urge you to approve

Epidiolex. We support every family demanding and deserving access to CBD no matter which project they use, and we believe this is the most reasonable, responsible step to take in addressing their unmet needs. Thank you.

DR. ALEXANDER: Thank you very much. We'll now move on to speaker number 9. Will speaker number 9 please step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. SMITH: My name is Lisa Smith, and I'm from Whitestone, Virginia. I'm speaking on behalf of my daughter Haley, who has Dravet syndrome. GW has supported my travel, but I am not being compensated.

This is Haley. Her first seizure was at 5 months of age, and it lasted over 25 minutes. Her second one was over 45 minutes. And when we went to her second neurologist, but our first long-term neurologist, Dr. Ralph Northam, he did not want to put her on a regular dose of medication because he felt she'd outgrow it.

And he also felt that it would impede her ability to learn and her brain development. And I'm very thankful that he did because I think we have more -- she functions now -- she's 17 but functions like at a 5-year-old because of that. I have a picture of my twin boys there, too because Dravet syndrome does not just affect the individual; it affects the whole family.

By age 5, Haley had tried and failed 13 different medications and was on two medical diets and failed those, too. She didn't have a diagnosis, so the medications she was on during the ketogenic and modified Atkins were contraindicated, and we knew that in hindsight. But also because there was not enough literature on Dravet, our doctor did not know to look at that as a reason for increased seizures.

We went back to VCU in Richmond in 2005 and were under the care of Dr. Pellock, which we love and we miss greatly. He got to the point -- she was finally diagnosed by him when she was 7, and when we would meet with him, it was a collaborative

event. He would ask what the experts like Nicole would say on her message boards because he didn't know how to treat Haley. By the time she was 14, she had tried and failed 17 different medications and combinations of them.

She also had a VNS implanted, and the doctors said there's nothing left. So what do you do when you have a 14 year old and there's nothing -- they said they would prescribe CBD if they would not be arrested at a state or federal level. We were greatly encouraged because GW was going to come to VCU in 2014-2015, but the red tape prevented the study from starting on time, so we took matters in our own hands because we were losing our daughter.

So we changed the bill in Virginia, and Haley's on the governor's lap only because she wants to get to the microphones.

(Laughter.)

MS. SMITH: That's the only reason. She's like I see a way to get there.

At the age of 14, her seizures were over a

thousand a year, and the rescue drugs that we had at the time never worked.

She could have had up to 12 milligrams of Ativan in the emergency room, 5 milligrams of Vorsan [ph], and she'd still continuing seizing. So there was no stopping them.

Haley started a strain of CBD since we passed the law to allow CBD and THCA oil in Virginia, and you can see the difference, just right there. Just look at her eyes. But if you want a more scientific base, since you're a bunch of scientists here, here are her seizures over the years. And I just want to remark that at 2002 was when she started her drugs, and they just kept going up despite the 17 different pharmaceuticals. And in 2012, it just took off. It dropped with the CBD, and you noticed in 2016 we stopped counting. That's because we decided to enjoy our daughter and not count. She still had seizures, 1 to 2, 3 a day, but the rescue drugs worked a little better.

But what she's doing now is she's learning. She's totally obsessed with firefighters, and she's

learning her states by the forest fires. So pole up, ladder in that picture is about firefighters. She's engaging in pretend play. The family's able to go do things. The picture on the left is us on a Disney cruise, which we never would have entertained prior to the oil. So I just appreciate having it, but because we have a different oil than what GW offers, what we don't have is input for a neurologist's assistance and [indiscernible] oil or any federal protections. But in the end, it's all about quality of life. We might not hit the study results of more than 50 percent decrease in seizures, but our quality of life has increased 100-fold.

So I encourage you to pass this and vote on because once it's out in the public, then there will also be more awareness for Dravet syndrome, and no one will have to wait six and a half years like we did to get diagnosed. Thank you very much.

DR. ALEXANDER: Thank you very much. Will speaker number 10 please step to the podium and introduce yourself? Please state your name and any

organization you are representing for the record.

MR. GATTONE: Good morning. My name is Philip Gattone. I'm president and CEO of the Epilepsy Foundation, a leading patient voluntary health agency solely dedicated to the welfare of 3.4 million Americans and thousands of families who have lost loved ones and their families. I've not received any compensation for travel support to appear today. My remarks are solely that of the Epilepsy Foundation.

I come before the committee today to express the urgency my community feels for new and better therapies for epilepsy. I also offer my remarks as the father of an adult son with epilepsy. My son endured thousands of seizures in his life and two brain surgeries. And because of the new therapies that were available, my son is now 31 years old and he's living a fairly typical life, albeit without 12 centimeters of the right side of his brain.

But not everyone who has epilepsy is so lucky. One-third of people living in the United States with epilepsy have found no therapy that

stops their seizures. In a numbers perspective, that's more than 1 million families in the United States. Despite significant advances made over the last several years, the number of people with epilepsy who don't achieve seizure freedom with current therapies has not changed.

Epidiolex represents hope for the many individuals living with refractory epilepsy. Barbara Kroner is here in the audience today with her daughter Ellie, who is a beautiful 19-year-old young woman who started having seizures at 3 months of age and was later diagnosed with Aicardi syndrome. Ellie has tried 19 different anti-seizure medications, the vagus nerve stimulator, and had two brain surgeries. In February of 2014, Ellie received her first dose of Epidiolex as part of a clinical trial and went from having 3 significant seizures every day, lasting up to 15 minutes each, to having many, many seizure-free days.

Ellie is not alone. I'm also privileged to be standing with Polly VandereWoude, who is here

with me today to share her story.

MS. VANDEREWOUDE: Thank you, Phil.

Good morning. My name is Polly VandereWoude, and the Epilepsy Foundation supported my travel at today's hearing. In 2010 when my daughter Olivia was only 2 months old, she had her first seizure. From that day until her first dose of Epidiolex in 2014, Olivia suffered 8 to 15 clusters of seizures lasting 8 to 10 to over 30 minutes a piece every day of her life.

Epidiolex is by far the most effective medication she has taken, and it has the fewest side effects. Olivia was unable to find success with 6 failed medications, the ketogenic diet, the vagus nerve stimulator, and she was ruled out as a candidate for brain surgery.

At the young age of 4, Olivia was running out of treatment options. The cocktail of medications left her sedated, her respiratory drive suppressed, and she was prone to frequent infections and hospitalizations. Fortunately, Olivia was selected for one of the first

compassionate use trials out of New York University.

During her time on Epidiolex, Olivia has experienced some great improvements. She was able to wean off all but one other seizure medication, and her overall health improved. She has not been hospitalized for an infection since starting Epidiolex. She has seen a 45 percent reduction in her seizures from over 1200 a year to 650.

In 2014, after beginning Epidiolex, she experienced her first seizure-free day, and that's grown from 28 in 2015 to 80 in 2016 and 2017. So while not seizure free, it has been a huge improvement in her quality of life.

Olivia is peaceful, sweet, gentle, and loving, and while she has significant disabilities, since Epidiolex, she has smiled, vocalized, made eye contact, shows her personality, and is more closely connected to the people in her life. This is a first for her and for our family. It's brought a sense of normalcy and has been a lifeline.

Thank you for the opportunity to testify today. I ask that you approve Epidiolex. Olivia's had the benefit of four years on this medication and there are hundreds and thousands of kids who could really benefit from this medication. Thank you.

DR. ALEXANDER: Thank you very much. I should have mentioned at the outset, but let's hold our applause, and then at the end of all of the speakers, we can join together to thank all of them for their contributions to the hearing.

We'll move to speaker number 11. Will speaker number 11 please step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. HEMANI: Hi. My name is Abby Hemani, and I am here on behalf of my 8-year-old daughter Nora, who has Dravet syndrome. GW Pharma supported my travel, but I'm not being compensated to speak her today.

Nora had her first seizure when she was 3 months old, and since then, she has had countless

thousands of seizures. Her seizures have come in all different shapes and sizes, and they've evolved over time. In her early years, we tried many different treatments, but none stopped her seizures and all came with unwanted and often risky side effects.

In 2014, Nora was approved to try Epidiolex. You've heard from the doctors and scientists here today about the data on this new drug, and I'm a big supporter of data. But sometimes data doesn't tell the whole story, and that's certainly true for Nora. According to the data, Nora's Epidiolex treatment would be deemed a failure.

Before she started Epidiolex, Nora had about 1 45-second tonic-clonic seizure every 2 weeks, and after she started Epidiolex, Nora continued to have 1 45-second tonic-clonic seizure about every 2 weeks. Nothing changed, at least with respect to this primary endpoint. But you see, tonic-clonic seizures weren't the biggest problem for Nora in 2014. Instead it was the hundreds or sometimes thousands of seizures she had each day that had no

classification but that her doctors and I dubbed her intention myoclonic. And intention myoclonic looks a lot like a regular myoclonic seizure, but it has a very specific trigger, and that's focus. Focus on a fine motor task.

This is just one of the many varied and unusual seizure types that kids with Dravet syndrome experience. So every time Nora tried to draw or use a spoon, her arm would jerk like this.

(Gestures.)

MS. HEMANI: And every time she tried to kick a ball, her leg would jerk in much the same way.

Before she developed these intention myoclonics, Nora had always been a happy and eager learner despite her significant developmental delays. But these seizures were getting the best of her, and by the time she started Epidiolex, she had pretty much given up. She stopped drawing, she stopped trying to feed herself, and she even stopped her favorite activity in the entire world, blowing bubbles because every time she tried these

tasks, she seized.

Nora went from being a happy, playful, joyous child to one who was often withdrawn and frustrated, and then we started Epidiolex. Within a week of her first dose, Nora's intention myoclonics stopped cold. They just vanished and they've never returned. Instead, what returned was Nora's smile, her laughter, and her incredible lust for learning and achievement.

Unlike with every other medication we've tried, this change came at absolutely no cost. To the contrary, while other medications had made her tired, cranky, or withdrawn, on Epidiolex, she became sharper, quicker, and more engaged. And these changes appeared dramatic even to teachers and therapists who had no idea about her new medicine.

I recognize that Nora's experience is anecdotal rather than data driven, but I also know that it's not unique. Our community is replete with stories like Nora's, and these stories have given us something we never expected to have, hope.

So Nora and I ask you to please consider these experiences as part of your decision-making process and to give everyone suffering from Dravet syndrome and other severe epilepsies the same opportunity that Nora has had.

I'll close with a brief message from Nora herself, showing off both her speech and her fine motor skills. There's no volume, but she said, "Thank you. Muah!"

DR. ALEXANDER: Thank you very much. Will speaker number 12 please come to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. NEWCOMER: Good morning. We are the Newcomer family, Anders, Jennifer and Sage. We are here to support our daughter Emma and the approval of CBD oil to treat seizure disorders. Our travel here today is supported, but we are not compensated in any way for our time.

DR. ALEXANDER: Can you just speak a little closer to the microphone, please, sir?

MR. NEWCOMER: We would like to tell you

about Emma, whose image you see, and our experience dealing with her seizure disorder.

MS. NEWCOMER: At 18 months old, Emma was diagnosed with epilepsy. What started as simply myoclonic seizures soon turned in to a mixed seizure disorder. Emma also developed tonic, atonic, clonic, tonic-clonic, and absence seizures. She had seizures every single day of her life and often up to a hundred or more per day. But the seizures were often accompanied by violent vomiting and left Emma lethargic and dysregulated for the remainder of the day. It's hard to describe how this impacted us and our other two children. It affected every area of our lives.

The seizures came without warning, and they came quickly and devastatingly. Whether we were running an errand, in the store, in the car, at the playground, or opening presents on Christmas morning, we became accustomed to having our hearts ripped out a bit with each one. With every new drug, ketogenic diet, new set of side effects, we continued to watch her suffer, and we suffered

along with her, feeling more and more hopeless until we started the CBD oil.

MR. NEWCOMER: Too often I went to work while Emma suffered potentially life-threatening, brain-damaging clusters of seizures. I was never able to focus completely on my job while part of me was still at home with my family in crisis.

Emma continued to have uncontrollable seizures. Her doctors told us they did not know what else to do. We came to Dr. Thiele who never stopped trying to find a way to help. Emma's current therapy regimen works. It really works. That is a gift to a beautiful, charismatic young lady and her family.

Thank you for your thoughtful consideration of this vitally important matter, the benefits of the medicinal use of CBD oil to treat a disorder often unresponsive to other therapies. Please support the approval of medical usage of CBD oil therapy for persons with epilepsy.

MS. NEWCOMER: My sister is 15 months younger than I am. This means that every memory I

can recall takes place at a time when Emma is in my life. I remember her first seizure and multiple others, including those that hospitalized her three times within a span of a few months. These episodes were normal for the majority of her life, and it was normal for me to see my little sister curled up on the floor after numerous seizures.

Now my sister wakes up in the morning with a smile hiding mischief. She comes home in the afternoon and sends us running around for her, laughing while we scramble to find what she wants. I love seeing her enjoy life rather than be dragged down by it. It's different for our sister because my parents had other lives before us. Their version of normal has been changed repeatedly. My normal has always been tied to Emma and the effects her seizures had on her. To see them lose their grip on my sister's life means so much to me because she now has room to be happy inside and angry and experience things she couldn't before.

Now we ask you to observe a moment of silence for those who have died as a result of this

terrible disorder.

(Moment of silence.)

MR. NEWCOMER: Epilepsy has been an incurable disorder. CBD oil treatment provides hope that a cure may be imminent. Simply put, CBD oil works, from up to 100 or more seizures a day to less than 1 per month. Thank you for the opportunity to speak today.

MS. NEWCOMER: Thank you.

DR. ALEXANDER: Thank you very much. Will speaker number 13 please step to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. GILMORE: My name is John Gilmore, and I have a daughter Lily who suffers from Lennox-Gastaut syndrome. GW Pharma has supported my travel, but I'm not being compensated by them to testify at today's hearing. I'm testifying as a father of a child with LDS [sic].

Lily is a 17-year-old young lady who at 6 months old was diagnosed with infantile spasms despite attempts with multiple medications, diets,

and other treatments that eventually led into LGS when she was around 4 years old. Lily suffers from five different types of seizures; myoclonic jerks, tonic, tonic-clonic, atonic or drop attacks, and atypical absence, and has had seizures just about every day of her life since the first diagnosis at 6 months old.

Her EEGs have shown consistently that she was having some sort of seizure activity in her brain every 4 seconds. This has caused her to have global delays, she is nonverbal, has mobility issues, and basically functions like a toddler and needs someone with her 24-7 to monitor for seizures to keep her safe.

She has averaged between 650 to 850 seizures a year, which means she's had over 14,000 seizures in the last 16 and a half years. This is not including the time she has been in status or has had clustering seizures. We never know what each day will bring. Is she going to have a sudden drop-attack seizure and really hurt herself? Is she going to go into status and we will have to

administer emergency meds and rush her to the hospital? Or is this the day she does not wake up due to SUDEP?

The pictures on the screen are just a sampling of what Lily looks like on a good day and a bad day, which is 7 weeks in the hospital. This is what my wife and I think about every second of the day. Our life is centered on continuously finding a medicine or therapy that will help control her seizures while also trying to give her the best quality of life we can. It is an extremely delicate balance that is incredibly stressful and heartbreaking for the entire family.

Watching my daughter suffer daily rips a little piece of my heart out every day. As the father, you're supposed to be able to protect your child from harm and fix things for them. Despite all of our attempts so far, I've not been able to come close to accomplishing this. Even with all this against her, Lily still manages to smile and enjoy the few moments she is not having seizures. She has shown and taught all of us what through

strength really is and what's really important in life. She is the one who gives our family the strength to continue this fight to find a cure.

To date, Lily's been on over 25 different medications or treatments over this time period with no true success, yet she has suffered many side effects while taking these medications, including potential liver damage, kidney stones, severe malnutrition, lack of appetite, weight gain and loss, and vomiting daily. She's been on medication where we had to sign waivers acknowledging that we know that there was a potential risk of damage to her vision or could cause aplastic anemia. These are the kind of calculated risks that we've had to take over the years to try and help control Lily's seizures in the attempt to give her some type of quality of life.

In 2014, we were lucky enough to be enrolled in a pilot study for Epidiolex under Dr. Orrin Devinsky at NYU Langone's Comprehensive Epilepsy Center, and she continues to take Epidiolex today.

To date, we have seen no side effects besides slight fatigue. She's having less drop attacks, and we've even seen multiple seizure-free days in each month.

About a year into the study, we conducted a 24-hour EEG. When we met with Dr. Devinsky to review, he said her EEG was less chaotic and looked better, meaning her brain was not having seizure activity every 4 seconds. This was a statement that we have never heard since Lily was 6 month old.

Because of this, she has been able to make small strides cognitively. Her teacher and therapist have all reported positive feedback that Lily is making good progress within her goals. We've seen her be more aware of her surroundings and be more interactive with us and our extended family. Before Epidiolex, this was not the case.

Lily still has all her seizure types and continues to need around-the-clock care and monitoring. However, for our family, one day with less seizures is a great day. Epidiolex is a

necessary and proven effective treatment for people who suffer from severe seizure syndromes like LGS. The severe catastrophic and rare form of epilepsy has so few effective treatment options, so if a medication can reduce, stop seizures, and/or improve the quality of life for an LGS person, that is a medication that needs to be available to the LGS community.

I strongly ask of this committee to recommend that Epidiolex be approved. Thank you for your time today.

DR. ALEXANDER: Thank you very much. And I understand you're also representing speaker number 14.

MR. GILMORE: Yes.

DR. ALEXANDER: If you could just remain at the podium and let us know who you're representing and if there's any organization that you're also representing for the record.

MR. GILMORE: Okay. Again, my name is John Gilmore, and I'm happy to be representing the LGS Foundation on behalf of its executive director

Christina SanInocencio.

The LGS Foundation is the leading nonprofit organization in the world dedicated to Lennox-Gastaut syndrome. As you may know, LGS is a rare and severe form of epilepsy that begins in early childhood and typically persists for the duration of the individual's life. Here are some startling statistics that I'd like to open with to give you some sort of framework about the devastation of this disorder.

Ninety percent of individuals diagnosed will continue to have lifelong uncontrolled seizures through their life. Ninety percent also have moderate to severe cognitive impairment. Lennox-Gastaut syndrome affects between 14,500 and 18,500 children under the age of 18 in the United States and over 30,000 children and adults in the U.S. While this number may seem small or insignificant, rare forms of epilepsy like LGS lead to the highest healthcare utilization of the epilepsies due to frequent emergency room visits, poor seizure control, and other services needed.

Eighty-five percent of individuals with LGS have sleep disturbances. The majority of LGS patients take more than three antiepileptic medications but continue to have daily seizures. LGS patients have a decreased quality of life and have a 24 times higher risk of death than an average person. Many patients have hundreds of seizures per day. More than two-thirds are nonverbal or have limited verbal skills, yet despite these statistics, there's a dearth of effective treatments and limited research being done in this disease state.

The LGS Foundation's mission is to improve the lives of individuals living with Lennox-Gastaut syndrome through research, programs, and education. The organization was founded in 2008 in an effort to provide support to families living with LGS and fund research but has grown tremendously over the past 10 years and has been working tirelessly to make a profound impact in the lives of people with LGS. They're committed to making sure that every person who's affected by LGS has the best quality

of life possible, the fewest seizures possible, and the fewest side effects possible.

I'd like to quote the executive director of the LGS Foundation, Christina, with the following.

"Lennox-Gastaut syndrome is devastating and new treatments are desperately needed. Despite a few FDA-approved medications already on the market, patients continue to have life-threatening, debilitating seizures. We need more companies to bring products to the market that can make a difference."

You've heard and will hear from families with the rare epilepsy syndromes at this hearing, but not all voices can be heard due to the fact that many caregivers can't leave their children to be here. Many of our kids are too medically fragile to travel to be here or a family member can't afford to take a day off of work to testify. There are many voices you may not be hearing that would like to be here but can't. We think this is a real-life example that speaks to the fragility and everyday circumstances that LGS caregivers

face.

I'll wrap up with saying that on behalf of the LGS Foundation, more treatment options are needed for our community. Because LGS has many different causes, not all individuals are the same in terms of phenotype or presentation of symptoms, and not all will respond to treatment in the same way, yet, we can't deprive our families of a potential option that may actually help, no matter what it is, what the mechanisms of action may be, or how it is marketed.

I hope that the LGS Foundation's voice is heard at this hearing, as they are the leading organization in the world dedicated to improving LGS patients. Thank you for your time and thank you for listening.

DR. ALEXANDER: Thank you very much. This marks the conclusion of the open public hearing. Please join me in thanking all of the participants.

(Applause.)

Clarifying Questions (continued)

DR. ALEXANDER: The open public hearing

portion of this meeting has now concluded, and we'll no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

I'd like to just first if I can give the opportunity to the sponsor to address any of the questions. There were one or two that I sort of called out. And if you have any clarifications you'd like to make regarding earlier questions, please do so now. And following that, the FDA as well, if there are any comments the FDA wishes to make before we turn to the question at hand.

DR. KNAPPERTZ: Thank you very much, Dr. Alexander. I believe there were two outstanding questions. The first one was regarding the residual THC trace concentration in our product. It is 0.1 percent. The specifications that Dr. Bonson showed were slightly higher, but we agree with Dr. Bonson's assessment on the concentrations, which are 10 or 20-fold lower than

those seen with the very low doses of 5 milligrams of dronabinol. I just wanted to confirm that our good manufacturing, controlled-exacting standards of manufacturing, will produce these very low trace amounts in a very consistent fashion.

The second question I believe related again to the dosing. I have not much to add to my original comments. We studied 5, 10, and 20 milligrams per kilogram per day. The resultant exposures from 10 and 20 milligrams vary largely but are dose proportionate, and there is efficacy seen throughout the spectrum of the resultant exposures. We cannot speak to 5 milligrams per kilogram per day, which I think was a nested question, but I'm going to ask Dr. Devinsky, who has some individual case experiences with dose adjustments.

DR. DEVINSKY: As an investigator in the expanded access program and in two of the large RCTs and the smaller dose pharmacokinetic trial, I have a large number of patients who are on Epidiolex. And after they completed the

double-blind portion, or if they were in the EAP, I had the opportunity to dose the patient essentially in collaboration with the parents who were reporting on seizure frequencies and side effects. And in many cases, we went high, up to 50 milligrams per kilogram per day in the EAP, and then if we didn't see benefits, we would traditionally come down on dose.

So there are many, many patients in whom I've tried to go down towards a dose of 5 or 2 milligrams per kilogram per day, and in the large majority of those, seizures increased, and I had to go back up on the dose. Again, it's anecdotal, but I think more studies would be needed to define if there are lower doses that would be equally effective.

DR. ALEXANDER: Thank you very much.

Are there any additional comments from the FDA regarding this morning's discussion thus far?

(Dr. Dunn gestures no.)

Question to the Committee and Discussion

DR. ALEXANDER: Okay. In that case, we will

now proceed with the question to the committee and panel discussions. I'd 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.

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The designated federal officer will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We'll then

continue in the same manner until all questions have been answered or discussed.

So if there are no questions or comments concerning -- so the question to the committee is, is the benefit-risk profile of cannabidiol favorable for the treatment of seizures associated with LGS or DS in patients 2 years of age and older?

If there are no questions or comments concerning the wording of the question, we'll now open the question to discussion. So in other words, this is an opportunity for us to discuss before the vote if there are clarifying questions. And of course, we're not interested in how you would vote on this question, but rather if there are any clarifications to the question; otherwise, we would vote first, and then have an opportunity to explain the rationale for our votes.

(No response.)

DR. ALEXANDER: Okay. So if there's no further discussion, we'll now begin the voting process. Please press the button on your

microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly, and after you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. ALEXANDER: Everyone has voted. The vote is now complete. Now that the vote's complete -- you want to read it into the record?

DR. CHOI: For the record, we have 13 yes, zero no vote, zero abstentions.

DR. ALEXANDER: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. Why don't we begin here at this end?

DR. HOFFMANN: Richard Hoffmann. I voted yes. It was really a no-brainer for me. There's three high-quality studies of large sample size for

a rare disease, the robust efficacy results of around 20 percent across all three studies, and the adverse drug reaction potential is very manageable I think with labeling and education. Thank you.

MS. BOYCE: Danielle Boyce. Yes.

DR. de WIT: Harriet de Wit, and yes, I think the case has been made, and there's obviously a real need, and the safety concerns are negligible to my mind.

DR. ACRI: Jane Acri. I voted yes. Again, I feel that the efficacy was well demonstrated and the safety concerns could be managed with labeling and monitoring.

DR. MENDELSON: John Mendelson. I voted yes. This is clearly a breakthrough drug for an awful disease. The presenters from the community were fantastic. I think the question will be phase 4 monitoring for safety since it's a very novel drug with novel mechanisms of action. But at this point, this is a spectacular advance.

DR. KRYSCIO: Richard Kryscio, a yes vote for reasons already stated.

DR. YEH: Ann Yeh, a yes vote for all the previous reasons.

DR. ONYIKE: Yes, the data for benefit is very, very clear. It's not disputed. And there's nothing new regarding the adverse effects. What is put forward is stuff that the medical community and the people who will be living with this drug already know.

DR. GREEN: Mark Green. I voted yes. It's really an honor to be part of a meeting that's making an important decision based on science and the public's input rather than a political discussion.

DR. ALEXANDER: Caleb Alexander. I voted yes for the reasons stated.

DR. KNOPMAN: David Knopman. I voted yes for the reasons stated, and I appreciate the opportunity to have participated.

DR. PERLMUTTER: Joel Perlmutter. I voted yes, and an outstanding presentation by both the company and the FDA in reviewing this.

DR. CAVAZOS: Jose Cavazos. I voted yes for

the same reasons. Thank you.

DR. ALEXANDER: Non-voting members, any comments that you'd like to make for the record?

DR. GORDON: This is Mark Gordon. I'd like to thank everyone who presented and say that I too feel that this is an important advance for the patients who suffer from these epilepsy syndromes.

DR. ALEXANDER: Okay. To summarize, I heard robust efficacy results; clear evidence of benefit; three high-quality studies for rare disease; adverse drug reactions manageable with labeling and education and monitoring; clearly a breakthrough drug, an important advance; presenters and community participants were fantastic; and outstanding presentations by the FDA and the sponsor.

Are there any final comments from the advisory committee regarding the conversation we've had thus far?

(No response.)

DR. ALEXANDER: If not, I'd like to take this opportunity to -- any final comments from the

FDA?

DR. DUNN: Two comments. The first is that I neglected in my opening remarks -- and was reminded of the need to do this by the public presentations for which I and the FDA people here are very appreciative. I neglected to make explicitly clear that we are reviewing this application on an expedited time line in light of the recognized unmet medical need and the importance of this product for the market. So I wanted to make sure that was understood, particularly to the patient community that is here, is that we have been working internally to accelerate that review process as much as we can.

Second, although I offered my advanced thanks to the people affected by these syndromes that are here, particularly after the public testimony, I want to again offer my heartfelt thanks and appreciation on behalf of all of us at FDA. I assure you that your comments are listened to and are terribly, terribly meaningful to us. So thank you very much. And thank you to the

committee, as always, for your service.

Adjournment

DR. ALEXANDER: Great. And I just want to echo those thanks. There's an extraordinary amount of work that goes into preparing for this type of meeting, years in the making. So I'd like to thank the sponsor for your hard work, the Food and Drug Administration, the committee, all of the participants that we heard from today, and those of you that are guests that have joined us that we didn't hear from during the open public hearing.

So this meeting is now adjourned, and panel members, please take all personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so that it can be recycled.

We'll now adjourn the meeting. Thank you again.

(Whereupon, at 11:45 a.m., the meeting was adjourned.)