FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GENETIC METABOLIC DISEASES

ADVISORY COMMITTEE (GeMDAC) MEETING

Friday, August 2, 2024

9:00 a.m. to 4:59 p.m.

Meeting Roster

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Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

Introduction of Committee

DR. ALEXANDER: Good morning, and welcome. I would like first to remind everyone to please mute your line when you're not speaking, and also a reminder to everyone to please silence your cell phone, smartphones, and any other devices if you have not already done so. For the media and press, the FDA press contact is April Green [sic - Grant]. Her e-mail is currently displayed.

My name is Dr. Robert Alexander, and I will be chairing this meeting. I will now call the August 2, 2024 Genetic Metabolic Diseases Advisory Committee meeting to order. We'll start by going around the table and introduce ourselves by stating our names and affiliations. We will start with the FDA to my left and go around the table.

DR. CAVAZZONI: Good morning. I'm Patrizia Cavazzoni. I'm the Director for the Center for Drug and Evaluation and Research.

DR. STEIN: Good morning. I'm Dr. Peter Stein, the Director of the Office of New Drugs in CDER, FDA.

DR. ALEXANDER: Dr. Maynard?

DR. MAYNARD: Good morning. I'm Dr. Maynard. I'm the Director of the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine in CDER, FDA.

DR. PILGRIM-GRAYSON: Good morning. I'm Dr. Catherine Pilgrim Grayson. I'm the Acting Director of the Division of Rare Diseases and Medical Genetics in the FDA.

DR. RUZHNIKOV: I'm Maura Ruzhnikov. I'm a clinical reviewer in the Division of Rare Diseases and Medical Genetics, FDA.

DR. KNOBLE: Naomi Knoble, Associate Director, Division of Clinical Outcome Assessment, FDA.

DR. WEIS: I'm Shawna Weis. I'm the Acting Lead Pharmacologist in the Division of Medical Genetics at FDA.

DR. LEE: Good morning. My name is Wonyul

Lee. I'm the statistical reviewer in the Office of Biostatistics, FDA.

DR. STERN: Hi. My name is Sydney Stern, and I'm a pharmacokineticist with the Division of Translational and Precision Medicine, FDA.

DR. ALEXANDER: Dr. Kishnani, do you want to introduce yourself? Go ahead.

DR. KISHNANI: Yes. I'm Priya Kishnani. I'm a clinical and biochemical geneticist, Duke University Medical Center.

DR. FISCHBECK: I'm Kenneth, or Kurt, Fischbeck. I'm recently retired from the NIH, so now a NIH Distinguished Investigator Emeritus. Before that, I was head of the Neurogenetics Branch and Intramural NINDS.

MS. BERGGREN: My name is Kiera Berggren. I'm a research speech language pathologist at Virginia Commonwealth in the Department of Neurology.

DR. BERRY: Good morning, everyone. I'm Jerry Berry. I'm a biochemical geneticist at Boston Children's Hospital and a faculty member of

the Harvard Medical School.

DR. CHOI: Moon Choi, Designated Federal Officer.

DR. ALEXANDER: Robert Alexander, Chief Scientific Officer at the Banner Alzheimer's Institute in Phoenix and a research professor at the University of Arizona.

DR. CHUNG: Hi. Wendy Chung, medical geneticist and professor at Harvard Medical School and Chair of Pediatrics at Boston Children's Hospital.

DR. MINK: Jon Mink, pediatric neurologist, recently retired as well from the University of Rochester, and currently a private consultant in the Rochester area.

DR. LE PICHON: Jean Le Pichon. I'm a child neurologist and a professor at Children's Mercy in Kansas City.

MS. CHAMBERLIN: Good morning. I'm Sarah Chamberlin. I'm Founder and Executive Director of Flok Health.

DR. HEINZE: I am Elizabeth Heinze, and I'm

a patient representative.

DR. KRAFT: I'm Walter Kraft. I'm a clinical pharmacologist and internist at Thomas Jefferson University in Philadelphia.

DR. LIEBERMAN: Good morning. I'm Andy Lieberman. I'm a neuropathologist at the University of Michigan.

DR. ELLENBERG: Good morning. I'm Susan Ellenberg, Professor Emerita, Biostatistics, Medical Ethics and Health Policy at the Perelman School of Medicine, University of Pennsylvania.

DR. KRYSCIO: Good morning. It's Dick Kryscio. I'm a biostatistician at the University of Kentucky.

DR. COON: Hello. Cheryl Coon. I'm a psychometrician and the Vice President of the Clinical Outcome Assessment Program at Critical Path Institute.

DR. TUCKER: Good morning. I'm Carole Tucker. I'm Professor Associate Dean of Research at the University of Texas Medical Branch.

DR. GLASSCOCK: Brad Glasscock. I'm the

industry representative. I am the Head of Global Regulatory Affairs at BioMarin, and I just wanted to take a moment and congratulate the FDA for forming this committee of this inaugural meeting. It's a committee dedicated to focus on rare diseases, which is something that many of us in the rare disease community have been asking for. So thank you for establishing this committee, and it's my honor to represent the industry here today, so thank you.

DR. ALEXANDER: Okay. Thanks, everyone.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some which are very strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory

Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Choi will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's meeting of the Genetic Metabolic Diseases Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other

agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their 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 discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of new drug application, NDA, 214927, for arimoclomol, submitted by Zevra Denmark, for the treatment of adults and pediatric patients 2 years of age and older with Niemann-Pick disease type C. This is a particular matters meeting during which specific matters related to Zevra Denmark's 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 the FDA's invited industry representative, we would like to disclose that Dr. Bradley Glasscock is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Glasscock's role at this meeting is to represent industry in general and not any particular company. Dr. Glasscock is employed by BioMarin.

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

DR. ALEXANDER: We will now proceed with FDA initial remarks starting from Dr. Cavazzoni.

FDA Initial Remarks - Patrizia Cavazzoni

DR. CAVAZZONI: Good morning. My name is Patrizia Cavazzoni, and I am the Director for the Center for Drug Evaluation and Research at FDA. I would like to welcome you to the first meeting of the Genetic Metabolic Diseases Advisory Committee. Also, I would like to thank all the participants in today's meeting, including patients, caregivers, advisory committee members, and other groups. I will provide some initial remarks for this meeting.

FDA convenes advisory committee meetings for a variety of different purposes. Generally speaking, the FDA selects products or topics for advisory committee meetings when there are complex issues that would benefit from broader expert input and discussion. Advisory committees allow the FDA

to receive valuable input from many different groups such as clinicians, industry experts, academics, patients, and caregivers, when evaluating the potential benefits and risk of a new therapy. This is an essential part of FDA's work.

Many genetic metabolic diseases are very rare and impact a very small number of patients. For most, there are no available therapies. We recognize the challenges facing patients and families and the huge efforts to develop treatments for these rare diseases. Today, we're holding the inaugural meeting of the Genetic Metabolic Diseases Advisory Committee. This committee was specifically created to provide the FDA independent, knowledgeable advice and recommendations on technical, scientific, and policy issues around treatment for genetic metabolic diseases.

FDA is committed to facilitating the development of safe and effective drugs for rare diseases, including engagement with external experts and the rare disease communities to discuss

these development programs. This new advisory committee will provide a dedicated forum for discussion of complex topics with specialized and diverse technical and scientific experts in the field of metabolic genetics.

I will now turn the meeting to Dr. Pilgrim-Grayson, the Acting Director of the Division of Rare Diseases and Medical Genetics, to provide opening remarks for today's meeting.

DR. ALEXANDER: We'll now proceed with FDA's opening remarks, starting from Dr. Pilgrim-Grayson.

FDA Opening Remarks - Catherine Pilgrim-Grayson

DR. PILGRIM-GRAYSON: Thank you, Dr. Cavazzoni.

Good morning, everyone. I'm Dr. Catherine Pilgrim-Grayson, and I'm the Acting Director of the Division of Rare Diseases and Medical Genetics. I'd like to welcome you to the first meeting of the Genetic Metabolic Diseases Advisory Committee. It's our privilege to host this inaugural convening today.

Today, we'll discuss the new drug

application for arimoclomol, proposed for the treatment of Niemann-Pick type C, which I'll sometimes refer to as NPC. I would like to extend my thanks to all who are attending, either in person or virtually, and participating in the meeting today. Thank you to the public attendees, and especially the patients with NPC and their families.

For those of you who have provided written comments or who will speak today, we are deeply appreciative and we look forward to hearing your insights. We do recognize the significant unmet need for therapies for this disease. Thank you to all the members of the advisory committee. We appreciate that you have taken the time to review the materials and for joining us today to discuss the topics under consideration. Your perspectives and input are also valuable to the agency.

Before describing some of the complex issues we'll discuss today, I want to stress that we have not made any final decisions on the approvability of this application for arimoclomol. Our comments

in the background package are preliminary and do not yet take into account today's proceedings. Our presentations should not be viewed as necessarily indicative of our final decision. In our review, we have faced many challenging considerations, and the reason we're here today is to gain your input into some of these scientific uncertainties so that we may incorporate them into our assessment.

Arimoclomol is a new molecular entity and is an orally available small molecule. The mechanism of action has not yet been fully elucidated, but the applicant proposes that it may increase transcription of several genes involved in lysosomal function and so facilitate the proper folding and maturation of certain NPC proteins. The proposed indication is the treatment of adults and pediatric patients 2 years of age and older with NPC.

NPC is a rare disease with an estimated prevalence of 1 to 3 cases per million in the United States. The condition is an autosomal recessive lysosomal storage disease resulting from

bi-allelic mutations in NPC1 or NPC2. Dysfunction leads to progressive neurovisceral symptoms and the median age of death is 13 years. There's a clear unmet need. There are no approved treatments for NPC in the United States. The current standard of care is primarily supportive. Miglustat, which is approved in the United States for patients with other diseases, is often prescribed off label for patients with NPC and is considered the current standard of care by treating clinicians.

Clearly, NPC is a devastating disease with substantial impact on patients and families, and addressing this need with effective therapies is a priority. In developing therapies, the voices of patients, families, their caregivers, and healthcare providers have been invaluable, and I want to stress again my gratitude to the patients and families who have helped facilitate research and drug development, and thanks to those who are participating in the meeting today.

Before I move to discuss the preview of the details of this application, I want to set the

stage with a reminder about what constitutes substantial evidence of effectiveness for a given drug, and I would like to remind you that this applies to all drugs, including those that are for rare diseases and for common diseases.

FDA has generally interpreted substantial evidence of effectiveness as a requirement for two adequate and well-controlled clinical investigations. FDA may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence if FDA has determined that such data are sufficient to establish effectiveness.

This approach is often used in development programs when it's not feasible or practicable to conduct more than a single adequate and well-controlled trial. This does reflect agency openness to flexibility in the approaches, especially for conditions like NPC where no satisfactory alternative therapies exist.

Confirmatory evidence is generated from quality data from appropriate sources such as

clinical data, mechanistic or pharmacodynamic evidence, or animal data. You may hear me and my colleagues today refer to confirmatory evidence as additional evidence and the information provided as additional data. The quantity of this additional evidence needed to support effectiveness may vary and is impacted by the features and results of the adequate and well-controlled trial.

It may be possible for a highly persuasive clinical investigation to be supported by a lesser quantity of confirmatory evidence, whereas a less persuasive trial may require a greater quantity of compelling confirmatory evidence to allow for a conclusion of substantial evidence of effectiveness.

It's paramount to keep the current clinical context in mind, that NPC is a rare and devastating illness with unmet need. We are aligned in our shared goal to have safe and effective treatments for NPC. We recognize that certain aspects for drug development that are feasible for common diseases may not be feasible for rare diseases and

that development challenges are often greater with increasing rarity of the disease. We apply flexibility in this situation to address particular challenges posed by each disease while upholding our regulatory standards.

Recognizing that it is appropriate and necessary to tolerate some degree of uncertainty in the context of development programs for rare diseases, it is ultimately necessary that we have reasonable evidence to support a drug's effectiveness. Today's discussion will focus on whether the submitted data provide reasonable evidence of arimoclomol's effectiveness, which brings me to the questions that we'll be seeking your input on today.

I've just discussed the regulatory standard, substantial evidence of effectiveness. Today, we're asking for your scientific assessment, your assessment of the information that was submitted by the applicant to support a conclusion that arimoclomol is effective. We are asking you whether the evidence currently in front of you,

from the single randomized-controlled trial and the confirmatory evidence, support a conclusion that the drug is effective in the treatment of NPC.

So just some brief words about the submission, the original submission for arimoclomol was received in July of 2020. The applicant conducted a single adequate and well-controlled clinical trial, which I will refer to as NPC-002, and proposed confirmatory evidence from in vitro, animal, and clinical pharmacology data. The primary analysis compared arimoclomol to placebo on the main change in baseline to month 12 on the 5-domain Niemann-Pick Disease Type C Clinical Severity Scale, also known as 5DNPCCSS, the 5 domains being swallowing, speech, fine motor, ambulatory, and cognitive functioning.

The application received a complete response in June of 2021. This means that the FDA did not approve the application. This was due to the following deficiencies. There were concerns with the 5DNPCCSS, particularly with the swallow and cognition domains. There were concerns with the

prespecified primary analysis for the 5DNPCCSS endpoint and uncertainty regarding the treatment effect. Weak and contradictory confirmatory evidence of effectiveness was also a concern.

In the current resubmission received December of 2023, the applicant modified the analysis of the primary endpoint by removing the cognition domain and rescoring the swallow domain, so now we have a rescored 4-domain Niemann-Pick Disease Type C Clinical Severity Scale or R4DNPCCSS. The applicant also provided additional confirmatory evidence from clinical data and from nonclinical studies. Today, we will discuss whether the applicant has adequately addressed the deficiencies with this new information. There will be presentations from the applicant and from the FDA regarding these data.

I'll try to provide a very brief preview of the post hoc efficacy results of the R4DNPCCSS. The point estimate of treatment difference ranges from minus 1.5 to minus 1.2, depending on the analysis methods used, and the results favor the

arimoclomol arm. With regard to these results, however, the agency does note some remaining uncertainty with the R4DNPCCSS. Drs. Maura Ruzhnikov, Wonyul Lee, and Naomi Knoble will review for you the study design results and uncertainties in detail.

The applicant provided additional nonclinical/clinical pharmacology and clinical evidence. My FDA colleagues from the Division of Rare Diseases and Medical Genetics; the Office of Biostatistics; the Division of Clinical Outcomes Assessment; the Patient-Focused Statistical Support Team; the Office of Pharmacology/Toxicology; and the Division of Translational and Precision Medicine have reviewed these data, and we'll discuss them in detail. We will consider whether the potential confirmatory evidence, including the concerns that we have about them. Related to the nonclinical/clinical pharmacology and clinical data, we'll ask you to look at the strengths and limitations of them.

As you listen to the data presented today,

consider the following: the existing uncertainty regarding the estimated treatment effect on both the 5-domain and the 4-domain NPCCSS, primarily focusing on the 4-domain rescored NPCCSS; the validity of the 5DNPCCSS and the R4DNPCCSS; the adequacy of the additional clinical and nonclinical data to serve as confirmatory evidence to support the efficacy of arimoclomol; and the strength of the overall evidence to support the efficacy of arimoclomol.

I will now conclude these opening remarks with a preview of the discussion and voting questions that we would like the committee to keep in mind as we hear the presentations today. The first question will ask you to discuss your assessment of the efficacy results of the NPC-002 trial. In your discussion, we would like you to comment on the 5-domain Niemann-Pick Disease Type C Clinical Severity Scale and the Rescored 4-domain Clinical Severity Scale, and we'd also like you to discuss your assessment of whether the trial results demonstrate a treatment effect of

arimoclomol on Niemann-Pick disease type C.

We would also like you to discuss your assessment of the other data, particularly the additional clinical and nonclinical data, with respect to support for the efficacy of arimoclomol, and we would like you to vote on whether the results of Trial NPC-002, in concert with the other evidence, support a conclusion that arimoclomol is effective in the treatment of patients with NPC. We would like you to provide a rationale for your vote, and if you vote no, to provide recommendations for additional data that may support a conclusion that arimoclomol is effective.

This concludes my FDA opening remarks. Thank you for your attention. I'll now hand the meeting back over to Dr. Alexander. We're looking forward to a productive meeting, and we look forward to your input in this important matter. Thank you.

DR. ALEXANDER: Thank you, Dr. Pilgrim-Grayson.

Both the Food and Drug Administration and

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

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships they may have with the industry, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of this 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 the presentations

from Zevra Therapeutics.

Applicant Presentation - Louise Himmelstrup

MS. HIMMELSTRUP: Good morning. I'm Louise Himmelstrup, Vice President for Regulatory Affairs at Zevra Therapeutics. I've been dedicated to the arimoclomol and the NPC program for more than six years. I would like to thank the FDA and the committee for their time to prepare for today's meeting on arimoclomol. Additionally, thank you to the NPC community, including patients and their families, for their participation and support.

Niemann-Pick disease type C, also known as NPC, is an ultra-rare neurodegenerative, atypical lysosomal storage disorder. NPC affects between 600 to 900 patients in the U.S., which is far below the thresholds for both orphan diseases and ultra-rare diseases. NPC impairs the body's ability to transport cholesterol and other lipids inside cells. Over time, this accumulation causes progressive dysfunction of the nerves, brain, and other organs. NPC is typically diagnosed in early childhood and causes premature mortality. The

median age at death is 13 years. Despite decades of research and development, there are currently no approved therapies in the U.S.

Arimoclomol is a small molecule oral capsule that has been developed as a treatment for NPC. Results from our clinical program demonstrate that arimoclomol slows the NPC progression, which is a clinically meaningful benefit in a disease characterized by relentless progression. Additionally, long-term data show that arimoclomol is well tolerated with an acceptable safety profile through five years.

We are here today to review data supporting our proposed indication for the treatment of adult and pediatric patients aged 2 years and older. An important consideration for today's meeting is FDA's draft guidance on demonstrating substantial evidence of effectiveness. For rare diseases like NPC, with such a small patient population and a high unmet need, the guidance provides a regulatory pathway to demonstrate substantial effectiveness with a single adequate and well-controlled clinical

study that is supported by multiple sources of confirmatory evidence. Rather than providing two clinical trials like the standard approach for non-rare diseases, confirmatory evidence is used to substantiate the treatment effect observed in a single trial.

As we will discuss today, Zevra's resubmission for arimoclomol aligns with this guidance and demonstrates substantial evidence of effectiveness that arimoclomol slows NPC progression. Our resubmission includes updates and new analyses that were all implemented based on recommendations the FDA included in its complete response letter to the original arimoclomol new drug application.

First, our pivotal efficacy study is a positive adequate and well-controlled randomized clinical trial. The trial showed a statistically significant result for arimoclomol on the prespecified primary efficacy endpoint. The treatment effect was also significant when we applied FDA's recommended estimate; and second, the

confirmatory evidence for arimoclomol is consistently aligned, mutually reinforcing, and taken together confirms the benefit observed in the clinical trial. The confirmatory evidence comes from several sources, including clinical data, natural history data, data from our expanded access program, animal models of NPC, and studies that revealed a better understanding of the arimoclomol mechanism of action.

We're here today to answer the questions FDA raised in our complete response letter and posed to the committee today. First, we will address uncertainties about updates to the pivotal trial's primary endpoint, a composite endpoint known as the Niemann Pick Type C Clinical Severity Scale. In agreement with the FDA, one revision included removing the cognition domain. Another update included revising the swallow domain scoring methodology based on FDA feedback and a qualitative study with NPC and swallow experts. We also will share information regarding the validation of this tool using objective functional measures.

The NPCCSS is the only instrument validated for NPC. Second, for questions about the estimated treatment effect of arimoclomol, we will show that the study met its prespecified primary endpoint with the prespecified analysis. The study also met the revised primary endpoint with FDA's recommended analysis, and the endpoint results were robust across various sensitivity analyses.

And third, we will discuss the strength of the clinical and nonclinical confirmatory evidence. This includes evidence of benefit in our 4-year, open-label extension of our pivotal trial and change in disease course when transferring from untreated to arimoclomol treatment. Further, the favorable outcomes are supported by effect on the objective measure of weight and sustained stabilization over three years in the U.S. Expanded Access Program. Our presentation will show how the pivotal study and confirmatory evidence together demonstrate the substantial evidence of effectiveness of arimoclomol.

Here's the agenda for the presentation. We

also have additional experts with us today. All outside experts have been compensated for their time and travel to today's meeting. Thank you. I'll now turn the lectern over to Dr. Patterson.

Applicant Presentation - Marc Patterson

DR. PATTERSON: Good morning. My name is Marc Patterson. I'm a child neurologist at Mayo Clinic from where I am joining you remotely today. I've been involved in the care, management, and research on patients with Niemann-Pick disease type C since my fellowship at the National Institutes of Health, which began 34 years ago. I had the privilege of participating in the first controlled clinical trial that was executed at NIH and published in 1993, as well as in almost all of the subsequent trials of agents that have been studied in this disease. Perhaps most importantly, I have had the privilege of caring for several hundred families afflicted by this disease over this period of time.

To give some more background on Niemann-Pick disease type C, as you've already heard, this is an

atypical lysosomal storage disorder. Classic lysosomal storage diseases are those characterized by enzyme deficiency, which leads to the accumulation of substrate in the lysosomes. In contrast, the gene products of the 2 genes mutated in NPC produce proteins which are involved in the trafficking of macromolecules; so this is a trafficking defect rather than an enzyme defect, the consequence of which is the storage of multiple substrates within the lysosomes.

The disease is characterized by relentless neurological progression which first manifests in utero, or early infancy, or as late as maturity. The best data we have on incidence suggest that it is around 1 in 100,000 births, reinforcing the qualification of NPC as an ultra-rare disease. The disease is also highly heterogeneous and variable. Generally speaking, the core symptoms vary with age, and the common feature is a progression towards death. The rate of progression is determined by the age of neurological onset.

Children with perinatal presentations often

have severe liver involvement which may be accompanied by pulmonary infiltrates. The mortality associated with this early onset is quite high within the first couple of years of life. The infantile presentation is dominated by neurologic progression. Children are typically hypotonic with delayed development initially, and then show signs of neurologic regression, which is often rapid but may occur more slowly in some cases.

The most frequent presentation occurs in middle childhood, where children have a more insidious onset. Some may appear to have difficulties with concentration and may be misdiagnosed as having attention deficit disorder. Others appear simply to be clumsy, and in others, uncontrollable epileptic seizures may occur. Many children suffer from sleep disorders.

In the teenage years and early adulthood, the onset is dominated by cognitive impairment, presenting as an early onset progressive dementia. Many patients also have a dramatic psychiatric presentation which may mimic schizophrenia,

treatment-resistant depression, or bipolar disorder. As the disease progresses, there is a tremendous burden on patients and caregivers, which only progresses over time.

As you have heard, routine clinical care for patients with Niemann-Pick disease type C requires a multidisciplinary team. This is typically led by a neurologist or geneticist, but requires the participation of multiple additional experts, including psychiatrists, gastroenterologists, physical medicine and rehabilitation specialists, as well as occupational physical therapists and speech therapists.

Unfortunately, there are currently no FDA approved therapies for Niemann-Pick disease type C. Routine care may include miglustat for appropriate patients. Miglustat is an amino sugar which inhibits the synthesis of glycosylceramide and thus acts as a form of substrate reduction therapy. This is currently approved for certain patients with type 1 Gaucher disease in the United States and is frequently used off label in the U.S. to

treat Niemann-Pick disease type C. However, because this molecule forms bonds with a broad range of ligands, including enzymes in the intestines, many patients may experience gastrointestinal adverse effects which may lead to intolerance of the agent.

The heterogeneity of Niemann-Pick disease type C makes it very difficult to measure this disease and its manifestations across a wide range of ages. There are no established surrogate endpoints or readily measurable biomarkers which have been shown to address disease progression; therefore, progression needs to be measured by using composite clinical scales whose goal is to try to embrace the breadth of the disease and measure progression in a granular fashion.

The Niemann-Pick Type C Severity Scale was developed specifically to produce a valid and reliable tool that measures the severity of this heterogeneous disease, including its varying signs and symptoms across a range of ages in clinical trials. The development of the NPC Clinical

Severity Scale goes back more than 20 years. The scale was initially developed by colleagues in Spain. Subsequently, some of their data and concepts were used by our colleagues at the National Institutes of Health, who developed the 17-Domain NPC Clinical Severity Scale.

I had the privilege of being involved in the development of that scale and subsequently in the development of the simplified 5-domain version. These 5 domains -- specifically ambulation, fine motor skills, speech, swallowing, and cognition -- were selected to capture the key symptoms which were regarded as the most important manifestations of the disease by patients, caregivers, and clinicians. Clinicians score each domain from 0 to 5 using defined criteria. Higher scores indicate more severe clinical impairment. This scale is recommended by clinical experts for use as a primary outcome measure in clinical studies.

The sponsor subsequently adapted the 4-domain NPC Clinical Severity Scale based on

recommendations from the FDA. The cognition domain was removed with agreement with the FDA to address concerns that a single item would be unable to fully evaluate a broad concept such as cognition in a 12-month trial. While cognition is clearly one of the most important manifestations of NPC, I agree that it makes sense to remove it from the assessment in the context of this clinical trial.

Based on concerns from the FDA that the swallowing domain did not reflect a linear progression, a panel of NPC and swallowing experts reviewed the scoring methodology and made recommendations as to how it could be improved. Importantly, these experts only reviewed the methodology and did not make their recommendations based on study data.

The revised methodology was applied to the original source data captured in the clinical trial. In my opinion, in the context of the arimoclomol clinical trial, the resulting 4-domain scale is appropriate for evaluating NPC disease progression. Since one of the topics for today

relates to the adequacy of the revised swallow domain, let me walk through these changes next.

The original scoring methodology for the swallow domain could yield incorrect equivalencies in disease severity. If the patient had no dysphagia, they were scored at 0. If the patient coughed while eating, they were scored 1. Additional points were added depending on whether or not the patient experienced intermittent or consistent dysphagia with liquids or foods. The use of a feeding tube for supplemental feeding was automatically at 4, and if the patient only received nutrition through a feeding tube, they were scored 5.

In the complete response letter, the FDA identified situations where patients could reach the maximum score but have differing levels of swallow dysfunction. Let me illustrate with two examples. First, assume patient A coughs while eating and has regular difficulty swallowing both liquids and solids but does not need a feeding tube. The original scoring methodology would

result in this patient receiving a score of 5; then consider patient B who required a feeding tube for all of their nutritional needs. This patient would also end up with the maximum score of 5. I agree with the FDA's assessment that a patient who does not require a feeding tube at any time is not equivalent in swallow dysfunction to a patient who requires a feeding tube all of the time.

The updated scoring methodology was designed to reflect linearity in disease progression. With this, each step-wise increase in patient's level of swallow dysfunction is matched with a numeric point increase in score. Intermittent dysphasia is scored as a 2 and persistent dysphasia as a 3, regardless of whether dysphasia occurred with a liquid or a solid. The only way to receive a score of 4 or 5 is if the patient relied on a feeding tube.

This updated scoring methodology was applied to the data that were collected during the clinical trial. Here is the full 4-domain NPC Clinical Severity Scale, along with abbreviated descriptions

for each scoring category. Higher scores reflect more severe clinical impairment with a maximum score of 5 in each domain and 20 overall. On each domain, each 1-unit change was designed to reflect a loss of complex function and increased disability due to NPC. Note that some domains do not take on values for all possible scores between 0 and 5. Jumps between these scores reflect greater degrees of worsening.

Since we just reviewed the updated scoring for the swallow domain, I'll provide examples on other domains for how the scale is linked to patients reaching certain milestones that clinicians were trained to recognize and reliably score.

For ambulation, the score of 1 means that the clinician observes the patient to be clumsy, striking objects, and experiencing difficulty walking along a straight line as their age-related peers would be able to do. This individual would move to a score of 2 if they were observed to have, frankly, ataxic gate with a broad base and

difficulty making terms.

Turning to speech, the score of 3 would mean that clinicians found the patient to be nonverbal but still able to communicate their needs using hand gestures such as a thumbs up or down pointing to pictures. The only worst thing that is possible in the speech domain is to reach a 5 for minimal communication, which would mean that the patient cannot communicate their needs in any meaningful way. As you can see, each step-wise change can be unambiguously assessed by a disease expert and each step represents meaningful worsening.

Deploying this tool was accompanied by specific training for investigators on how to collect the data based on the domains in the NPC Clinical Severity Scale, and while we all try to be as consistent and precise as possible in administering instruments, we must bear in mind that we are dealing with neurologically impaired children across a broad range of ages. If you do not actually spend time sitting in an examination room with a child, particularly a neurologically

impaired child, it may seem very reasonable to use a large number of scales to try to assess different aspects of the disease, but it's important to recognize that that is not a realistic goal for most children with NPC.

Those of us who are fortunate enough to have our own children or grandchildren, or to care for them, recognize that children do not always wish to do what we ask them to do whether they have a neurologic disease or not, and if they are neurologically impaired, it may be exceptionally difficult in some cases; therefore, the well-defined scoring criteria must be applied using a flexible approach to accurately evaluate each domain in children.

Additionally, the arimoclomol trial included several standardized procedures. Patients were scored according to a detailed scoring manual. There was also a requirement for the same NPC experts to evaluate patients at each visit, and all investigators, myself included, had to undergo rater training before enrolling patients in the

trial.

It's important to underscore that the NPC Clinical Severity Scale is the only validated and appropriate tool to specifically measure Niemann-Pick disease type C severity and progression across multiple domains. The reliability and validity of the tool has been established at the domain level. With regard to construct validity, the correlations between NPC domains and relevant objective performance tests range from 0.45 to 0.99. The instrument has also shown high intra-rater and inter-rater reliability.

Lastly, allow me to describe how we determine the minimum clinically important difference for the instrument. Using an anchor-based approach, we found that a 1-point worsening or greater on the 5-domain scale represented a clinically meaningful transition, reflecting a loss of complex function and increased disability. This finding was reinforced in qualitative interviews with patients, caregivers, and NPC experts.

The community consensus was that a 1-point change in any domain score would be clinically meaningful. The majority of participants also reported that a slowing of progression in any one of the domains would be impactful. For example, this is the difference between a patient being able to eat by themselves or needing a caregiver to feed them, or the difference between a patient having difficulty swallowing during eating some of the time or all of the time, or between needing a wheelchair or not.

Thank you very much for the opportunity to present and for your attention. I will now turn the presentation back to the sponsor.

Applicant Presentation - Dan Gallo

DR. GALLO: Thank you, Dr. Patterson.

My name is Dan Gallo, and I'm the Senior Vice President of Medical Affairs and Advocacy at Zevra. The arimoclomol clinical program included three studies in NPC, where disease severity and progression were evaluated using the NPCCSS endpoint; an observational study called Study 001,

where we evaluated the rate of disease progression on the NPCCSS in a heterogeneous population of NPC patients receiving routine clinical care; and our pivotal randomized placebo-controlled trial was Study 002, which involved a 12-month, double-blind treatment phase where patients were randomized in a 2 to 1 ratio to arimoclomol or placebo. We also conducted an open-label extension of Study 002, where patients received arimoclomol for up to four additional years.

Here's the design of pivotal Study 002. Fifty were enrolled, including 27 who rolled over from Study 001. Patients were randomized 2 to 1 to receive arimoclomol or placebo for a 12-month, double-blind phase. As in Study 001, all patients were permitted to remain on the routine clinical care, and randomization was stratified by use of miglustat at baseline. After the double-blind phase, patients were eligible to continue to the open-label extension where all patients received open-label arimoclomol. Forty-one of the 50 patients in the double-blind phase continued

into the open-label extension.

Here are the baseline demographics and disease characteristics. The average age of patients was approximately 11 and ranged from 2 to 19. The average time since first symptoms was about 8 years, and most patients were on miglustat at baseline, which they were permitted to continue through the study. All 3 patients with double null mutations, predictive of a more severe and rapidly progressive disease course, were randomized by chance to the arimoclomol group.

Study 002 met its prespecified primary endpoint, which was the change from baseline in the 5-domain version of the NPCCSS at 12 months and assessed using a mixed model for repeated measures. The treatment effect was 1.4 points with an associated p-value of 0.0456.

Now, let's look at the results in the 4-domain endpoint. The results of both the 4-domain endpoint and the FDA recommended analysis method, based on the while-on-treatment estimand, were congruent with our prespecified analysis.

Arimoclomol demonstrated a clinically meaningful and statistically significant reduction in NPC disease progression compared to placebo from baseline to 12 months. The overall treatment difference was 1.5 points of less progression than placebo, with a p-value of 0.041.

Subgroup analyses for the 4-domain NPCCSS show a treatment effect that consistently favors the benefit of arimoclomol by age; age at first neurological symptom; sex; baseline score; and among patients with no double null mutations. Since all 3 patients with a double null mutation were in the arimoclomol group, a treatment effect relative to placebo could not be calculated for those with this mutation.

For the subgroup of patients who did not take miglustat, the estimated treatment difference numerically favors placebo and has wide confidence intervals. As FDA outlined in their briefing document, this result is challenging to interpret, and we agree for the reasons I'll review on the next slide.

We saw a small number of patients in the study who did not receive miglustat as part of their routine care. In total, 8 patients on arimoclomol and 3 on placebo did not take miglustat. This subgroup had substantial baseline imbalances that would predict a worst disease prognosis for the arimoclomol group.

The average age at first neurological symptoms was 4 years with arimoclomol and 10 with placebo. The average baseline symptom severity score was nearly double in the arimoclomol group, and all 3 patients with double null mutations were randomized to arimoclomol; therefore, we agree with the FDA's conclusion that these baseline imbalances that favor the placebo group make it difficult to interpret the subgroup who did not take miglustat.

We also performed several sensitivity analyses, which showed that the primary endpoint findings were robust. The first line in the chart shows the updated primary analysis of the 4-domain scale based on FDA recommendations, which I showed previously. This analysis estimated the

while-on-treatment estimand using an ANCOVA model. This is followed by additional sensitivity analyses that showed that the estimated treatment effect remains similar to the updated primary analysis.

To ensure that the favorable results were not driven by outlying values, we performed a non-parametric Wilcoxon rank sum test based on the ranks of the data, and this too was statistically significant. The last row shows that the prespecified analysis based on the 5-domain scale using the MMRM model also achieved statistical significance.

I want to acknowledge that the FDA provided many more sensitivity analyses in their briefing document. We agree with their conclusion that some nominal p-values were below the 0.05 and others were above, but that the point estimates of the treatment effect consistently showed slower progression with arimoclomol compared to placebo.

To further explore the effects of arimoclomol, next we'll transition from statistical models to the actual patient-level data on disease

trajectory. On this plot, each point on the Y-axis will represent an arimoclomol patient; the X-axis will show their overall 4D-NPCCSS score from baseline to 12 months. The open dots represent the score at baseline; green dots reflect 12-month scores that were improvements from baseline; purple dots reflect no change from baseline at 12 months, which is our goal; and pink dots reflect a worsening from baseline.

After one year of treatment, 10 patients receiving arimoclomol had an improvement of at least 1 point and 12 had no change in disease severity. For placebo-treated patients, keeping in mind the 2 to 1 randomization, we see that the majority experienced a worsening of disease severity over the same time period and no patients in the placebo group exhibited an improvement.

Because of the 2 to 1 randomization, it is helpful to look at these data in terms of percentages. At 12 months, 29 percent of patients in the arimoclomol group had improved scores and 35 percent had no change; so 65 percent of patients

were stable or improved. For placebo, no patients improved and 40 percent had no change; so overall, 65 percent of patients on arimoclomol had a favorable response compared to 40 percent in the placebo group with no change.

In summary, across analyses, the clinical data from our pivotal trial consistently show that arimoclomol slowed the natural course of this devastating disease. We used the NPCCSS as our primary endpoint, which is a validated instrument that came out of the halls of the NIH. We updated the endpoint and statistical analyses based on FDA requests and recommendations.

The trial showed a clinically meaningful and statistically significant effect at 12 months in both our prespecified analysis, as well as using the FDA recommended while-on-treatment estimand and statistical approach. And finally, the treatment effect was robust to multiple sensitivity analyses, all of which supported the benefit of arimoclomol. Thank you. I'll now turn the presentation over to Dr. Mickle to present the confirmatory evidence.

Applicant Presentation - Travis Mickle

DR. MICKLE: Thank you. I'm Travis Mickle, Co-Founder of Zevra and their Senior Advisor. I'll review the supportive data from clinical and nonclinical sources, which provide confirmatory evidence of the effectiveness of arimoclomol. Let's start with the clinical evidence.

The designs of our clinical studies enable pre-post analyses to further evaluate the benefits of arimoclomol. We compared patients who transitioned from routine care or placebo to arimoclomol, allowing patients to serve as their own control. We looked at the annual change in the 4D-NPCCSS scale.

The first analysis includes 17 patients. In year 1, they received routine care as part of the observational Study 001. In the second year, they were randomized to receive arimoclomol in the double-blind phase of Study 002. The second analysis includes 13 patients. In year 1, they were randomized to placebo in the double-blind phase of Study 002. In year 2, those same patients

received arimoclomol in the open-label extension. For the second analysis, it's important to note that both patients and physicians were unaware of their randomized assignment during the double-blind for the first 2 years of the open-label phase.

Let's start with the analysis of the annual change in the 4-domain scale. In the first paired analysis, the 17 patients who received routine care in Study 001 had scores worse than on average by 1.6 points on the 4D-NPCCSS, but when those same patients received arimoclomol during the double-blind study the following year, their annual disease progression was reduced to 0.9.

The second analysis among the 13 patients who received placebo in the double-blind and got arimoclomol in the open label showed similar results. Their annual worsening was 1.9 during the first year on placebo, but they worsened by only 0.3 points after transitioning to arimoclomol in the first year of the open-label extension. Both analyses show a slower rate of disease progression after initiation of arimoclomol.

NPC can cause below average weight gain in children due to their swallowing issues and other complications, so weight is an important objective measure of development in these patients. Since children grow at different rates by age and sex, we evaluated annual changes using Z-scores.

In the following analysis, we compared their weight to the CDC's childhood growth curve for their age and sex to determine the Z-score. This standardized measure allowed us to appropriately assess weight changes in growing children. The annual change for a patient was calculated as the difference between the Z-scores at baseline and the end of the 1-year period; therefore, a score of 0 indicates average growth, while negative values reflect below average growth in standard deviation units.

In the placebo group, the average change in weight over that year was half a standard deviation less than what would be expected for children the same age. In the first year of the open-label placebo, patients switched to arimoclomol had a

dramatic increase in weight trend. Patients on arimoclomol in the double-blind and the open label were closer to what would be expected for their age compared to the healthy population. This trend mirrored what was seen in the previous example with the 4D-NPCCSS when patients initiate treatment with arimoclomol after transitioning from placebo in the double-blind, but now with an objective measure.

Next, let's review the natural history data. The FDA requested an analysis comparing patients in our open-label extension with external comparators from the NIH Natural History Cohort Study who had at least 4 years of follow-up data. To compare these non-randomized groups, we used inverse probability of treatment weighting. Due to age differences between the groups, we focused on patients who are at least 4 years old.

We weighted the analysis based on age, sex, miglustat use, age of onset, and baseline score. In this analysis, we see that over 4 years, there's more than a 1-point difference in the rate of progression with arimoclomol treatment. These

results mirror what we see in the double-blind in in the previous examples of untreated patients switched to arimoclomol. We agree with the FDA that this analysis has limitations. Even with this in mind, we still see a consistent treatment effect favoring arimoclomol.

Next, I'll share some data from the arimoclomol Expanded Access Program. Outcomes in the U.S. EAP were collected over time across 14 sites under a clinical protocol. Physicians were trained on the administration of the NPCCSS and provided a scoring manual to ensure consistent evaluation. These data show changes in the 4-domain NPCCSS from baseline at every visit for 82 patients in the U.S. Expanded Access Program. A slow rate of disease progression was observed in both children and adults. About half of the population in the EAP were children, but these data are difficult to interpret without a comparator group.

To provide a comparator for the EAP patients in the United States, we utilized the NIH Natural

History Cohort. The analysis was limited to patients aged 4 to 30 years to address the fact that the EAP data set included more adult patients and the NIH data set included more infants. No other inclusion or exclusion criteria were applied. This left 56 patients in the EAP data set and 44 in the NIH. The average age, baseline 4-domain NPCCSS, and miglustat use were higher in the EAP.

This graph will show changes in the 4-domain NPCCSS from each patient's baseline at every visit. We see that the overall trend among arimoclomol-treated patients in the EAP was stable over the 36-month period. The trend in the NIH cohort was an increase relative to baseline.

Here, each green triangle represents a change in score from baseline for a patient in the NIH data. As you can see, few patients in the natural history study showed any improvement, as indicated by the yellow shaded area. In fact, these red boxes reflect that three of the improvements in the NIH cohort were actually patients receiving arimoclomol. In contrast, when

we look at the EAP patients treated with arimoclomol, we see quite a few patients improving. While these data are not a randomized comparison, the trend suggests a slower rate of disease progression with arimoclomol, consistent with our other clinical data.

Next, I'll review the nonclinical data supporting an effect from arimoclomol. Let's look at arimoclomol's mechanism of action. Lysosomes are responsible for the removal of waste products from a cell. NPC1 proteins are primarily responsible for clearing free cholesterol from lysosomes, which is an important component of healthy cell and lysosomal function, as well as the overall process of autophagy, which is a recycling of cellular components.

Let me describe the intracellular processes that lead to healthy lysosomal function. The process begins with transcription factors. When TFEB and TFE3 are localized to the nucleus of the cell, they activate the expression of the genes responsible for lysosomal protein synthesis. These

genes are collectively known as the coordinated lysosomal expression and regulation network of genes or the CLEAR gene network for short. Among the CLEAR genes are those responsible for NPC, which govern the expression of NPC1 protein. We will primarily focus our attention on the NPC1 gene and protein.

In a healthy cell, this expression allows for functional protein to be formed and folded in the endoplasmic reticulum, matured in the Golgi, and trafficked to the growing lysosome where NPC1 can be embedded in the lysosomal membrane. Once there, NPC1, with support from the other proteins expressed by the CLEAR network, plays a critical role in removing cholesterol and other lipids from the lysosome.

In a healthy cell, this leads to normal autophagy and healthy neuronal function; however, in a patient with NPC, this process is disrupted by a mutated NPC gene. The process starts the same with the transcription factors locating to the nucleus and activating the CLEAR genes, except in

this case, NPC1 is misformed. The mutated NPC1 gene has now expressed the wrong NPC1 protein, which in turn leads to mutated proteins being formed in the ER, of which few make it into the Golgi, and even fewer mature and locate to the lysosome. Even if some do, they may be less effective at clearing cholesterol, leading to an accumulation of cholesterol, dysfunctional autophagy, and neuronal death.

In patients with NPC, arimoclomol improves lysosomal function by two unique pathways. Treatment with arimoclomol forces the transcription factors into the nucleus to activate the overexpression of the CLEAR network genes. These genes then express more of the dysfunctional NPC1 protein, as well as the other proteins in the CLEAR network. With this overexpression, the ER now creates more NPC1 and other CLEAR network proteins, of which more reach the Golgi, go through maturation, and locate to the lysosome. In most cases, the NPC1 protein is still not fully functional, although there is more of it in the

lysosomal membrane, leading to more cholesterol clearance.

CLEAR network proteins are also present in higher concentrations; therefore, arimoclomol works through both NPC1 dependent and independent mechanisms to improve autophagy, reduce cholesterol accumulations, and prevent cell death. Several lines of evidence supporting this mechanism were generated during the process of preparing the resubmission.

To determine the mechanism of action for arimoclomol, we examined a number of in vitro models but primarily focused on studies in fibroblasts. These included wild type and mutant fibroblasts for patients with various genotypes. High concentrations of arimoclomol were required to measure a potential effect. This is common for fibroblasts and generally not unexpected because they have notoriously high cellular and potential target turnover rate when used for in vitro assays. In vitro doses were influenced by the model used, so the observed ratio of in vitro to human plasma

concentrations in our studies can be difficult to interpret.

Because NPC is an ultra-rare disease, our dosing in clinical trials was based on a safety margin from animal toxicology models. This approach to dosing was appropriate. As you can see in the table, patients in our clinical trials achieved arimoclomol exposures several times higher than those were effective in NPC mouse models.

Arimoclomol upregulates the CLEAR network of genes, leading to an increase in NPC1 protein, which ultimately improves lysosomal function. Some of the data supporting these conclusions start with the in vitro models of gene expression where we observed a significant upregulation of the NPC1 gene, resulting in approximately a 4.5-fold increase. This heightened gene expression subsequently leads to elevated NPC1 protein concentrations where we see a similar magnitude of increase as with gene expression, and as a consequence of increased NPC1 protein, there's a substantial reduction in the concentrations of

cholesterol detected in NPC patient fibroblasts following treatment with arimoclomol.

This in vitro link from gene, to protein, to cellular function is further confirmed by the results of our in vivo studies. We studied two mouse models of NPC disease. NPC independent mice represent double null mutations with no functional NPC1 protein. NPC dependent mice represent point mutations with some dysfunctional NPC1 protein. This type of mutation is more representative of the patients in our study and the NPC patient population overall.

We evaluated several key endpoints in different studies. We looked at the ability of arimoclomol to increase the levels of mature NPC1 protein in the brain; we examined myelin basic protein, a well described marker of neuronal health; and we evaluated survival.

This graph shows mean levels of mature, properly folded NPC1 protein in the brain of either wild type mice in pink or in NPC dependent mice that were either treated with arimoclomol or were

untreated. There was a comparable concentration of protein in arimoclomol-treated mice compared to that measured in healthy wild type mice. In addition, the concentration of NPC1 protein in treated animals was approximately 50 percent higher than that found in untreated animals. Examination of myelin basic protein gives a similar trend where concentrations of myelin basic protein were well above untreated animals. Given the wild type control and the comparison to untreated NPC mice, this effect can only be attributable to arimoclomol.

Improved brain concentrations of mature NPC1 and myelin basic protein also led to an increase in the survival of animals dosed with arimoclomol. Here, I show data from in vivo models of NPC dependent mice. More arimoclomol-treated animals survived through 16 weeks and no untreated animals survived past 18 weeks. With arimoclomol, survival was greatly improved. Mean survival times were increased from 16.7 weeks for untreated mice to 18.3 weeks in treated mice.

Our nonclinical and clinical studies also revealed a consistent complementary mechanism with miglustat, and mechanistically, these complementary MOAs make sense. As we already know, in the untreated lysosome, proper function is impeded by an accumulation of cholesterol. As a result of poor lysosomal function, other lipid byproducts also accumulate. Glycosphingolipids are one of these byproducts.

With treatment of arimoclomol, we see enhanced clearance of free cholesterol. Since NPC1 is primarily responsible for the transport of cholesterol, glycosphingolipids are still present in high amounts. While improved, the lysosome is still impaired versus that of a healthy cell. We can see that miglustat through the inhibition of glycosylceramide creates less glycosphingolipids than any processing in the lysosome. With the addition of miglustat, lysosomal function can improve the active removal of cholesterol by reducing the amount of glycosphingolipids reaching the lysosome.

Evidence of these complementary mechanisms was seen in concentrations of cholesterol analyzed by filipin staining and NPC patient fibroblasts. This slide shows the percent difference versus control in unesterified cholesterol detected for different combinations of arimoclomol and miglustat.

With arimoclomol alone, we see a dose-dependent reduction in cholesterol. At the highest concentration, this was a 42 percent reduction versus vehicle control. With miglustat alone, we see a similar dose-dependent effect with a 44 percent reduction in cholesterol, but we see even greater reductions in cholesterol when both are taken together at the maximum concentrations, up to a maximum 78 percent reduction seen in the lower right compared to the control.

This in vitro effect is just one part of the data collected on the combination of arimoclomol and miglustat. Here, we can see an overview of how these complementary MOAs have been explored in multiple models. The addition of miglustat had an

effect with arimoclomol regardless of the model, the combination providing greater clearance of unesterified cholesterol in vitro than either drug alone. When these drugs were used in combination, we saw further enhancement of CLEAR gene upregulation, and in vivo we saw improved survival. These findings are in alignment with the clinical trial, where we saw statistically significant treatment effect for arimoclomol on the primary endpoint among patients on both therapies.

In summary, converging confirmatory evidence across multiple sources leads to one reasonable conclusion, that the clinical outcome observed in the pivotal trial is both real and significant. Additional clinical data provided consistent evidence that arimoclomol slows disease progression, and these effects are maintained long term. These benefits were also consistent with trends in weight. When arimoclomol patients were matched with NIH patients, arimoclomol saw slower disease progression over 4 years. In the EAP, when compared to a similar set of patients in the NIH

database, we also saw a slower rate of progression.

Arimoclomol targets the biochemical pathways most affected by NPC through the CLEAR gene network, which is critical for improved lysosomal function. This mechanism translates to tangible benefits in NPC mice, with increased brain concentrations of mature NPC1 and myelin basic protein and increased survival, and the positive effects of arimoclomol shown in the in vitro and in vivo studies were enhanced with miglustat.

But the overall most significant observation was the consistent benefit of arimoclomol observed across all studies and analyses. While each individual experiment has its limitations, the collection of mutually reinforcing data taken together confirm the results observed in our pivotal efficacy trial. I will now turn the presentation over to Dr. í Dali.

Applicant Presentation - Christine í Dali

DR. I DALI: Thank you. My name is Christina í Dali. I'm a child neurologist and Vice President of Clinical Science at Zevra. I will

present the safety results supporting that arimoclomol is well tolerated with a safety profile that does not add to the patient's disease burden.

The safety database for arimoclomol is considerable for an ultra-rare disease. We have treated a total of 668 individuals with arimoclomol across all clinical programs. For Niemann-Pick type C, the primary safety data come from the 51 patients enrolled in Study 002; 28 of these have been treated 4 years or more.

This slide shows the arimoclomol safety profile in Study 002. Most patients reported at least one adverse event during the one-year, double-blind phase. Nearly all adverse events in the study were mild to moderate in severity. The three most common AEs were vomiting, diarrhea, and constipation, which importantly occurred at similar rates across groups.

Serious adverse events were more frequently reported by patients in the placebo group, and 3 patients in the arimoclomol group experienced an AE leading to discontinuation from the study.

There was one death reported in the double-blind phase of Study 002. The patient was 8 years old and passed away following an event of cardiorespiratory arrest approximately 8 months into the study. The event was determined to be related to underlying disease and unrelated to study drug.

Looking at the adverse events that led to discontinuation, there was one event of blood creatinine increase and 2 events of urticaria/ angioedema. All events were moderate in severity and resolved without intervention following discontinuation of therapy.

Arimoclomol is well tolerated and did not add to the high burden of NPC disease. We observed a similar incidence of adverse events between the arimoclomol and placebo groups in the one-year double-blind phase. No new safety concerns emerged in the 4 years of the open-label study. This is also supported by data from an additional 206 patients with NPC that have received arimoclomol for up to 3 and a half years in the

global Expanded Access Program. In summary, and as stated in the FDA briefing document, no significant safety concerns or risks were identified with the use of arimoclomol in patients with NPC.

Thank you. I will now turn the presentation over to Dr. Kristina Julich.

Applicant Presentation - Kristina Julich

DR. JULICH: Thank you. I'm Kristina Julich. I'm the Chief of the Pediatric Neurogenetics Center at the University of Texas at Austin Dell Medical School and Dell Children's Medical Center. I've been involved in the Niemann-Pick type C community for years, including actively managing patients on arimoclomol as principal investigator in the arimoclomol Expanded Access Program. Now that we've heard the pivotal study results and the additional supportive evidence of effectiveness, I'm glad to offer my perspective on the arimoclomol data.

There are four key points that support the use of arimoclomol as a safe and effective treatment for patients with NPC. First is my

assessment that the clinical results show a benefit for patients. The clinical trial used the appropriate endpoint, the NPCCSS, to evaluate meaningful changes applicable across a heterogeneous population. Study 002 did show a slowing of disease progression.

Second is that arimoclomol is safe. The clinical data show arimoclomol to be very well tolerated. This agrees with my own experience with patients who've been enrolled by me in the EAP. These data assure me of the safety profile, and patients and their parents are comforted by the fact that arimoclomol doesn't add to the underlying anxiety caused by disease progression.

Third is the additional clinical and nonclinical evidence confirming the benefits seen in the trial. Across the data, I see consistent evidence. This includes consistent biological evidence that arimoclomol has an effect on the disease pathology and the results align with my personal experience with 5 patients who have enrolled in the EAP program, some who have been

enrolled for longer than 3 years. I monitor my patients approximately every 6 months, and I've observed that several of these patients have remained stable. Granted that this is anecdotal and uncontrolled, but it aligns with the study and the other evidence.

Finally, the mechanism of action makes sense and predicts for a benefit. I'm very encouraged the sponsor has demonstrated a probable mechanism of action that is consistent with preservation of neurons and models of NPC and supports the reliability of the observed clinical benefits. Overall, the data shows that arimoclomol will address an urgent need for a safe and effective treatment for NPC.

Thank you. I'll now turn the presentation over to Louise Himmelstrup.

MS. HIMMELSTRUP: Thank you. This concludes our presentation, and we are ready to take your questions.

Clarifying Questions to the Applicant

DR. ALEXANDER: Okay. Thank you,

Dr. Himmelstrup.

We will now take clarifying questions to the presenters. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it will be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

So let me start. This is Robert Alexander, and I have a question for Dr. Gallo. I wonder if you have a display of the prespecified secondary endpoints in Study 002 which you could show us and comment on the results.

MS. HIMMELSTRUP: I will ask Jason Connor to respond.

DR. CONNOR: Hello. I'm Jason Connor, statistical consultant to Zevra and ConfluenceStat. I don't know that we have the slide with the

secondary endpoints. Oh, here it is. Okay.

I would reiterate that the primary endpoint was achieved, and the primary endpoint is really the only endpoint specifically validated for the disease.

DR. ALEXANDER: Sorry to interrupt, but they weren't the prespecified secondary endpoints in the study, though, I believe. These are ones which are derived from the NPC, or were they? I thought from the briefing document that the secondary endpoints in the study were not statistically significantly different.

MS. HIMMELSTRUP: Yes.

DR. ALEXANDER: Is that correct?

MS. HIMMELSTRUP: Yes, that's --

DR. ALEXANDER: You don't actually have a display with those prespecified ones from the study?

MS. HIMMELSTRUP: So there were trends in the secondary endpoint for the NPC specific endpoints, but not much support from the other endpoints. I think it's important to take a step

back, and the NPCCSS is the only validated tool for this disease, and that's where we see a slowing of disease progression.

DR. ALEXANDER: Well, just one last -- the CGI was in the study, though, right?

MS. HIMMELSTRUP: Yes.

DR. ALEXANDER: Do you have a display of the CGI results?

MS. HIMMELSTRUP: I can tell you there was no difference on the CGI, with a p-value of 1.

DR. ALEXANDER: Okay. Thank you.

Who has their hand up? Dr. Fischbeck?

DR. FISCHBECK: Yes. I actually have three questions, but I could do one now and the others later, if there's time.

DR. ALEXANDER: We have extra time, so you can probably do all three, if you want.

DR. FISCHBECK: Well, it's a question about the post hoc analysis. I'm not a statistician, but my understanding from the statisticians is that post hoc analysis is not statistically valid, I guess because you can pick and choose from the data

to get the result that you want.

Here, it's interesting because the FDA encouraged the post hoc analysis, and you followed the FDA a recommendation, so it might be good to hear from the FDA about that later, why they recommended a post hoc analysis. But I wonder if you have any justification for using the post hoc analysis here; in other words, going back and reanalyzing the data from the previous study rather than gathering new clinical data or doing a new clinical study.

MS. HIMMELSTRUP: I'd like to turn over to Jason Connor, our statistical expert, to reply.

DR. CONNOR: Hello. Jason Connor again. I agree. Usually we think of post hoc analyses as something goes wrong in the clinical trial, and we throw out these patients and think about other endpoints. Here, the trial hit its primary outcome, and the analyses that were done post hoc were done at the invitation of FDA. Even the worst patients in this trial we saw, all three were randomized to arimoclomol, and nevertheless, the

primary endpoint was achieved both with the prespecified endpoint and with the updated one.

The post hoc analyses that were done removing cognition, it still hits statistical significance. The post hoc analysis that was done changing the swallowing domain, as you heard Dr. Patterson say, that swallowing domain change was done by experts in the swallowing field without knowledge of the data, so it's not like -- oftentimes as a statistician, I hear people ask me, too, "Well, what if we throw away these patients? This one was tricky; let's not include him." None of that happened here.

So absolutely, they're post hoc, but they were all done changing the scale without knowledge of individual patient-level data. The original analysis was achieved, and even the updated post hoc analysis, it still achieved statistical significance, both changing the endpoint and updating to the preferred estimand. So right; it's post hoc, but it really just supports hitting all those prespecified endpoints.

DR. FISCHBECK: Thank you.

DR. ALEXANDER: You want another one?

Then, let's go to Dr. Coon.

DR. COON: Hi. Cheryl Coon. My first question is for Dr. Patterson. I assume it's still online.

MS. HIMMELSTRUP: Yes.

DR. COON: Okay. I'd like to understand the process for assigning values to each of the response categories in the scale. There was a lot of information about the swallow domain, and that made a lot of sense, but the ones where it's jumping from two categories to four, and there's nothing in between, was there a clinical reasoning for that or was there psychometric reasoning, and what sort of evidence is there to support those score assignments?

MS. HIMMELSTRUP: Yes. I'll turn over to Dr. Patterson.

DR. PATTERSON: Yes. Thank you. It's Marc Patterson here. Thank you for the question. As I say, this score was a modification of the 17-domain

score originally developed at NIH, a process by which it was simplified. The domain was selected, as we said, independently by clinicians and by patients and their caregivers. I just wanted to emphasize those points first.

What we wished to have was a scale where there were very clear distinctions between each level. As we said in this case, I think you're probably alluding to each domain where there's a jump from 3 to 5 between a nonverbal patient who has functional communication skills and one who has no communication. This is an easy distinction to make, and one which is clear and can be assessed by the clinical raters, and I think its meaningfulness is apparent. Similarly in terms of the fine motor manipulation, you can see a jump between mild and moderate dysmetria or dystonia, which again is a fairly clear distinction.

I should emphasize, again, that the raters were all trained in advance. In fact, when the scale was developed, it was based on video recordings of patients who were actually examined

by me. The raters who developed the scale were all NPC experts who independently rated these patients, and you've already seen the results of the reliability and validity of the scale determined in that fashion. I hope that answers your question, but I'm happy to expand further if it would be helpful.

DR. COON: That was helpful. Thank you.

I do have a second question. Do we have time?

DR. ALEXANDER: Yes, go ahead.

DR. COON: Okay. Thank you.

In the briefing materials, as well as the presentation, it was stated that the primary endpoint met statistical and clinically meaningful levels of difference. What was your definition for clinically meaningful? What were you using to make that statement? And that's my last question. Thank you.

MS. HIMMELSTRUP: Yes. The clinical meaningful was determined based on two methods. We did an anchor-based method, and we have done

interviews, qualitative studies with the patient, caregivers, and clinicians, to determine what is a meaningful difference to them, and the results of those studies are that preventing worsening is clinically meaningful.

DR. ALEXANDER: Thanks.

Dr. Mink, did you have a question?

DR. MINK: Yes, I have a couple questions about the rating scale to follow up on the previous question about rating scale. I understand the explanation about the 2-point change in ambulation, fine motor skills, and speech, but I wonder, particularly in the clinical trial setting, if you enter the trial with, say, a 2 on ambulation and you get a bit worse, that requires a 2-point increase. So particularly in a study like this, I'm wondering if the data have been evaluated for potential bias over representation of those who are more likely to have a 2-point change on their next bump rather than a 1.

Then the second question is about ceiling effects. It looks like from the briefing

materials, at least one individual was enrolled at 20 on the 4-domain scale, which is at the ceiling and therefore could not possibly get worse. Can you address those please?

MS. HIMMELSTRUP: So we will address your two questions. For the first one, I'd like Dr. Patterson to explain what happens, for example, ataxic gait to the next level of a 4. For your second question, I'll ask Jason Connor to respond.

Dr. Patterson?

DR. PATTERSON: Yes. Thank you. Marc Patterson here. I want to make sure I understand the question Dr. Mink is asking. One of them, I think, probably requires some statistical response, and I don't have the raw data to answer that because I think he was concerned that there might be bias towards certain types of patients and progression, if I understand his question correctly.

DR. ALEXANDER: Yes, he did mention that.

DR. PATTERSON: Yes. And all I could say that we attempted to rate the patients in a

consistent fashion. I don't know from my personal experience that I perceived any bias but, again, I think to answer that question would require looking at detailed data and analysis, and I don't have that level of granular data in front of me at the moment. Maybe [inaudible - 2:03:12].

DR. CONNOR: Great. This is Jason Connor again. So I agree, there are those 2-point changes. So you saw this plot on for the whole NPCCSS score. This is showing you the ambulation-only change, and apologies the pink is sort of harder to show up here. But you can see that, for example, there is one placebo patient there at the bottom that went from 1 to 4, so they in fact moved from 1 to 2, and then that 2-point jump. I see the arimoclomol patient there in the middle.

But I think one key, too, is this was a 12-month trial, so many trials we run are relatively short, but 12 months here did allow for longer times to see that progression of the disease. But I agree if there were minor changes

worsening within the one step, that may not be captured., but as Dr. Patterson has said, part of the scale, the reproducibility is high because the difference in these stages are pretty evident and reproducible to raters.

DR. ALEXANDER: Do you want to answer the question about being at ceiling on the one subject?

DR. CONNOR: Can I see that slide back up? I think there are ceiling effects; for instance, ambulation 5 is wheelchair bound, so once someone is wheelchair bound, they can't go up higher in the score; but I apologize if there was a more subtle part to that question, if you could repeat it.

DR. MINK: Not just on this specific item, but on the whole 4-domain, or prior to that, the 5-domain, it looked like at least one individual was at the ceiling for the total score at the time of enrollment.

DR. CONNOR: That's right.

DR. MINK: Do you know was it more than one? All I can see is the min and max.

DR. CONNOR: Oh, yes. Can we see -- I think

it's CO-33. Right. So there were 2 placebo patients and 2 arimoclomol patients who both had achieved the ceiling by the end of the trial, and you can see the one placebo patient in fact didn't have much worse to get there and went to 20, so there were two in each group. And just as a reminder, there's 2 to 1 randomization, so that's effectively twice as many in the placebo group, but we did see some of those ceiling effects.

DR. ALEXANDER: Dr. Ellenberg?

DR. ELLENBERG: Susan Ellenberg. So there were, I think, 8 patients who dropped out, seven on drug arm and one on the placebo arm. Can you tell us when they dropped out, at what time, and what the reasons were? We know that there was one death and three who dropped out because of adverse events, but I'd like to know the reasons why the other dropped out. Then I would also like to know -- I think it's slide 33 -- whether any of the patients who showed improvement were people who dropped out early and that improvement was based on an imputed score.

MS. HIMMELSTRUP: Yes. I'd like to hand over to Christine í Dali for the reason for discontinuation, and then continue on to Jason Connor for the second part of the question.

DR. ELLENBERG: And the timing of the discontinuation; at what point did they --

MS. HIMMELSTRUP: Yes.

DR. I DALI: Thank you. Christine í Dali, VP Clinical Science, Zevra. As I said, 3 patients discontinued due to safety. That was fairly early on. Then we had 2 patients who met the early escape criteria. That was prespecified in the protocol that if patients met these criteria early on in the study, they were unblinded and switched to open-label treatment. Then we had one patient who withdrew due to consent, which was also during this study, and then we had this one fatal event.

DR. ELLENBERG: And at what point did they drop out?

DR. I DALI: Yes. I need to get that slide up, hopefully, but you can maybe discuss.

DR. CONNOR: I think we can show this.

Jason Connor again.

Professor Ellenberg, this shows all the patients you're referring to. The two urticaria patients, their last follow-up visit was at 3 months, and to answer the other part of your question, both of those patients were actually illustrating improvement at the time of that dropout. And then the urea/creatinine increase, patient number 6, we tracked all the way to 8 months. That patient was also seeing a difference.

So with respect to your question -- back to CO-33 -- there were a total of 10 arimoclomol patients who experienced improvement. Three of those were patients that you see here who didn't go all the way out to 12 months. So these values were used in FDA's then recommended while-on-treatment estimand, but even then, when we were doing our imputing process and imputing them to the placebo median of 1, still saw a statistical significance.

So treating, for instance, these 3 patients, all who actually observed improvement out to 3, out

to 8 months, when we would use the placebo median for imputation and treat them as 1 worse, still achieved statistical significance in the ANCOVA model.

DR. ELLENBERG: Alright. I'm not sure I really followed that.

DR. CONNOR: Well, I'm happy to put that back up and go slower or to answer specific questions.

DR. ELLENBERG: Why don't you show slide 33?

DR. CONNOR: Okay. Sure.

DR. ELLENBERG: And which ones of those did not actually have a 12-month value?

DR. CONNOR: Okay. And can I get SD-4 on my screen?

So I don't know which specific dots, but there are 3 patients, a minus 1, a minus 1, and a minus 2. So like I said -- and I apologize, I don't know exactly which of the 10 people who improved those are -- 3 patients, one who improved by 2 in just 3 months of follow-up, and then 2 patients improved by 1, one at 3 months and one

at 8 months, when they left the trial due to AEs; so seven of the other blue dots who were improvers were patients who completed the whole 12-month trial.

DR. ELLENBERG: Okay. Thank you.

DR. CONNOR: Yes.

DR. ALEXANDER: Alright. Let me remind everyone to state your name before speaking.

Let's go to Dr. Kishnani online.

DR. KISHNANI: Thank you. This is Priya Kishnani, and I had a question around the measures. I understand that cognition, we removed that from the 5-point to the 4-domain. So was cognition assessed in any other way, like using the Leiter or anything else to know how these patients were doing?

Another question is, as I read through the briefing package, to me, it appears that the benefit really is in the patients who have received both miglustat and arimoclomol. Is that a fair statement? I needed some clarification on that.

MS. HIMMELSTRUP: Yes. To begin with the

the cognition domain, we did not add other measures of cognition in the trial, and the reason why we removed the cognition domain is it's a very broad concept in the NPCCSS scale, and we did not have an objective measure to validate it up against.

For your second part of the question around miglustat, what we know is that miglustat and arimoclomol, they have different complementary effects or mechanism of actions, and the nonclinical data suggest that arimoclomol has a benefit on its own. It also shows benefit that is enhanced when used together with miglustat.

This study design, Study 002, which is in a very small population, it was designed to evaluate arimoclomol benefit in a representative population of NPC treated with routine clinical care, so it makes it difficult to assess the contribution of miglustat in that question, to fully answer the question whether there's an additive effect also due to the imbalances that we show in the group that did not receive miglustat. So overall, the benefit seen in this trial is on top of routine

clinical care, so there's no one-size-fits-all recommendation since patients might not be good candidates for miglustat.

Maybe you would appreciate a comment from Dr. Marc Patterson on his perspective, if there are any specific groups of people we should not treat.

DR. KISHNANI: I just wanted clarification what you're calling routine standard of care, is that with miglustat, because to us as clinicians, that's a very important aspect since it's not approved here in the U.S.

MS. HIMMELSTRUP: Yes, miglustat is considered part of routine clinical care. Eighty percent received miglustat as routine clinical care in the trial, which is in line with the general use in the U.S.

DR. ALEXANDER: Okay. Thanks.

Dr. Lieberman.

DR. LIEBERMAN: Yes. Hi. Thanks. Andy Lieberman. I just wanted to gain some clarification on the proposed mechanism of action. I'm not sure which individual in the group is best

to --

DR. ALEXANDER: Speak into the microphone.

DR. LIEBERMAN: -- was it necessary to have this induction of the CLEAR network for any of the phenotypic rescues that you showed in the briefing package, filipin or effect on Endo H sensitivity? Was this CLEAR network induction seen in any of the animal models?

If you looked at all the gene expression changes induced by arimoclomol, by a hypergeometric test or some sort of statistical analysis, does the CLEAR network pop out? You showed us maybe a half dozen genes that go up. I'm just trying to get a sense of the strength of this data set for the mechanism of action.

MS. HIMMELSTRUP: I'll hand over to Dr. Travis Mickle.

DR. MICKLE: Yes. Thank you. Travis Mickle from Zevra. Dr. Lieberman, I think those are all very good points. When we first looked at the research project that was brought forward with arimoclomol, we were looking across all the

different in vitro/in vivo models that were possible. I think to answer the first part of your question, there is no good phenotype/genotype comparison that we could make from the clinical data to the in vitro data. We had access to various -- sorry; I'm just bringing up a slide if I need it -- patient fibroblasts that we could study the effects in. There was no systematic approach. There were 10 CLEAR genes that were actually investigated. Not all of those 10 showed upregulation in the same degree, and then we focused on the ones that gave us the particular effect that we were looking for to look at the various genes.

So if we could look at the CLEAR gene network upregulation. I'm looking for actually just the different genotypes that we measured in the patient fibroblasts. We may not be able to get you that particular slide. If the chairman would be so generous to allow --

DR. ALEXANDER: Yes, why don't we come back to that because I know we have a number of other

members who have questions. Thanks.

Dr. Chung?

DR. CHUNG: Hi. Wendy Chung. Most of the data you've shown us today is for the 4-domain severity scale, and I'm just curious because we're asked to comment on the 5-domain scale, in general. I understand cognition was difficult to assess, but was this just noisy and there was back and forth? Did it add nothing and everyone was not changing? Can you either give us an impression or show us any of the data on the 5-domain scale for those individuals and how they were doing over time?

MS. HIMMELSTRUP: Particularly on the cognition domain?

DR. CHUNG: It could be the cognition subportion of the scale or the 5-domain scale overall. Just to give a sense of the original prespecified analysis, it would be helpful to understand that.

MS. HIMMELSTRUP: Yes. The prespecified 5-domain NPCCSS analysis is what you see here at the bottom. That's on the hypothetical estimate

MMRM analysis.

DR. CHUNG: So for instance, there's a beautiful graph you've got by participant, individual participants, and then moving back and forth, you probably didn't prepare that in advance, but do you have that for the 5-domain?

MS. HIMMELSTRUP: You're thinking about this graph? I don't have it for the 5-domain. I can see if I can get it after the break.

DR. CHUNG: Impressionistically, was there, qualitatively, any comments on how people changed?

MS. HIMMELSTRUP: Yes. I think Jason Connor can provide a bit more flavor to it.

DR. CONNOR: Hi. Jason Connor again. Yes, I think your first observation was right, that it's just kind of noisy, for reasons to describe the cognition; especially when a lot of these kids are already neurologically undeveloped at 2-3 years old, it's hard to precisely identify changes at that level, and even in some of the older kids, too. But it was basically noisy and didn't add anything either way.

DR. ALEXANDER: Okay. Thank you.

Dr. Kryscio?

DR. KRYSCIO: Dick Kryscio again. I have a question, just a clarification from Dr. Connor. Could you put up slide 29? We've heard a lot about dropouts. When people dropped out, how did you get 34 measurements at month 12?

MS. HIMMELSTRUP: Dr. Connor?

DR. CONNOR: Thank you. Jason Connor again. This plot, the final analysis is just an ANCOVA, so it's not like the MMRM that's including things at every time. This used everyone's last known value graphically at each time, which is why you're seeing Ns not changing, and this sort of implies an MMRM. We showed this graphically, but the final analysis is an ANCOVA that just uses a patient's last observed value before treatment; or some of the patients that had rescue but actually then stayed on arimoclomol, we used theirs even after the unblinding. That way, in the progressive disease, we thought that was conservative if the patients could continue to progress.

DR. KRYSCIO: Can you clarify what assumptions you make when you're doing an ANCOVA and there's missing data?

DR. CONNOR: Right. If we can go back maybe to SD-4, in the primary analysis -- I should say the primary updated analysis -- we used patients' last known value, not necessarily just the 12 months. For instance, the 3 patients here that we saw -- the urticarias, the urea/creatinine -- we did use their improvement.

The patients who had early escape, you can see the one patient in fact went to 12 months, so we had their whole 12-month data. Patient level 5 with the early escape was already at the maximum part of that scale, and then the patient who died, the value was used for their last known measurement, which was 18 out of that maximum of 20, and even when we do sensitivity analyses and supporting FDA's sensitivity analyses; for example, here's even FDA's sensitivity analyses.

Then these in the bottom -- and happy to speak to the ones in the bottom which we were able

to replicate -- these are even imputing patients randomized to arimoclomol who were unable to complete the trial as if they had received placebo, and in all those cases, you can see the treatment effect holds up. Even if the right tail of the confidence interval is just above 0, we see these treatment effects still on the order of 1.2 in the worst-case scenarios.

DR. KRYSCIO: But in all those analyses, what assumptions are you making?

DR. CONNOR: So I think in the ANCOVA, we're not making any assumptions other than using the last known value that that would project forward. Understandably, that's maybe anti-conservative in a progressive disease like this, which is why I brought up this slide, which is showing worst-case scenarios and assuming, in fact, patients never even got arimoclomol.

So there was the one patient that saw an improvement up to 8 months. This is assuming the patient didn't have arimoclomol and, in fact, was imputed to a 1-point change over a multiple

imputation. I think that patient in FDA's case averaged a 1.5 worsening. So the bottom rows here are these worst-case scenarios that, again, showed a 1.2-point improvement.

DR. KRYSCIO: I'm less concerned about the value than the assumptions you're making when you're doing, say, imputation.

DR. CONNOR: So again, in the ANCOVA, we didn't impute anything. We used the last known value prior to treatment or prior to going off treatment.

DR. ALEXANDER: Thank you.

Ms. Berggren?

MS. BERGGREN: Hi. Kiera Berggren. I was looking for a little more clarification on how you define dysphasia in this when you revised the scale.

MS. HIMMELSTRUP: Yes. I'd like to invite our expert, Dr. Lisa LaGorio, to reply.

DR. LaGORIO: Good morning. I am Dr. Lisa LaGorio, and I am an assistant professor and a speech language pathologist at Rush University

Medical Center in Chicago, and it's been my pleasure to have been working with Niemann-Pick patients and their families for the last 10 years, and I also was one of the swallowing experts that was part of developing the rescoring, the revised scoring, of the swallow domain.

So you asked about how are we defining dysphasia, so let's bring that slide up and show you. Let's take a look on the right-hand side; that's the revised scoring. So normal was no dysphasia, so that meant these people were eating and drinking regular food, thin liquids as appropriate to their age, and since all patients were over the age of 2, they were eating a regular diet; coughing while eating were those people that might have a random cough come up once in a while.

Intermittent dysphasia was defined as patients who might have more troubles if they were tired or the time of day, but if they really focused on eating, focused on drinking, maybe used a special sippy cup or a straw, then they were considered to not have dysphasia, whereas the

people that had true dysphasia, the level 3, they were people that were on modified diets, modified liquids, but were still orally eating.

Then level 4 were those people who were still orally eating but weren't able to maintain enough caloric intake or enough hydration, so 50 percent or more orally. If it was less than 50 percent orally, they needed a supplement, so they got a supplemental through the G-tube, so they were level 4. Then level 5 are all those people that were G-tube only.

All of these levels were written out on the training manual, so let me just bring that slide up. The training manual people, they were trained, they saw videos, they scored it, and there were really good inter- and intra-rater reliability with all of the scoring.

MS. BERGGREN: And that was going to be my next question, was what was that inter- and intra-rater reliability? Do you have the numbers on that by any chance?

DR. LaGORIO: I don't have the numbers, but

they were like 0.9, something

MS. BERGGREN: Okay. Thank you. That's all.

DR. LaGORIO: You're very welcome.

DR. ALEXANDER: You might stay up there for a minute. I just had a question. The swallowing data from the study was rescored, and I assume the NIH study had to be rescored, too, to create comparable, the 4-item version of this scale.

First off, is that correct, that the data was rescored for the analysis for the 4-item scale?

DR. LaGORIO: Yes. After the revision of the swallowing scale, they did go back and rescore.

DR. ALEXANDER: Yes. So also the NIH data had to be rescored too, I assume, or the natural history study data had to be rescored?

MS. HIMMELSTRUP: With regards to validation, we re-ran the analysis on content validity comparing the --

DR. ALEXANDER: Yes. I'm just really talking about the mechanics of the rescoring, so that was done by the sponsor, and was it done

blinded to treatment group or visit, or they just rescored the data without knowing --

MS. HIMMELSTRUP: Yes. The qualitative study was performed based on an interview guide, a protocol, a psychometric analysis, and a recruitment plan that was reviewed by the agency before doing the study. So that was not based on data; that was based on an interview on the scale itself.

DR. ALEXANDER: Okay.

Dr. Kraft?

DR. KRAFT: Walter Kraft. Some of the exposure-response or dose response in the preclinical package was variable, and with that in mind, for optimization, the mechanism of action putative was location, or translocation, of the transcription factors to the nucleus. Is there any thought as to exactly how that small molecule would facilitate that translocation as far as the mechanism?

MS. HIMMELSTRUP: I'd like to turn over to Dr. Travis Mickle.

DR. MICKLE: Yes. Travis Mickle, Zevra. We don't have a particular molecular target that's been identified at this point. We do know the various steps that are all involved and have seen, whether that's protein concentration increases with NPC1 or gene upregulation, and then of course the seen consequences with the in vivo studies of increased survival, NPC1 protein in the brain, and so forth.

DR. KRAFT: And if I could just follow up, was there dose dependency for adverse events in the preclinical animal models? And that's all of my question.

DR. MICKLE: By adverse events, these were disease models that we had, so fairly adverse as far as all the animals themselves. The main one that we measured, more objectively of course, was survival; so if we could bring up that survival from the presentation, and I'll just show that again.

In this particular case -- this is just one of the two models -- this one is actually the

double null which we didn't show in the main presentation -- and if we could also have the point mutation -- but you can see here, in survival, we do see an increase versus that of the disease model, and in the point mutation that I described before, there's a more substantial increase with arimoclomol.

Now, the dose dependence here was variable, so there seemed to be a point in which the lower doses did not achieve any difference, and at the higher doses, due to the fact that they were administered through their drinking water, there seemed to be a taste aversion or some other effect where you had this inverse kind of U-shaped curve. But in every one of our studies, we did observe at least a minimal survival benefit, if not, substantial, like in this particular instance, where we can distinguish the effect that we see in each one of those studies with survival.

DR. ALEXANDER: Okay.

Actually, let's go to Dr. Tucker.

DR. TUCKER: Yes. Thank you. Carole

Tucker. Two quick questions, and the first one is about the measure. When I look at this measure -- sorry; I just lost my train of thought doing that. Did we look at the measurement characteristics across domain? So for instance, the fine motor skill in the very last category, it says a gross motor limitation but it's in the fine motor scale.

So I'm just curious about any factor analysis, or domain, or anything where we've looked at dependency across domains within those. That's a question probably for Dr. Patterson, and I'm looking at slide 20, and then I have one other quick question.

MS. HIMMELSTRUP: Dr. Patterson, can I ask you to comment on the severe step of the fine motor skills?

DR. PATTERSON: Yes. I don't have the data on factor analysis, which is being asked about. Perhaps the statistical team can comment on that. If I understand the thrust of the question, each domain might not be purely measuring the function

of the domain.

I think that's a reasonable question because the disease, of course, affects multiple levels of the nervous system, and separating one from another to some extent is artificial, so one would typically expect that someone who has severe impairment, fine motor impairment, would typically have quite pronounced gross motor impairment, as well as language and swallowing impairment. They do tend to travel [inaudible - 2:33:10] -- a clinical observation, which has been consistent over the years. Perhaps we could bring up some data, or one of those statistical consultants could respond because I think you're asking more about a statistical analysis of these data.

DR. TUCKER: Actually, I think what you stated covers it a little bit. Being familiar with other similar scales for other severe diseases, we do see within the more mild cases not as big a relationship, say, between fine motor, or speech, or rote; it's really at those high levels. So it seems like this measure combined, there may be some

overlap or additional measurement.

Then my other fairly quick question is actually back to the measurement, and in this case, I'm looking at slide 29 and slide 30. What I'm noticing is in the placebo group, you only had 4 people that at baseline had greater than an 8, so there seems to be -- you can also go to the next slide, if you want -- these are changed scores. And when I add that 2.1 -- and I know there are group differences, but the placebo group mean started out as 6.7.

This is probably for the person -- well, maybe it is you. The ari [ph] -- I cannot say it, or whatever --

DR. PATTERSON: Arimoclomol.

DR. TUCKER: -- the study drug started out at a 9.2. So just out of curiosity, does that tend towards the ceiling effect, or a difference, if more people in the placebo group were milder and more people in the treatment group were already maybe near a worsening? So you may not see significant change in the group that's worse

because you're seeing this coalescence across response categories and domains.

Sorry. I'm not stating that clearly but, Dr. Patterson, you're shaking your head.

MS. HIMMELSTRUP: I think it's more a question for our statistical expert --

DR. TUCKER: Okay.

MS. HIMMELSTRUP: -- Jason Connor, so I'd like to turn over to him.

DR. CONNOR: This is Jason Connor again. Yes, ceiling effects and baseline effects are always important considerations in a scale that does have borders like this, but the ANCOVA that we fit models the changed score based upon both baseline miglustat use and baseline NPCCSS score. So thinking back to the original models from grad school, it's like saying comparing two people with the same baseline, what difference do we expect, and that's everything you see in these plots. So this is all controlling for that baseline score.

DR. ALEXANDER: Okay. Let's go back to Dr. Kishnani.

DR. KISHNANI: Yes. I actually wanted us to look at slide number 34. Actually, let me just look one more moment here; slide number 32 actually. I'm sorry; just give me a moment. It's slide 30.

If you move there, the double function null mutations, at the bottom where it says it's not available, is that because there was no placebo group? And if that is the case, then I would really like to know -- I take it that those are the patients who are under 2 years of age when they had their first neurological symptoms, but then is there a way for us to look at them in slide number 33? Who are those patients?

MS. HIMMELSTRUP: Yes. I'd like Jason Connor to respond. First, I want to clarify that the three double null patients were randomized by chance to the arimoclomol group. We did not stratify for double nulls.

DR. CONNOR: Hi. Jason Connor again. Right. To reiterate, we couldn't find a treatment effect, or estimated treatment effect, in that

group because there were none in the placebo; so we didn't have a comparator there, just the way the randomization worked out, and those 3 patients are two 3-year olds who went from 14 to 20. So in the arimoclomol group, the 2 patients who went up to 20 there at the top of the plot, those are both double null patients who started the trial at 3 years old.

Then the third is a 2-year-old patient at the bottom left of the plot who went from a 2 to a 4, but as you see here, the two worst patients on arimoclomol were both those young double null patients who we would expect to have rapidly progressive disease.

DR. KISHNANI: I see. So they did do worse than others; is that --

DR. CONNOR: Right, yes. The two worse arimoclomol patients up in the top here were the double null patients, and we did see one double null patient randomized to arimoclomol who only progressed from 2 to 4.

DR. KISHNANI: Got it. Then you looked at slide 34, where it says 35 percent of the patients

worsened. Do we have any deeper phenotyping on who these patients are, where they started, what their characteristics are, so that there can be a better understanding?

MS. HIMMELSTRUP: Yes. I'll ask Jason Connor to comment.

DR. CONNOR: Jason Connor again. So we did look and try to predict, for example, who was most likely to improve or worsen. We tried that in all trials, and it's challenging in all trials. It's particularly difficult in a trial of just 50 patients like this, so we looked at that, but it was difficult. As you said, the double nulls predictably get the worst, but otherwise we were unable to predict who might be most or least likely to benefit from arimoclomol.

DR. KISHNANI: And in terms of safety, for the urticaria and the angioedema that these patients experienced, these were different patients; correct? I believe it was in three.

MS. HIMMELSTRUP: Yes, so it was 2 patients experiencing urticaria and angioedema.

DR. KISHNANI: And the way they got better was they discontinued study drug, or --

MS. HIMMELSTRUP: They discontinued, and then it resolved, yes.

DR. KISHNANI: And so there was no further investigation to understand what the cause for this was? Were they sick? Was there an infection, COVID, something that altered their immune system?

MS. HIMMELSTRUP: I'd like to ask Christine í Dali to comment.

DR. I DALI: Christine Dali, VP Clinical Science. These two patients with urticaria happened at the same month in the same country. They developed during one day with urticaria and angioedema, and due to the risk of unblinding the whole site, we decided together with the PI to discontinue the patients and all symptoms resolved. We did not do any challenging later on for the same reasons. Thank you.

DR. ALEXANDER: Okay. Thanks.

Dr. Fischbeck?

DR. FISCHBECK: Yes. Maybe related to that,

or separately, there were no NPC2 patients enrolled in this study, and I wonder if you would want to have them included in the label even though they weren't studied. It's much less common than NPC1. Maybe that would apply to the double nulls as well.

MS. HIMMELSTRUP: So we did include NPC2 in the inclusion criteria, but no patients enrolled in the study with the mutation and NPC2 gene, so we do not have clinical data to to support that effect. But if we go back to the mechanism of action, we have both the NPC1 dependent pathway and the independent pathway, so in theory, the NPC2 patients should benefit from the pathway with the upregulation of the genes and improved autophagy, and overall cell biogenesis improvement.

DR. FISCHBECK: Could I ask the last question I have?

DR. ALEXANDER: If it's quick because we only have a few minutes.

DR. FISCHBECK: Well, I think it's quick.

The nonclinical data, which there is some new data included in the analysis, was based on

mice, where the treatment was started at 3 weeks of age, well before they became symptomatic or manifesting the disease at 9 weeks. Also, it was administered in the drinking water rather than given by gavage, which dealt with these issues. It's more difficult, but it's, I think, more accurate in terms of how much drug the animals are getting, and I wonder if you have any justification for that; not treating after disease onset as the patients are presenting and using drinking water rather than gavage.

MS. HIMMELSTRUP: I'll turn over to Dr. Travis Mickle to respond.

DR. MICKLE: Yes. Travis Mickle with Zevra. The rationale to treat the animals at a younger age was based on research suggesting that there could be an advantage to do so. Again, our intent, even in the patients, is to provide that treatment as soon as possible. If there's going to be a clinical benefit, you want to slow that progression and see what that effect would be in mice.

Now, the issue with gavage versus drinking

water, I certainly understand very well, and ideally you would want to use gavage.

Dr. Lieberman is one site in the world that does these studies very often, as well as the other in Oxford, which, again, as part of our academic research partner here, that was the limitations of the laboratory. They could only perform this in a drinking water scenario.

DR. ALEXANDER: Thanks.

Dr. Ellenberg?

DR. ELLENBERG: Thank you. Susan Ellenberg. I have a few remaining questions, if there's time, but I want to go back to Dr. Kryscio's question about the assumptions under the analysis, and this is really for Dr. Connor. He said there are no assumptions made in the ANCOVA, but if you're using the last observation carried forward, then there's certainly an assumption.

The assumption is that they're not going to change after the last observation. And since there were more dropouts on the treatment arm, it seems like there were more patients without the

opportunity to decline further after they dropped out, and I wanted to see if I was misunderstanding something.

MS. HIMMELSTRUP: Yes. I'll turn to Dr. Jason Connor.

DR. CONNOR: Jason Connor again. Yes, thanks for letting me clarify. I agree completely on those assumptions of not having time to progress if we're using those last values, and that's why I tried to show this slide with Dr. Kryscio. So yes, if we're just using the ANCOVA, and it's subtle, I think what that plot implies is we're estimating a 12-month treatment effect; and that's what I was trying to say, that we weren't with the while-on-treatment estimand that FDA recommended. We were looking at the effect at the last time the study drug was taken, which was 12 months or may have been before.

We have our own, but I'll show FDA's here because I think this is more conservative but really still supports the point. This is looking at 12-month effect sizes, and the three methods at

the bottom, the worst case, the multiple imputation, the placebo median, these are all looking at cases really assuming the patient wouldn't even get the drug at all that are using placebo estimates, meaning the patient didn't even stand to benefit from arimoclomol.

So we had the patient who actually improved glycosylceramide glycosphingolipids by 8 months, and as a reminder, we saw no one improve in the placebo group, but we had a patient leave for an adverse event after showing an improvement up to 8 months. Then the bottom estimates here show if in fact they hadn't received drug, and are just placebo patients, and do get worse.

So even in these circumstances when we allow those few patients who had adverse events who dropped out to be considered like placebo patients, where they didn't have an opportunity to benefit, even out to 12 months in their progressive disease, we're still seeing improvements of 1.2 to 1.3 points.

DR. ELLENBERG: Okay. So when they dropped

out, after they dropped out, they they did not remain in the study at all. They did not have any further measurements.

DR. CONNOR: I don't know if the patients who dropped out for safety, if we kept getting -- okay, so I'm hearing no for that, that we didn't have those further measurements.

DR. ELLENBERG: Okay. Can I ask anything else?

DR. ALEXANDER: Sure.

DR. ELLENBERG: Okay.

DR. CONNOR: For the patients with escape, we did use their further measurements. So the patients who were on arimoclomol and had progressive disease and escaped, they actually changed over to arimoclomol because we didn't know if they were placebo or not. So we actually used their measurements --

DR. ELLENBERG: Their measurements.

DR. CONNOR: -- ongoing, so we did go out to 12 months for their measurements.

DR. ELLENBERG: Okay. I wanted to know if

the patterns of adverse events differed by study arm such that there might have been some unblinding because of the types of adverse events people had.

DR. CONNOR: So I'm seeing no, but I invite Dr. í Dali to answer that question.

DR. I DALI: Christine Dali, Clinical Science, Zevra.

DR. ELLENBERG: Can you adjust the mic? I can barely hear you.

DR. I DALI: Okay. Sorry. This is an overview of the adverse events during the double-blind, and as you can appreciate, the same amount of events in the arimoclomol group and in the placebo group, and we really did not show any differences between the two groups.

DR. ELLENBERG: I understand that there was no difference in terms of the total, but what I'm asking is, is there a difference in the pattern? So for example, somebody dropped out on the treatment arm for urticaria. Now, if a lot of people got mild itching on the treatment arm but didn't on the placebo arm, that could have caused

some unblinding because that's what I'm asking.

DR. I DALI: Yes, but we didn't see anything of that at all, no differences in the pattern.

DR. ELLENBERG: And I have --

DR. ALEXANDER: Let's go to Dr. Coon first because we're running out of time.

DR. COON: Cheryl Coon. I think you showed the patient-level analysis plot for the overall 4-domain, as well as the ambulation, and in the FDA documents, the revised swallow is also shown. Do you have it for the other three domains, that individual plot, please?

MS. HIMMELSTRUP: Yes. I'm showing speech here, which is the first domain here. So you see, again, the same pattern with the improvements in the arimoclomol group and no improvements in the placebo group. Let me show the fine motor skills as well, and here you will recognize the pattern. So that was the two remaining domains of the 4-domain.

DR. COON: Thank you.

DR. ALEXANDER: Okay.

I just want to go back to this, because maybe it's just me, and I'm having trouble understanding. So the difference between the 5-domain and the 4-domain versions, one difference is the cognition domain was eliminated, but the second difference is that the swallowing value was recalculated based on the new scoring rules; is that correct?

MS. HIMMELSTRUP: Yes, that's correct.

DR. ALEXANDER: Okay. Then when you do these comparisons versus natural history like the NIH, you went through that same rescoring exercise with the NIH data, or is that the original scoring for the swallowing domain?

MS. HIMMELSTRUP: Particularly for the NIH data sets, it's the original for the main scoring without revising the swallow domain score.

DR. ALEXANDER: So it's a little bit apples and oranges perhaps? So it was a different scoring rule for the NIH? When we're seeing those curves of the NIH versus your data, the swallowing domain was scored differently in the NIH versus what

you're showing us for arimoclomol?

MS. HIMMELSTRUP: No. We have used the same scoring methodology on both our data and the NIH data. So you see there the 4-domain without revising the swallow domain, so we are comparing the same scoring for both arms.

DR. ALEXANDER: It seems like people were nodding that you didn't rescore the -- did you recalculate the individual swallowing values in the NIH data, is my question.

MS. HIMMELSTRUP: No, we did not recalculate --

DR. ALEXANDER: Okay.

MS. HIMMELSTRUP: -- for the NIH data.

DR. ALEXANDER: Alright. Thank you.

Did you want to ask one more question, Dr. Ellenberg, before we go to lunch?

DR. ELLENBERG: Thank you.

The difference between the use of miglustat was intriguing. You showed results of comparing the two treatment groups in those who did and did not take that, but I'm interested in whether you

compared within the treatment arm those who did and did not, were and were not taking miglustat at the time. There doesn't seem to be any interaction there.

MS. HIMMELSTRUP: Yes. I'll ask Jason Connor to comment on that.

DR. CONNOR: Jason Connor again. I don't think we formally compared or did any statistical tests given there were just 8 patients randomized to arimoclomol who were not on miglustat, and I think all those patients had a reason not to be. Maybe Dr. Patterson can speak to that, but it's hard to compare because there's usually a reason patients weren't randomized to miglustat. For example, I think younger patients couldn't be; none of the double nulls could be who progressed faster. So there were fundamental differences in who did and didn't get miglustat in the arimoclomol group.

DR. ELLENBERG: I think it was 28 versus 5.

DR. CONNOR: Twenty-eight versus 8, I believe.

DR. ELLENBERG: Twenty-six versus 5 on this

slide.

DR. CONNOR: Twenty-six versus 5, then plus 3 double nulls. So there were 8 arimoclomol patients not on miglustat; five were the standard mutation, and then three were the double nulls.

DR. ELLENBERG: Right. And given that the numbers are quite small, still, did there seem to be any qualitative differences in how they responded?

DR. CONNOR: The off miglustat patients responded less well than the patients who were on miglustat, yes.

DR. ALEXANDER: Okay. Thanks.

We will now break for lunch. We will reconvene again in this room at 12:20 Eastern Time. Please take any personal belongings you may want with you at this time. Panel members, please remember that there should be no chatting or discussion during the lunch break, no chatting or discussion about this topic.

(Laughter.)

DR. ALEXANDER: Additionally, you should

plan to reconvene around 12:15 p.m. to ensure you are seated before we reconvene at 12:20. Thanks.

(Whereupon, at 11:25 a.m., a lunch recess was taken, and meeting resumed at 12:20 p.m.)

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

(12:20 p.m.)

DR. ALEXANDER: Okay. I think we'll resume.

We will now proceed with FDA's presentation, starting with Dr. Maura Ruzhnikov.

FDA Presentation - Maura Ruzhnikov

DR. RUZHNIKOV: Hello, everyone. I'm Dr. Maura Ruzhnikov, FDA. I'm a geneticist and a child neurologist, and a clinical reviewer in the Division of Rare Diseases and Medical Genetics. I'm going to provide a quick clinical overview of the drug development program for arimoclomol for NPC. Some of this will be a little bit of a review and hopefully a refresher after the lunch break.

This presentation will be followed by more in-depth discussions of the clinical efficacy assessment provided by my colleagues from the Division of Biostatistics and Clinical Outcome Assessment, and then several presentations detailing additional in vitro and in vivo pharmacological and clinical data intended to provide support for the results of the pivotal

trial.

As we heard earlier today, NPC is a rare disorder. It's caused by recessive mutations in one of two genes, causing dysfunction or complete loss of function of their encoded proteins, NPC1 and NPC2. This causes the accumulation of several important lipid species in the lysosomes and late endosomes of cells in the brain and several visceral organs. We've heard previously about the purported mechanism of action of arimoclomol, and we'll hear more about this from Dr. Weis shortly.

The clinical spectrum of NPC is heterogeneous, with the primary manifestations, severity, and rate of progression varying both with age and within each age of onset subgroup, making predictions of the expected disease trajectory challenging, with the onset of disease symptoms outside of the perinatal or infantile period, or early infantile period. While visceral symptoms such as increased liver or spleen size are often also present, the predominant symptoms are neurodegenerative.

Some of the hallmark neurological symptoms of NPC are listed here and include vertical supranuclear gaze palsy; cataplexy; ataxia; dysarthria; dysphasia; cognitive and psychiatric symptoms; epilepsy; and the loss of previously attained developmental milestones and other skills.

There are no FDA approved treatments for NPC. The current standard of care is primarily supportive; however the substrate reducing therapy, miglustat, is approved for the progressive neurological symptoms of NPC in several other countries. In the United States, miglustat is FDA approved for use in other indications, and off-label use is common amongst trained clinicians. It is also recommended in international management guidelines for NPC.

Despite widespread use of miglustat, NPC remains progressive and life-limiting, without a significant change in survival in recent years. We have heard from patients, caregivers, family members, clinicians, and researchers, through multiple patient listening sessions and scientific

meetings, that there is an urgent unmet need for treatment options for this devastating disorder.

The FDA evaluation of efficacy was primarily focused on the pivotal trial Study NPC-002. This was a placebo-controlled, double-blind study of 50 individuals with NPC. The study subjects were treated either with arimoclomol or placebo, in addition to their standard care regimens for one year, after which eligible subjects had the option to enroll in open-label extension study for up to 4 years.

Prior to the initiation of Study NPC-002, the applicant also completed an observational study. The observational study covered varying time periods ranging from 6 to 14 months with the intention of gathering information throughout their course of disease while continuing their baseline therapies. The majority of these same subjects then enrolled in the pivotal trial followed by the open-label extension.

As we've heard, the primary endpoint for the pivotal trial was the change in scores on an

abbreviated version of the Niemann-Pick Disease Type C Clinical Severity Scale or the NPCCSS. The change was measured from the baseline at the time of enrollment to the end of the double-blind study period. The endpoint was constructed from the 17-domain and NPCCSS, and was abbreviated to consist of the 5 domains thought to be most meaningful to patients, caregivers, and clinical experts in NPC. These 5 domains, as you've heard, are cognition, ambulation, fine motor, speech, and swallow.

Interactions between the agency and the applicant for the arimoclomol drug development program began with the opening of the IND in 2016. The original NDA seeking traditional approval of arimoclomol for NPC was submitted in July of 2020. Prior to the original NDA submission, there were a number of meetings between the applicant and the agency, and advice was provided focusing on the primary endpoint nonclinical data to support the proposed mechanism of action, the statistical analysis plan, and the adequacy of proposed

confirmatory evidence.

During the original review cycle of this NDA, there were no significant clinical safety concerns raised. After a thorough agency review, a complete response letter was issued in June of 2021. The main deficiencies outlined in the complete response letter included uncertainties regarding the validity of the 5-domain NPCCSS with specific concerns raised regarding the cognition and swallow domains, the applicant's prespecified efficacy analysis and estimated treatment effect, as well as the adequacy of the additional data that was submitted to provide confirmatory evidence to support a drug effect.

Since the agency's complete response letter was issued, there have been ongoing discussions with meetings, written submissions, and advice letters between the applicant for this resubmission and the agency. The applicant has attempted to address the deficiencies outlined by the agency, and the NDA for arimoclomol for the treatment of NPC was resubmitted in December of 2023.

Our current review of the applicant's resubmission is focused on the aspects of the submission that were new or have changed since the original submission. These include modifications to the primary endpoint, including removal of the cognition domain and rescoring of the swallow domain, post hoc efficacy analyses, and additional clinical and pharmacology data that was collected during the open-label extension of NPC-002. There were also additional nonclinical studies submitted and reviewed.

I will now turn the presentation over to my colleague, Dr. Wonyul Lee, who will discuss the primary efficacy results of Study NPC-002 in detail.

FDA Presentation - Wonyul Lee

DR. LEE: My name is Wonyul Lee. I'm the statistical reviewer for this application. I'm going to present the primary efficacy result from the pivotal trial. This NDA includes a single phase 3 study, Study CT-ORZY-NPC-002, which will be referred to as Study NPC-002. This study was a

randomized, 12-month, double-blind, placebo-controlled, superiority trial in subjects with NPC. A total of 50 subjects were randomized in a 2 to 1 ratio to receive arimoclomol or placebo. Randomization was stratified by miglustat used at baseline. Most subjects received open-label miglustat as part of their clinical care. The prespecified primary efficacy endpoint is change from baseline to month 12 in 5DNPCCSS score. The 5DNPCCSS score is the sum of the scores from 5 domains in NPC Clinical Severity Scale, ranging from 0 to 25, with the higher scores indicating worst outcome.

During the double-blind phase, subjects on either arm meeting early escape criteria due to fast disease progression were allowed to switch to open-label arimoclomol for the remaining part of the 12-month, double-blind phase. Two subjects in the arimoclomol arm took an early escape route. A total of 17.6 percent of the subjects in the arimoclomol arm, including one of the subjects who took early escape and 6.2 percent in the placebo

arm, discontinued study prior to 12 months. In the arimoclomol arm, one subject died, 3 subjects discontinued study due to adverse events, and one early escape subject discontinued the study after experiencing the worst score.

I will present the efficacy results in the original submission in the next few slides. The prespecified primary analysis method in the original submission is a mixed model for repeated measures, which will be referred to as MMRM. Based on the prespecified MMRM analysis, the estimated treatment difference is negative 1.4 with a p-value of 0.0456, which achieved statistical significance; however, the primary analysis had a few limitations. First, it did not use the data after early escape; second, it did not use the last measurement for the subject who died.

The figure on the left shows the 5DNPCCSS score over time for subjects who died or took an early escape. These subjects are all in the arimoclomol arm. In this figure, higher scores indicate worse outcomes. The orange line presents

the score trajectory for the subject who died. The green lines present the observed scores for the subject who took an early escape. The applicant's MMRM analysis excluded the observed data in the red boxes. The excluded data indicate disease worsening for the subjects in the arimoclomol arm. This analysis treats 5DNPCCSS scores at the visits after early escape or death as missing and assume that these subject have similar scores as other subjects in the arimoclomol arm at these visits.

To investigate the impact of the excluded data in the prespecified analysis, FDA conducted two post hoc analyses, including the data in the red boxes in the previous slide. The first one is MMRM, which resulted in an estimated treatment difference of negative 0.97. The second one is ANCOVA analysis, which resulted in an estimated treatment difference of negative 1.17. The FDA's post hoc analysis provides a smaller treatment difference estimate and wider confidence intervals compared to those from the prespecified analysis.

For the remainder of my presentation, I will

present the efficacy results in the resubmission. In the resubmission, the applicant proposed to use the rescored 4-domain NPC clinical severity score, referred to as R4DNPCCSS, as the primary efficacy outcome. R4DNPCCSS score is obtained by removing the cognition domain and rescoring the swallow domain in the 5DNPCCSS score.

This proposal is a part of the applicant's attempt to address the validity concern of the primary 5DNPCCSS endpoint in the original submission. FDA agreed with the removal of the cognition domain prior to the resubmission. Details regarding the validity concerns about the endpoints will be provided by the next presenter, Dr. Knoble.

In the resubmission, the proposed post hoc primary efficacy endpoint is a change in the R4DNPCCSS score from baseline to the last visit while on treatment. This post hoc endpoint incorporates data observed after early escape and the last observed score for the subject who died. The proposed analysis method for the new endpoint

is ANCOVA, including baseline miglustat use and baseline R4DNPCCSS score. This ANCOVA analysis is referred to as the while-on-treatment strategy in this presentation.

To facilitate a comprehensive efficacy evaluation in terms of R4DNPCCSS score, FDA conducted a post hoc ANCOVA analysis of change in R4DNPCCSS score from baseline to month 12. This post hoc analysis is referred to as the treatment policy strategy in this presentation. For subjects who died prior to month 12, outcome is defined as the worst change from baseline prior to death. For the subjects who prematurely discontinued the study prior to month 12, their outcomes are considered missing and explicitly imputed.

This figure presented here shows the R4DNPCCSS score over time for subjects who prematurely discontinued the study prior to month 12. R4DNPCCSS scores at month 12 are missing for 5 subjects in the arimoclomol arm and one subject in the placebo arm. The reason for discontinuation for the top 2 subjects in the

arimoclomol arm is consent withdrawal. The reason for discontinuation for the bottom 3 subjects in the arimoclomol arm is experiencing an adverse event.

This slide shows the missing data imputation method that the FDA considered for the treatment policy strategy, which included three missing data imputation methods. Method 1 uses the worst observed change within each subject. Method 2 uses the maximum value between the worst observed change within each subject and the median change at 12 months in the placebo arm.

Method 3 is a multiple imputation method. The multiple imputation method is implemented as follows. A random number is generated from the observed distribution of change from baseline to 12 months in the placebo group. A total of 100 imputed data sets are created, and the results from these data sets are combined using the Rubin's rule.

Method 2 and 3 primarily rely on the placebo data for imputation, which may lead to more

conservative results. All three methods here assume that the subjects who reached the worst possible score of 20 remains the same after treatment discontinuation.

This slide presents the imputed values for missing data in the FDA's post hoc ANCOVA analysis of R4DNPCCSS endpoint. For method 3, which is a multiple imputation, this table presents the mean and standard deviation among 100 imputed values within each subject. For subject B, who reached the worst possible score of 20 at month 6, the imputed change from baseline is 6 for all three methods. For the rest of the 5 subjects, imputed values from method 3 are larger than those from methods 1 and 2.

This table presents the efficacy results for post hoc analyses of R4DNPCCSS endpoint. The result numerically favored the arimoclomol arm. Point estimate of the treatment difference ranges from negative 1.5 to negative 1.2, depending on the strategy used for handling study discontinuation.

This table presents the subgroup analysis

results by baseline age; age at first neurological symptoms; sex; miglustat use at baseline; and baseline R4DNPCCSS score. Except for the subgroup of subjects who did not take miglustat, the estimated treatment difference in all subgroups numerically favored the arimoclomol arm. For the subgroup of subjects who did not take miglustat, the estimated treatment difference numerically favored the placebo arm; however, it is difficult to interpret this subgroup analysis given the small sample size with only 3 subjects in the placebo arm and 8 subjects in the arimoclomol arm.

In summary, the prespecified primary analysis result for the primary 5DNPCCSS endpoint in the original submission achieved statistical significance; however, it has limitations due to exclusion of the data after early escape and data at the last unscheduled visit for the subject who died in the arimoclomol arm, and it is notable that the excluded data indicate disease worsening in the arimoclomol arm.

For the post hoc R4DNPCCSS endpoint in the

resubmission, the post hoc analysis results numerically favored the arimoclomol arm. While there is uncertainty regarding the estimate treatment effect for both the 5DNPCCSS and R4DNPCCSS endpoint, the point estimates in multiple analyses shows slow progression in the arimoclomol arm compared to the placebo arm during the double-blind period; however, there are concerns regarding the validity of these endpoints, which will be discussed by the next presenter, Dr. Knoble.

FDA Presentation - Naomi Knoble

DR. KNOBLE: Hello. I am Dr. Naomi Knoble, FDA, Associate Director of the Division of Clinical Outcome Assessment, and I will present measurement considerations for the arimoclomol development program. We are seeking the panel's thoughts on the impact, and/or potential lack of impact, of the processes used to assess the endpoint in NPC-002, the rescored swallow domain, and whether data from the revised 4-domain NPCCSS, inclusive of the swallow domain, constitutes a comprehensive

assessment of neurological function in NPC.

The FDA has evidentiary standards under federal rule and regulations specifying that endpoints, the methods of assessment of patients' responses, are well defined and reliable. Some of the evidence comprising well defined and reliable falls into two broad categories, validity and reliability. Validity and reliability evidence are necessary to support score interpretation, which is fundamental to understanding clinical trial results.

There are some critical aspects of validity evidence to support clinical outcome assessment or COA-based endpoints for labeling claims. One aspect is that COAs should be administered in a standardized manner to increase confidence that scores are valid and reliable. Another aspect of validity evidence is that all important aspects of what is being measured should be covered by the selected COA. Additionally, response options should be non-overlapping and distinct from other response categories so that there is confidence

that the scores reflect clear, distinct, clinical presentations. There are other aspects of validity and reliability; however, the aforementioned points were salient in the review of this application.

As my colleague, Dr. Maura Ruzhnikov, introduced earlier, the primary endpoint of Study NPC-002 was based on the Niemann-Pick Disease Type C Clinical Severity Scale. The scale was modified and expanded by researchers at the National Institute of Health for retrospective chart review and prospective patient monitoring. Foundational qualitative survey and interview research was conducted with patients, caregivers, and clinical experts, which identified that cognition, ambulation, fine motor, speech, and swallow were key outcomes for NPC, and then the NPCCSS was selected to measure these outcomes in Study NPC-002.

Regarding Study NPC-002, at the time of the complete response, there were concerns regarding the interpretability of the 5-domain NPCCSS scores specifically regarding the swallowing cognition

domains. These concerns included whether the NPCCSS administration was standardized in the study; whether the focus of measurement covered all important aspects of the clinical features; and regarding the response options. For speech, fine motor, and ambulation, in the resubmission, the applicant provided additional correlational evidence.

For the cognition domain, the severity ratings of cognition cannot capture the complexity of cognitive functioning. Cognition is clinically important in NPC; however, natural history research published by Dr. Audrey Thurm at NIH, published in 2015, indicated it would take more than one year to observe changes in the NPCCSS cognition domain score, making it unsuitable to show stabilization and/or changes as part of the primary efficacy endpoint.

Ratings were also dependent on the patient's environment, such as whether they were receiving educational services, which is not a clear indicator of cognitive functioning. The applicant

and the agency agreed to omit cognition from the primary efficacy endpoint for these reasons. I will discuss the swallow domain in more detail after discussing standardized administration.

Standardized administration is when the same assessment is administered to every patient at every assessment in the same way. This helps ensure reliable, consistent measurement over time. The NPCCSS has been used in the NPC natural history study and in other research programs beyond this specific drug program. In settings where the assessment used in the clinical trial is one that is used in clinical practice, there has been methodological discussion over how much standardization and training really is needed within a clinical trial.

In a qualitative interview study with clinicians completed by the applicant after the complete response, clinicians indicated that when scoring the NPCCSS, it is standard practice to observe the patient and ask the patient, and/or caregivers, to characterize the recent level of

functioning or impairments. These clinicians raised potential differences across steps that would be taken to determine a rating. If patients were rated by the same clinician throughout the study, the differences between clinician ratings may be diminished.

In Study NPC-002, the applicant provided clinicians with a scoring manual, NPCCS training, and indicated that patients were rated by the same clinician when feasible. It is unclear which clinicians performed ratings and with which caregivers at each visit, and the lack of evidence of standardization procedures in Study NPC-002 reduces our confidence in the reliability of the responses collected. Given the specific trial setting and assessment, the agency is interested in the panel's thoughts on the impact, and/or potential lack of impact, of the processes used to assess the endpoint in NPC-002.

Regarding the NPCCSS swallow domain, there were uncertainties identified by the agency regarding this domain, specifically whether the

domain was a comprehensive assessment of swallowing, which would include non-observable features referred to by NPC families as silent aspiration. It was not clear that the response options of the swallow domain were distinct, non-overlapping, and ordered by increasing severity, as there appeared to be several clinical presentations represented by the same severity score. The applicant rescored the swallow domain, and this is the point on which the agency seeks the AC panel's advice regarding whether the rescoring addresses the concern.

To address validity questions for the swallow domain regarding whether it was a comprehensive assessment of swallowing and response options, the applicant conducted a qualitative interview study with clinicians. Three NPC experts indicated that scores of 2 or 3 and the interpretation of supplemental tube feeding may vary across clinicians.

The interview study also indicated that from the perspective of NPC clinical experts and

swallowing experts, there is some variability in clinical perspectives and clinical management of non-observable features of swallow such as silent aspiration. Clinical experts made several recommendations for revisions to the scoring, including creating a linear score system.

Overall, this information indicates that selecting scores in the mid-range of the swallow domain may vary by clinician, which is also expected when applying a severity scale to a complex aspect of functioning. It also indicates, from the perspective of most clinicians, that the scale was appropriately ordered by severity. This finding was unexpected, as non-equivalent clinical presentations appeared to receive the same score. To further address validity questions regarding the swallow domain, the applicant provided correlations with NIH/NPC study data, and the agency conducted analyses with these data as well.

The NPCCSS swallow domain score was compared to the Penetration-Aspiration Scale, the PAS, and the American Speech Language Hearing Association

National Outcomes Measurement System, the ASHA-NOMS. The agency's cross-sectional and longitudinal analysis with the NIH data indicated differences in swallow scores across the PAS and ASHA-NOMS in the 0 to 3 range, indicating these scales measure different aspects of swallow. The applicant conducted independent analyses and arrived at a similar conclusion.

The swallow domain of the NPCCSS intends to measure swallowing dysfunction in patients with NPC over time. As an observational scale, only the aspects of swallowing that can be observed, described, or felt can be scored; thus, the oropharyngeal and other observable aspects of dysphasia and feeding are measured, whereas the non-observable aspects of swallowing, aspiration without a protective airway reflex or silent aspiration, are not.

Given these considerations, the advisory committee is asked to consider whether data from the revised 4-domain NPCCSS, as implemented in NPC-002, can be interpreted to represent a

sufficient assessment of swallow function in NPC, and if so, whether the revised 4-domain NPCCSS, inclusive of the swallow domain, constitutes a comprehensive assessment of neurological function in NPC.

Next, Dr. Shawna Weis will present the nonclinical evidence.

FDA Presentation - Shawna Weis

DR. WEIS: Good afternoon. My name is Shawna Weis. I'm the acting lead pharmacologist for this application. In this presentation, I will describe the nonclinical mechanistic studies that were submitted following the agency's complete response action for this NDA. The applicant is seeking approval for arimoclomol with a single adequate and well-controlled study plus confirmatory evidence. They propose that their package of nonclinical studies provides adequate support for the mechanism of action and that these data, in combination with other lines of confirmatory evidence, are sufficient to establish the substantial evidence of effectiveness for

arimoclomol for the treatment of patients with Niemann-Pick type C disease.

This is an overview of my presentation. I will summarize the basis of the complete response; describe the proposed mechanism of action and the data that were provided to evaluate the effect of arimoclomol with and without miglustat in cultured cells and in two different animal models of NPC; and then I'll end with the division's assessment of the nonclinical data.

In its complete response letter, the agency described the confirmatory evidence package as weak and contradictory, and recommended that the applicant conduct additional nonclinical and/or clinical studies to support their conclusion about the potential subgroup findings. In their resubmission, the applicant included additional reports of in vitro and in vivo nonclinical studies to define the mechanism of action for arimoclomol. As detailed in the briefing document, a considerable amount of data was generated of which we only have time to discuss a small portion.

Having reviewed it carefully, though, it is our overall assessment that the nonclinical data have significant limitations and have provided limited support for the effect of arimoclomol in NPC.

The applicant states that arimoclomol upregulates NPC1 and improves autophagic flux by activating the CLEAR network. The CLEAR network, or Coordinated Lysosomal Expression and Regulation Network, is a pathway that is induced by several cellular stressors, including starvation, pathogen infection, radiation, and toxicity. These stressors elicit molecular changes that are driven by the activation of transcription factors TFE3 and TFEB, which lead to their nuclear translocation. Once in the nucleus, they bind to gene promoters and mediate effects on gene expression.

There are over 450 described gene targets in this network of which the applicant selected 10 to evaluate the activities of arimoclomol and/or miglustat in patient-derived cells and in animals. The applicant states that these changes in gene expression improve NPC1 expression and cholesterol

clearance in NPC1-deficient cells, which they believe lead to improved functional outcomes.

To support the conclusion that arimoclomol acts via the CLEAR network, the applicant evaluated the effect of arimoclomol on nuclear translocation of TFE3 and TFEB in wild type and patient-derived cells. In this study, the cultured cells were treated at concentrations of up to 400 micromolar arimoclomol and nuclear translocation was assessed by fluorescence microscopy.

As shown in the violin plots, there was very modest, less than 2-fold increase in the level of TFE3 nuclear localization at 400 micromolar arimoclomol, which is 60 times the clinical Cmax, but there was no effect at lower concentrations. There also did not appear to be an effective NPC1 status because the magnitude of the effect in wild type cells was similar to that of NPC cells. The magnitude of the effect appeared to be similar to the effect of starvation. As shown in the right-hand panel in which fibroblasts were starved and refed, the magnitude of the effect on refeeding

was similar to the magnitude of TFE3 induction that occurred following the treatment with arimoclomol. There was little effect of arimoclomol or starvation on TFEB nuclear localization in the study.

Because TFE3 and TFEB are thought to drive expression of many stress-related genes, the applicant selected several that they believed were associated with NPC. We will focus primarily on the effects of NPC1 in this slide, but similar effects were observed with other genes, and these data are described in the briefing package.

As shown in the figures to the right, a minimal increase in mRNA level was observed; however, the magnitude of the effect was very small and the increase was largely only significant at concentrations that corresponded to 60 times the clinical Cmax. As you will see on the next slide, the effects on NPC1 gene expression were similar to effects on protein expression. As with other in vitro studies discussed in this presentation, the effects on cellular health and viability were

not assessed.

The applicant also evaluated the effect of arimoclomol in NPC1 expression across a range of patient-derived fibroblasts that carry different mutant alleles. There was an apparent effect of dose, but the effects were significant only at concentrations of between 200 and 400 micromolar in arimoclomol, and the upregulation was generally less than 3-fold relative to untreated controls. There was also no effect of genotype on the level of NPC1 protein, as the levels were not clearly higher in cells that contain 2 missense mutations versus those that contain a missense and a frameshift, or a deletion, which are the ones denoted in the red boxes.

The applicant also evaluated the effects of arimoclomol plus miglustat on CLEAR network gene expression. As before, arimoclomol alone had little effect. In general, the combination was dosed responsive, but there was additivity with the combination. The effect of NPC1 expression with the combination was significant at all doses of

miglustat, but it was greatest at the highest concentration of both agents. The concentrations represented 60-fold of the clinical Cmax for arimoclomol and 220-fold of the clinical Cmax for miglustat.

The applicant states that the primary effect of arimoclomol is the reduction of stored lysosomal cholesterol. They studied the effects of arimoclomol with or without miglustat on cholesterol levels in NPC fibroblasts. In this figure, cells were cultured for 14 days and then stained with filipin, which is a fluorescent dye that binds to free cholesterol. The cell line contained 2 copies of the missense allele, which they believe may respond best to treatment.

As shown in the violin plots, there was a modest reduction with each agent alone, and there was an additive effect of the combination. As with the induction of NPC1 shown in the previous slide, the peak effects occurred at the highest concentration of both agents. It's unknown what functional effect a change of this magnitude

represents, and given the high doses needed to produce the effect, the effect is indistinguishable from toxicity.

To summarize the in vitro data, arimoclomol induced a small increase in TFE3 nuclear localization, which was similar to the effect of starvation. There was a modest increase in expression of CLEAR genes and NPC1 protein expression in NPC fibroblasts when treated with arimoclomol, and there was a modest reduction in filipin staining. Miglustat appeared to exert an additive effect on the reduction of filipin staining. The limitations are that the exposures are extremely high, so it's not clear if this is translatable, and as previously stated, we cannot differentiate effects of the drug from the effects of toxicity.

I will now discuss the data that have been generated in NPC1 deficient mouse models. There were 2 murine models of NPC that were used. NPC null mouse was formed by a retrotransposon insertion into the coding sequence of the NPC1 gene

and does not express protein. This model develops an infantile-like form of NPC. The second model is a point mutation model. The disease is more slowly progressive in this model.

In the first study in the NPC null model, arimoclomol treatment was initiated presymptomatically. As shown in the Kaplan-Meier curve to the right, there was a minor and non-dose-related effect of treatment on survival which was maximal at the 30 milligram per kilogram dose level, which is denoted by the red line. The animals in the 300 milligram per kilogram dose level, which is denoted by the green line, appear to exhibit poorer overall survival. The applicant measured many parameters relating to rearing, gait, and step cadence. Effects on these parameters were minimal in magnitude, variable, and non-dose related.

The drug was administered in drinking water, as you've heard, and the applicant did not measure water consumption or PK to evaluate either the dose delivered or the exposures achieved, which make

these data very difficult to interpret.

The previous study was repeated at another testing facility using lower doses up to 30 milligrams per kilogram, which is the dose at which they saw the apparent effect on survival. Animals received dose up to 30 milligrams per kilogram in drinking water. Food consumption and water consumption was evaluated and found to be unaffected; however, PK evaluations were not performed. Importantly, there was no effect on motor function, gait, or survival in this study. Biochemical analyses revealed no effects on liver or brain glycolipids.

The applicant also evaluated the effects of arimoclomol plus miglustat in the NPC1 null model with arimoclomol doses of 0 and 30 milligrams per kilogram in the drinking water and miglustat doses of 0 and 600 milligrams per kilogram in the feed. As shown in the top figure, there was a very modest effect on survival with arimoclomol alone, which is denoted by the purple line, versus the untreated controls, which is denoted by the orange line.

Miglustat, the red line, also improved survival, and the combination, which is the green line, appeared to enhance the survival effect compared with the vehicle-treated group. Corresponding effects were observed on the maintenance of body weight, which is the lower figure. They did not evaluate PK, feed consumption, or water consumption in the study.

There were no effects of arimoclomol alone on motor function as measured by the latency to fall on the rotarod test, but there was a transient improvement in latency to fall in the miglustat arm, which is the red bar, and the miglustat plus arimoclomol arm, which is the green bar. There was no evidence of a greater response with the combination compared to miglustat alone, suggesting that the effect of the combination is inseparable from the effect of miglustat. There was a similar pattern of improvement on the distance traveled in the rotarod.

The applicant also evaluated the effects of arimoclomol in the point mutation model. As with

the other studies, dosing was initiated presymptomatically in the drinking water at 3 weeks of age. The study evaluated motor function, rearing, tremor, and a composite battery of physical observations called the SHIRPA battery, and they also performed computerized gait analysis.

There was a small but statistically significant increase in survival at 100 milligrams per kilogram dose level, which is the orange line, compared with the red line which are the controls, but not at the higher dose levels; and there was also a non-dose-related effect on time spent rearing and the number of rearing events at the lowest dose level of 10 milligrams per kilogram but not at the higher doses. As with the other studies, water consumption and PK were not evaluated, which makes the nonlinearity of effect difficult to differentiate from toxicity.

The effects of arimoclomol on liver and brain glycolipids were evaluated in animals treated at 100 milligram per kilogram dose level from the previous study. Many analyses were evaluated of

which we are only showing a few. There is a decrease in the glycolipid GA2 in the liver. There was also an increase in myelin basic protein in the brain. It is, in the absence of histopathology, difficult to determine if the increase in myelin basic protein correlates with a decrease in neurodegeneration. There were no effects on gene expression for the selected CLEAR network genes in the brain and there was an apparent increase in ubiquitin binding protein, SQSTM1, in the liver, but no effects on other parameters, including NPC1 or HSP1A1, were observed.

In conclusion, arimoclomol modestly increased expression of some CLEAR network genes and reduced filipin staining, but only at supratherapeutic concentrations, and the effects were indistinguishable from the effects of starvation. There appeared to be additivity on CLEAR gene expression in filipin staining with the combination of arimoclomol and miglustat. In animals, effects on survival and motor endpoints were small and variable, and they lacked a

relationship to dose and/or failed to repeat upon retest. The effects on survival appeared to show additivity with the combination in the mouse model.

As you have seen in the applicant's briefing document, they performed a cross-study analysis of the data that were obtained in animals. The agency disagrees with this approach, particularly given the small number of animals that were used per study and the long time periods that relapsed between the studies, but also because of the differences in test facility and staff, suggesting that the procedures could have been significantly different between the studies. In both models, the biomarkers were suggestive of a weak effect on glycolipids, particularly in the liver.

The animal studies had a number of limitations, including low animal numbers, uncertainty about randomization, criteria for humane endpoints, and blinding of assessors of the treatment assignments for these animals. The inability to clearly determine either the dose

delivered or the exposure achieved greatly limits our ability to interpret these studies. Overall, the data provides limited support for the effects of arimoclomol. While there may be an effect of the combination, the effects are impossible to differentiate from those of miglustat alone.

Next, you will hear from my colleague, Dr. Sydney Stern, who will present the clinical pharmacology data.

FDA Presentation - Sydney Stern

DR. STERN: Hi. My name is Sydney Stern, and I'm a pharmacokineticist with the Division of Translational Precision Medicine, Office of Clinical Pharmacology under the Office of Translational Sciences. I will be describing the clinical pharmacology evidence submitted under NDA 214927.

Today, I will go through the background of the biomarkers and their relation to the prior NDA submission and the current resubmission during the pivotal NPC-002 study and the open-label extension. Lastly, I will cover the exposure-response

relationship between arimoclomol exposure and the change from baseline to last visit while on treatment and the efficacy endpoint, the rescored 4-domain NPCCSS.

There are no known or generally established pharmacodynamic biomarkers that reliably correlate with NPC progression and severity in humans; however, lysosomal lipids such as unesterified cholesterol, glycosphingolipids, sphingomyelin, and cholestane-triol, or c-triol, have been investigated in NPC and have been shown to be elevated compared to healthy age-matched individuals.

Unesterified cholesterol is an accumulating substrate resulting from aberrant cholesterol trafficking. C-triol is a derivative of excess hepatic cholesterol and oxidative stress. Lyso-SM-509 is a novel lipid used in combination with c-triol in composite panels for early diagnosis of NPC. We note that Lyso-SM-509 has been renamed due to further structural analysis; however, to remain consistent with the applicant's

submission, we will use the name Lyso-SM-509 to reflect this biomarker. Lastly, heat shock protein 70, or HSP70, is a biomarker for target engagement to support arimoclomol's proposed mechanism.

There are several limitations applicable to all PD biomarkers discussed here. Notably, these PD biomarkers are nonspecific for NPC. While data clearly demonstrates that these biomarkers are elevated at baseline, their relationship with disease severity and progression is unclear. Lastly, it is unclear whether these blood-based biomarker concentrations reflect dynamics in other tissues such as the central nervous system.

Initially, these biomarkers were proposed by the applicant as confirmatory evidence to support the results of NPC-002. In addition to the previously mentioned limitations, no significant change from baseline to month 12, between the arimoclomol-treated patients and the placebo-treated patients, for any of the biomarkers were observed.

In the complete response letter, FDA recommended that the applicant conduct a short-term crossover pharmacodynamic study using sufficiently validated assays in a reasonable number of patients to clearly establish arimoclomol's effect on biomarkers related to its mechanism in NPC. In the NDA resubmission, the applicant no longer proposes the PD biomarkers to serve as confirmatory evidence but included the biomarkers from the double-blind phase and the open-label extension of Study NPC-002 as part of their response to the complete response letter.

Here, we summarize the biomarker findings in the original NDA submission and resubmission. All four biomarkers demonstrate no difference at any timepoint in the 60-month period, and biomarkers proposed did not show consistent increases over that period either. Limitations in the interpretation of this data include that there is significant missing data, low sample acquisition such that only 50 to 60 percent of the placebo- and arimoclomol-treated group had samples collected at

both baseline and month 12, and high inter-subject and intra-subject variability was observed. Therefore, the available PD biomarker data does not serve as confirmatory evidence for arimoclomol in Study NPC-002; however, because of the limitations outlined above, we also cannot conclude an absence of pharmacological effect of arimoclomol.

We evaluated the exposure-response relationship between the area under the curve at steady state and change in the rescored 4-domain NPCCSS from baseline to the last visit while on treatment in Study NPC-002. The area under the curve at steady state is the area under the plasma arimoclomol concentration time curve over one dosing interval derived from a population of the patients in the pivotal study. Of note, the majority of patients were receiving miglustat.

The exposure-response analysis is considered exploratory and for trend purposes. On the X-axis, you have arimoclomol area under the curve at steady state, and on the Y-axis, you have the absolute change in the 4-domain rescored NPCCSS. Each data

point represents a subject. Note that placebo-treated patients are on the left side of the slide at area under the curve and steady state at 0, and arimoclomol-treated patients are in the group in the middle of the plot.

The exposure-response analysis describes the relationship between the area under the curve and the observed clinical response. The results show an exposure-response trend that patients with higher arimoclomol exposure had a greater reduction in the rescored 4-domain NPCCSS, shown by a negative slope in the gray line, with a predicted 95 percent confidence interval, which is shaded.

We also conducted an exposure-response analysis for subgroups by miglustat use. There was only a minor reduction in the rescored 4-domain NPCCSS for patients who received arimoclomol alone, shown by the shallow slope in the yellow line. In comparison, an exposure-response trend was observed by those with concomitant miglustat, shown as the blue line. The conclusion in the subgroup analysis is limited considering the majority of patients

were receiving miglustat and other potential confounding factors could not be fully accounted for. The degree of change of the disease progression may depend on the baseline severity of the disease.

Overall, the PD biomarker data presented in the original NDA and resubmission demonstrate the same limitations included in the complete response letter, including missing data, low sample acquisition, and high variability within and between subjects. The available PD biomarker data does not serve as confirmatory evidence for arimoclomol in Study NPC-002. Arimoclomol's mechanism of action is unclear and heat shock protein 70 is unchanged from treatment.

The role of these PD biomarkers in disease progression and their correlation with the NPC clinical presentation remains unknown. Whether the systemic concentration of these biomarkers or change in them reflects CSF concentrations also remains unknown.

The exposure-response relationship alone is

not considered adequate as confirmatory evidence due to limitations in the data, despite that a trend in the exposure-response relationship has been identified, which potentially supports activity of arimoclomol. Thank you so much.

FDA Presentation - Maura Ruzhnikov

DR. RUZHNIKOV: This is Dr. Maura Ruzhnikov again. I'm, again, a geneticist and child neurologist, and a clinical reviewer in the Division of Rare Disease and Medical Genetics. I'm now going to present the additional clinical data submitted by the applicant intended to support the findings of their pivotal trial.

The additional clinical data submitted for review included the open-label extension of the pivotal trial, NPC-002; a comparison of the open-label extension data to selected subjects from an external natural history study of NPC; the observational study, NPC-001; and data from patients treated with arimoclomol under expanded access. The majority of this data was new and had not been previously evaluated during the first

review cycle, except for the results of a non-observational study, NPC-001, and the first year of the open-label extension study.

Starting with the open-label extension of NPC-002, there were 41 subjects who completed the pivotal trial and then enrolled in the open-label extension. Of those 41 subjects, 29 completed 4 years of open-label treatment. The majority of the withdrawals from the open-label extension were related to caregiver preference or progression of NPC not assessed as related to the study drug.

To evaluate the efficacy of arimoclomol during the open-label period specifically, we analyzed the two treatment arms after the end of the double-blind period separately, given their different duration of exposure to arimoclomol. Those who are randomized to arimoclomol and thus had up to 5 years of treatment are represented here in red, and those who are randomized to placebo and then had up to 4 years of open-label treatment are represented in blue. This graphic demonstrates only the open-label subjects who had clinical

severity scores available for analysis from both the beginning and the end of each year of the open-label extension. We assessed the mean change in severity scores for each year of the open-label treatment period year to year. The results of this analysis are demonstrated on the next slide.

In this graph, the Y-axis represents the mean change in the rescored 4-domain NPCCSS, while the X-axis is time in years from baseline to the end of the open-label extension period. The dotted lines represent the change in severity scores during the double-blind period. I will be focusing on the solid lines, which represent the mean change in severity scores, beginning with the first year of the open-label period, so starting at year 1 on this graph.

In the blue, the placebo cohort had a lower mean change in severity scores at the end of the first year of the open-label extension, indicating a slowing of disease progression on treatment when compared to the previous year while on placebo. For the next 3 years, those who continued on

treatment maintained a relatively stable numerical year-to-year change, including one period from year 3 to 4 of slight improvement.

In red, if we look at the arimoclomol cohort, we see that there is a period of higher mean change in severity scores in the first year of the open-label extension compared to the previous year, indicating a period of more rapid disease progression than the year prior while on continued treatment with arimoclomol.

Over the next 3 years, the mean year-to-year change numerically decreases again and remains relatively stable for each subsequent year for those who continued in the study. Thus, when subjects are compared between the study baseline and the end of the 4-year open-label period, the total study cohort appears to have remained relatively stable or to have a slower disease progression than might be expected; however, the review of the intermediate timepoints of the placebo- and arimoclomol-treated cohorts illustrates the heterogeneity within the individual

patients, which includes rapid progressors in the arimoclomol arm who were not stable during the open-label period.

Given the different disease trajectories of the two cohorts during the first year of open-label treatment with arimoclomol, we further investigated each cohort along with individual patient trajectories to aid in our interpretation of the study outcomes. Factors we evaluated in the individual patient profiles with more rapid progression included concomitant miglustat use, younger age of symptom onset, higher baseline clinical severity scores, and whether or not they had functional mutations on both copies of NPC1.

We found that subjects who were not taking concomitant miglustat and had both an early onset of disease symptoms and high baseline clinical severity scores had significant progression and appeared to drive the worsening of scores observed in the first year of open-label treatment; however, there was no single factor that was predictive of a worse outcome and there were also subjects with one

or more of these factors who did not progress rapidly.

To summarize the open-label study findings, the data appeared to show that the disease course was relatively stable with slowed progression in a portion of study subjects. This was not true for all participants, and a subset had rapid disease worsening while on arimoclomol. Our interpretation of the results of the open-label extension study are limited by an imbalance in clinical severity scores at baseline, with the arimoclomol cohort having higher mean scores than the placebo cohort and the lack of a direct comparison of year-to-year change over this time period. These limitations make it difficult to arrive at definitive conclusions regarding these results.

In an attempt to address the lack of a comparator in the open-label extension period, the agency requested that the applicant provide a comparison of the open-label data to an ongoing natural history study of NPC at the NIH. Only patients who had longitudinal assessments for at

least 4 years were included. This resulted in 32 open-label subjects and 23 patients from the NIH database for comparison.

Because there was a limited number of subjects in both arms, the applicant provided several methods for modified case matching or weighting to adjust for confounding factors using the variables of sex; miglustat use; baseline age; age of first neurological symptoms; and baseline clinical severity score. These were 4-domain scores. The swallow domain was not rescored for this comparison. The comparisons of mean scores over a 4-year time period numerically favored arimoclomol but did not approach statistical significance.

Overall, this comparison demonstrated a small numerical difference in mean scores between the two groups. An interpretation of the data was challenging due to the small number of available natural history subjects with longitudinal follow-up in which there were fewer natural history subjects than open-label extension subjects for

comparison. There was also an imbalance in which the NIH cohort subjects had milder baseline clinical severity scores and multiple natural history subjects had initiated off-label or other investigational products such as cyclodextrins during the time period included in the analysis.

The observational study, NPC-001, served as a brief historical control for subjects who subsequently enrolled in the pivotal trial. In this study, subjects were assessed at baseline and then at one additional timepoint that occurred between 6 and 14 months after baseline. Twenty-seven subjects who completed Study NPC-001 then enrolled in the pivotal trial.

This table demonstrates the mean change in clinical severity scores from baseline to the second assessment -- so between 6 and 14 months later -- in Study NPC-001 compared to the mean change observed during the pivotal trial for both the arimoclomol and placebo cohorts. The mean change in clinical severity scores from baseline to the second assessment in NPC-001 for the

arimoclomol cohort was 1.61.

At the end of the double-blind period of the pivotal trial, the arimoclomol cohort had a smaller mean change in their clinical severity scores of 0.78, indicating slower disease progression. This is in comparison to the placebo cohort who had a mean change in scores of 1.33 at the end of the observational study and a mean change during the pivotal trial of 1.44, indicating continued decline. It is important to note that these are not direct comparisons of year-to-year change over two consecutive years for each individual because the time periods measured in NPC-001 and NPC-002 are not necessarily equivalent.

In summary, a comparison of the mean change in severity scores during the observational study, NPC-001, with a mean change in scores of those same subjects when randomized to treatment, appears to show a slowing of disease progression with arimoclomol. The limitations of this analysis include that the study population and endpoints are not independent from the pivotal trial, the

potential biases included when study subjects serve as their own historical controls, and the aforementioned difference in assessment time periods. Given these limitations, definitive conclusions regarding a drug effect could not be made from this data on its own.

Lastly, the applicant provided expanded access data from their program. Although the primary purpose of expanded access is not for research, as noted in FDA guidance, if the patient outcome information collected is of sufficient quantity and quality to be highly persuasive, the information may be considered for use as confirmatory evidence. Typically, however, only limited and inconsistent information is available from expanded access, which provides an incomplete picture of events over the course of treatment.

In this study, the expanded access data did not provide for a group comparison to the study population due to several notable limitations, including differences in baseline characteristics, assessment timepoints, and the potential for use of

other or off-label therapies, amongst other unknown factors that are difficult to monitor during expanded access. For this reason, we are not able to make conclusions regarding potential efficacy from this data.

To summarize the additional clinical data submitted by the applicant, the open-label extension of the pivotal trial appears to show slowing or stabilization of NPC for up to 4 years in a portion of subjects. A subset had rapid disease progression while on treatment with arimoclomol in the first year of the open-label extension. A similar apparent slowing of disease progression was seen with arimoclomol in subjects who had completed the observational study and then were randomized to treatment in the pivotal trial.

As noted, there are limitations to these data. The comparison of open-label extension data to natural history subjects and expanded access data had significant limitations and has not been relied upon as additional support for the results of the pivotal trial.

To summarize the agency's findings of the remaining considerations for your discussions today, NPC is a rare serious disorder with unmet need for treatment. The pivotal trial demonstrates apparent slowing of disease progression; however, concerns with the primary endpoint decrease the persuasiveness of the results of this single adequate and well-controlled trial. Additional data submitted by the applicant as potentially supportive evidence included new clinical and nonclinical analyses. The additional clinical data suggest slowing or stabilization of disease severity scores with initiation of treatment with arimoclomol when compared to an observational period, and in some but not all patients with open-label treatment with arimoclomol for up to 4 years. Both of these lines of evidence have their limitations. The nonclinical and mechanistic data to support the findings demonstrated in the clinical studies are also limited.

Today, we ask you to consider whether the submitted data, including the pivotal trial and the

additional nonclinical and clinical data, support a conclusion that arimoclomol is effective in the treatment of NPC.

Clarifying Questions to the FDA

DR. ALEXANDER: Okay. Thank you.

We will now take clarifying questions to the presenters. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

So let me start -- Robert Alexander -- with a question to Dr. Lee, and if we could show slide 26. I guess my question is, I'm wondering, isn't there some merit to excluding the values in the red box, which was the approach of the sponsor initially?

In the case of the early escape, the two early escape subjects, once they're an early escape, I guess I'm assuming everybody knows they're on drug -- the subject knows they're on drug, the family knows they're on drug, the clinician knows they're on drug -- so that's clearly different and does introduce some bias. I mean, you could argue the bias might be in favor of the drug, but the fact of the matter is you don't really know what direction the bias takes. So excluding those data points, once they've been unblinded in a way, seems to make some sense to me.

Then in the case of the girl who died, taking the last value so close to the time of death, where it could have been confounded by non-disease factors, in particular, because it was determined her death was not drug related, also seems to make sense for me. So I just wondered what your response to that is.

DR. LEE: Wonyul Lee, statistical reviewer for this application. I agree with your comment regarding the exclusion of data after early escape.

I think that at this design stage, one purpose for excluding such data after early escape may prevent some bias due to unblind assessment of the COA endpoint, so I agree with your point on that, but in this particular patient, we don't see any improvement after early escape. Generally, it indicates disease worsening, so it may be arguable; which direction is bias. It could be arguable, but I was worried about potential overestimate of treatment effect if you exclude this data, indicating disease worsening, but I totally agree with your point.

For the death patient, the last measurement was collected at the unscheduled visit but is very close to the month 6 visit. The problem here is that it relates to the MMRM model they used for the primary analysis. Actually in that analysis, this analysis assumes that this patient has some measurement even after death, and then they rely on some assumptions where these data after death can be predicted or evaluated even after death, based on the other subject data. So it's somehow related

to the assumption of the model, so that was our major concern. So I believe that the last measurement reflects the disease status very well prior to the death, so I think it may need to be reflected in the analysis.

Does my answer address your comment?

DR. ALEXANDER: Yes, I think you answered the question.

Dr. Fischbeck?

DR. FISCHBECK: Yes. I wanted to put to the FDA the same question I put to the applicant about post hoc analysis. It may be my lack of statistical knowledge, but my experience has been colored by a sabbatical I did at Merck Research Labs, where there'd be company-wide discussion as to whether to move a product forward after preclinical and then clinical analysis. The statisticians there were like a high holy priesthood, and one clinician presented a post hoc analysis, and the statistician said, "No, no, no. No post hoc analysis."

So my question to the FDA is, when is it

appropriate to do a post hoc analysis, and what do you see as the shortcomings of doing that?

DR. LEE: So yes, making a decision solely based on post hoc analysis can be very problematic, but in this Study NPC-002, the primary analysis for the primary endpoint met the statistical significance, given that we recommended the post hoc analysis to address the potential limitation of the primary analysis, and thus assessed some robustness of the observed treatment difference effect in the prespecified analysis. So that's the main reason why we recommended the post hoc analysis.

You have to acknowledge that the handling of discontinuation is very tricky and challenging, especially given the very small sample size, so we have to see every angle of this feature for the analysis.

DR. FISCHBECK: Thank you.

DR. ALEXANDER: Dr. Kraft?

DR. KRAFT: Walter Kraft. This is a question for Dr. Stern and for slide 70.

Specifically, for the population PK model, was the enteral status one of the covariates? And really the question is, is a larger AUC a function of better absorption? Because the outcome measure, one of which is swallowing in tube feeds, can impact absorption. Thank you.

DR. STERN: Sydney Stern, the pharmacokineticist on the application. The area under the curve is the measurement of the plasma concentrations. It does not take into consideration measurements that may be affected by the COA. Could it be a product? That I would have to turn over to some clinical colleagues that would be able to define how that would affect the absorption of the drug?

DR. PILGRIM-GRAYSON: This is Dr. Catherine Pilgrim-Grayson, can you just please repeat the question?

DR. KRAFT: So AUC would be a function of the summation of absorption, elimination, distribution, and if you have more absorption because you have better enteral function, enteral

function may be captured in the swallowing and tube feed, perhaps those with less severe disease would have a higher AUC; so better outcomes, better enteral intake driving AUC rather than AUC driving slowing drug -- excuse me, disease progression.

DR. PILGRIM-GRAYSON: Thank you. I'll ask Dr. Maura Ruzhnikov to comment on that.

DR. RUZHNIKOV: Maura Ruzhnikov, clinical reviewer, FDA. It's a tough question to answer. I mean, it's a very good question. I think we don't have a good sense -- even if we look at all the domains that the clinical severity scale covers, for example, how come when you look at a certain timepoint, maybe one aspect is improving and another is not and vice versa, I think there's a lot that we don't understand about this disease and its progression in the first place. So I think this would be a really tough question to answer, but I see your point that better absorption may mean more exposure.

DR. KRAFT: And I guess the only thing that raises this is the confidence with which we ascribe

to the exposure-response is probably a little bit less, and it's, in a sense, exploratory anyway given the paucity of the PK samples.

DR. RUZHNIKOV: Yes, I think we would agree with that.

DR. PILGRIM-GRAYSON: May I just ask if any of our clinical pharmacology colleagues want to add to that?

DR. HONGSHAN: This is Li Hongshan, the pharmacometrics reviewer. I'm the reviewer to conduct the analysis. This AUC is not dependent on anything beyond the concentration measured, so this is a true value, not anything associated with swallow; no, this is the true measurement, and the efficacy is also the true measurement. So what you mentioned is not relevant to the analysis.

DR. ALEXANDER: Let's go to Dr. Coon.

DR. LIU: This is Jiang Liu --

DR. ALEXANDER: Oh, sorry.

DR. LIU: -- from pharmacometrics, and PoPPK also didn't detect that disease severity is a covariate for absorption, so that's why we don't

think this is a significant effect of absorption for this case.

DR. ALEXANDER: Okay. Thanks.

Are we done with that one? Okay.

Dr. Coon?

DR. COON: Thank you. Cheryl Coon.

Dr. Knoble, you raised concerns about the variability of ratings across clinicians, and I was wondering if the high ICCs that were reported in the test/retest study, if that addressed those concerns or if there were additional concerns beyond what the ICCs were showing.

DR. KNOBLE: Naomi Knoble, FDA. Thank you for your question. The ICCs that were reported were from an earlier study and were from a very specific training context. I think when we consider clinician-reported rating scales at a severity scale like this, we're dealing with a population of clinicians who are experts in their field and experts with a very rare disease. So to a reasonable extent, confidence needs to be given to their clinical expertise and ability to rate;

however, it is unknown how over several years, like in the open-label extension, that consistency held up over time.

DR. COON: Thank you.

DR. ALEXANDER: I think Dr. Glasscock is next.

DR. GLASSCOCK: Thanks. I just wanted to go back to Dr. Fischbeck's comment. In preparing for this meeting and noting a number of FDA post hoc analyses, I came across a couple quotes that I've seen in other CRL letters, and this was from FDA. "Prespecification of analyses is a bedrock principle of statistical interpretation of clinical trials."

I would just ask the committee to please keep that in mind when when thinking about the post hoc analyses that you're looking at, and I presume that the sponsor shared the statistical analysis plan with the agency in advance of unblinding the trial. Did you provide any comment on the criticism that you had after the fact, prior to unblinding?

DR. PILGRIM-GRAYSON: This is Dr. Pilgrim-Grayson. I'd like to ask Dr. Lee to answer that question.

DR. LEE: Wonyul Lee. Actually, I didn't follow your question. Can you restate your question?

DR. GLASSCOCK: Can you speak up a little bit?

DR. LEE: Of course.

DR. GLASSCOCK: It was a rhetorical question, but I presume the sponsor submitted the SAP in advance of unbinding the trial.

DR. LEE: Yes.

DR. GLASSCOCK: And did the agency provide any feedback on that SAP?

DR. LEE: Yes, we provided. Regarding the prespecified MMR analysis, we actually mentioned the concern about missing at random assumption of the prespecified MMR analysis, and actually we recommended considering some sensitivity or supportive analysis, assuming different assumptions for the missing data but, unfortunately, I did not

find any analysis assuming a different assumption for the missing data in the SAP. But we actually communicated and expressed our concern for the prespecified analysis.

DR. GLASSCOCK: Okay. Thanks.

DR. ALEXANDER: Let's go to Dr. Kishnani.

DR. KISHNANI: Could we go to slide 77?

Yes. As I'm looking at this, I needed some clarification. The numbers, the N keeps reducing, and we're drawing conclusions on the trend lines based on probably different patients. So I'm just wondering if there are individual data plots to say if there's any skewing of data based on certain patients doing way better or way worse than others.

DR. PILGRIM-GRAYSON: This is Dr. Pilgrim-Grayson. I'll ask Dr. Ruzhnikov to answer that question.

DR. RUZHNIKOV: Dr. Ruzhnikov, clinical reviewer for the FDA. I'll start with this question, and then I may ask my colleague, Dr. Wonyul Lee, to weigh in as well regarding your skewing question.

In general, I acknowledge this is a little bit hard to follow, so thank you for your question. We felt it was important to look at the mean change over each specific year for the exact reason that you state, is that over time, some of the patients end up leaving the trial and/or they hit a ceiling, which has been mentioned previously. So we really wanted to see what was happening, especially when after the original submission, it was noted that the arimoclomol-treated cohort was actually doing a bit worse in the first year of open-label treatment, which was a bit unexpected or of some concern.

So for each year, we took all of the patients who remained in the open-label study and had a measurement that we could determine the mean change for, so they had to have a clinical severity score measured for the beginning and the end of that year. So that is the reason that you have the patients start to drop off, and you see that after the first year of the open-label study, several of those rapid progressors either left the trial or

they hit a ceiling, so then we start to go back down to the trend we were seeing previously.

I want to pass it on to Dr. Wonyul Lee, as well, to answer the second part of your question.

DR. LEE: Wonyul Lee, statistical reviewer. Can you repeat your second question? Excuse me. What was your second question?

DR. KISHNANI: What I meant is that because we have certain patients that are dropping off over time, could they be the outliers, and as a result of which there might be a skewing of the data? And could we see individual plots to really see that this is representing -- going from, say, patient 28, to 22, to 18, we treat them as though they are similar, but someone who had a ceiling may have been excluded, and that may really change the trendlines.

DR. LEE: Can you pull up slide number 108? So actually, this figure shows the individual R4DNPCCSS profile over time for each patient. In this figure, you can see whether individual patient performed over time and when they stopped the

treatment or stopped the study. So regarding your question, I think you make a good point. Over time, you have a different number of samples for time, so direct comparison to one time to another timepoint could be misleading or could be very challenging, so I understand your concern.

Does it answer your question?

DR. KISHNANI: Yes, just that this is a limitation because --

DR. LEE: Yes.

DR. KISHNANI: -- it's giving us a viewpoint which may not really be representative because we're not tracking the same patients.

DR. LEE: You're correct.

DR. ALEXANDER: Thanks.

Dr. Tucker?

DR. TUCKER: Yes. Carole Tucker. This question is actually to Dr. Ruzhnikov, I believe. For the NIH study, it's noted that the swallowing wasn't necessarily rescored, but we also saw response deletions from several of the other subdomains. Was the NIH data rescored relative to

those? Then the second part of this question relates a little bit to the standardization, which may feed in.

When things are rescored, are people going back and looking at a videotape of it, or are they just deleting the scores that they have maybe numerically in a table somewhere? If that makes sense, because the mode of scoring, whether it's video or live, could make a difference that may be shared between the two.

DR. PILGRIM-GRAYSON: This is Dr. Catherine Pilgrim-Grayson. I'll ask Dr. Ruzhnikov to start and then Dr. Knoble to add.

DR. RUZHNIKOV: Dr. Ruzhnikov, clinical reviewer, FDA. At the timing that we had asked for the comparison of the open-label extension data to the natural history study, the rescoring of the NIH cohort was not completed, so what was sent to us was the 4-domain NPCCSS. So that means the cognition domain was removed, but it was a 4-domain, not a rescored 4-domain version of the NPCCSS, but the two were the same. And now I'll

pass it over to Dr. Naomi Knoble.

DR. KNOBLE: Naomi Knoble, FDA. We were not able to access the source data from the NIH data to understand for the swallow score, specifically how those scores were derived, so it was not possible to rescore it, which is why we worked with the NIH data as it was.

DR. ALEXANDER: Okay. Dr. Mink?

DR. MINK: Jon Mink. This is a question, actually, from the FDA briefing materials, something that wasn't presented in a slide, and it's maybe more of a process question for our committee.

Section 5.3.6 is efficacy results of key secondary endpoints, and it states that the responder analysis of patients' CGI-I score remains stable or shows that was the secondary endpoint. And then in parentheses it says, "For the FDA submission, this endpoint is considered a co-primary endpoint." And just for, I guess, my information and the information of the committee, as a co-primary endpoint, is that something that we

should consider differently from the other predefined secondary endpoints? And then second of all, just the information provided on the key secondary endpoints, to what significance should we attach those for our deliberations?

DR. PILGRIM-GRAYSON: This is Dr. Catherine Pilgrim-Grayson. I'll invite Wonyul Lee to answer that question.

DR. LEE: Wonyul Lee, statistical reviewer. Yes, CGI-I was one of the co-primary endpoints only for the U.S. submission, but there were some issues with the endpoint; especially this endpoint was introduced after trial initiation. Then for the protocol, CGI-I should be based on the CGI-S at the baseline, but CGI-S data were missing for most patients because it's introduced after trial initiation. In addition to that, there were some concerns about the response options in the CGI-I and some recall bias we were concerned about, so during the original review cycle, we determined that is not adequate for efficacy evaluation for those issues.

Does it answer your question?

DR. MINK: Yes. Thank you.

DR. LEE: Thank you.

DR. ALEXANDER: Just to follow up on that, basically, the key secondary endpoints are shown in table 30 of the FDA briefing document.

DR. LEE: Yes.

DR. ALEXANDER: I don't know if you have a slide of that, but the p-value was 1, I guess, for CGI-S. I mean, all the key secondary endpoints didn't show a statistically significant p-value, so are you telling us not to consider the CGI? I didn't quite follow your comment.

DR. LEE: Wonyul Lee. Can you repeat your question?

DR. ALEXANDER: Oh. I thought you were saying that we should not factor that in when we're trying to understand whether the drug worked or not.

DR. LEE: So we determined that that endpoint, the CGI endpoint, is not adequate for efficacy evaluation. That's our determination

during the original review cycle. Regarding the other key secondary endpoints, yes, none of them are remarkable in terms of observed treatment difference, although some numerically favored the arimoclomol arm. But this is a very small trial, and given the small sample size and usually an underpowered study, the lack of statistical significance for the secondary endpoints may not be unusual. Yes, that's my comment.

DR. ALEXANDER: Okay. Thank you.

While we're waiting for other people to come up with questions, let me ask Dr. Knoble a question. My question is, I guess in brief, is FDA applying the same standard to this NPCCSS endpoint that you apply to other endpoints that are accepted registration endpoints for neurology?

I'm asking because in the briefing document, there seemed to be complaining a little bit that they didn't use a diary to capture the observations of the family and that maybe they didn't always have the same rater in the clinic. But those aren't really expectations for, let's say, the CDR

sum of boxes, where we rely very much on the informant, and yet we don't require them to standardize their observations at home. I think we encourage having the same rater at every occasion, but it's not seen as a huge limitation because in the real world, that's hard to do.

So yes, I guess my question is, FDA, are you applying a somewhat higher standard to this scale than to other accepted rating scales?

DR. KNOBLE: Naomi Knoble, FDA, and thank you for your question. There are many points of flexibility with this particular rating scale that we've taken into consideration. Dr. Tucker had asked a question earlier in regards to factor structure or looking at how various domains corresponded. That's typically evidence that we would look for in a scale.

Typically, too, when a scale is rescored, we would look for additional independent evidence to support it, whether it were a clinician rating scale or some other type of scale, and we were not asking for that here. It is likely infeasible to

do and to gather that type of evidence in this very rare disease.

Your point is well taken that with a clinician rating scale administered by experts, in the neurology space, it is typical to grant the professional assumption that clinicians can adequately rate. We know for the cognition domain, for example, when you look at the Thurm, at al. 2015 paper, you see that cognition scores that were assigned, the largest population is only at the baseline. You see remarkable variation, even based on adoptive scores, which would be caregiver reports.

Adoptive scores that are in the 50s, which would be expected to be associated with significant severity, patients are receiving a cognition score of 1. So although there's, of course, the expectations that clinical experts can adequately provide scores, that's why we had some of these questions that you saw in the briefing package.

Have I addressed your question?

DR. ALEXANDER: I guess. I mean, this

question around standardization and whether there should have been a standardized way to capture the family's observation, I don't know if you could speak to that.

DR. KNOBLE: Sure, I can speak to that. It was a question that we raised as part of the rigor in our review that we do apply to all COAs, and also given that this is a rare disease, there are substantial points of flexibility that we've also brought to the review and the consideration of it as well.

DR. ALEXANDER: Okay. Thank you.

Dr. Kishnani?

DR. KISHNANI: Yes. I have a few questions around the preclinical data that has been presented. And maybe it's my own confusion here, but in some studies, if I look at one of the slides, it's only with female mice, and in some, it's both. Then there are doses going up to 500 mgs per kg, and then I think based on the 100 mgs per kg for motor function and survival, that was what was selected.

I'm just curious to understand whether this has been well balanced between male and female mice, and the other is how have we done the translation in terms of dose. If we look at some of the pre clinical studies, in particular the one on motor function which is slide 58, there is no difference between the miglustat treated alone versus the combination. So I just needed some more clarity on what kind of conclusions have we drawn because it's a wide range of studies, wide range of doses, et cetera.

DR. PILGRIM-GRAYSON: Thank you, Dr. Kishnani. This is Dr. Pilgrim-Grayson, and I'll invite Dr. Weis to answer the question.

DR. WEIS: Thank you for your question. This is Shawna Weis, Acting Pharmacology Team Lead. So those are all excellent questions. In general, they only looked at survival in females because the males were used for biochemical analyses, so survival analysis were conducted in the female animals. So that information about mobility, those are restricted to the female animals.

Your second question about the combination of miglustat and miglustat alone, yes, we do see that those do appear to be similar. This, I should point out, is in the null mouse, so this doesn't depend upon upregulation of NPC1, so it's very difficult for us to ascribe a treatment role for arimoclomol in this context.

I'm sorry. Can you please repeat your third question? Oh, is it about the exposure and dose?

DR. KISHNANI: Yes.

DR. KNOBLE: We have a very difficult time understanding how to interpret dose or exposure in these animal studies because they did administer the drug in feed and water. They did not measure PK, so we don't know how much the animals actually consumed, and we don't know the resulting exposures and how to compare them to humans, so it's very limited data.

In general, we would like to see a dose exposure analysis performed and they did not do that. As you undoubtedly picked up from the sponsor's presentation, there's a concern that at

higher doses, the animals might not have been willing to drink the water, so it's possible that the inverse dose response could be the result of failing to receive the drug; it could also be that the higher exposures were toxic, and we simply don't know the answer to that.

DR. ALEXANDER: Thank you.

Yes, go ahead, Dr. Berggren.

MS. BERGGREN: Hi. This is Kiera Berggren. I'm not sure who the best person may be to ask answer this question is, but I'm wondering if the mice developed swallowing difficulties.

DR. WEIS: Shawna Weis, Acting Pharmacology Team Lead. We don't know the answer to that. We do know that they decrease in body weight as they progress with disease severity, but whether that's just failure to thrive, inability to reach the water and the food, inability to swallow, we don't know the answer.

DR. ALEXANDER: Dr. Fischbeck, do you have a question? No.

Over here. Sorry. Go ahead.

DR. LE PICHON: J.B. Le Pichon. I'm a child neurologist in Kansas City. Thank you for taking my question, a couple of questions actually. The first one is, could you clarify for me, is it common in cell cultures, whether it's the HEK-293 cells, or whatever you're using, to have to use much higher concentrate of a substrate than in vivo? Is that an unusual observation in this study or is this something that's been seen in other studies?

DR. PILGRIM-GRAYSON: I'll ask Dr. Weis to answer this question again.

DR. WEIS: Shawna Weis, Acting Pharmacology Team Lead. Yes, there can be a disconnect between in vitro and in vivo. It's usually not as large as 60-fold or 220-fold, but there can be somewhat of a disconnect in terms of the ability to extrapolate. It really depends on the endpoint and it depends on the the modality. So some biologics are a little bit better; small molecules can be really different.

We didn't completely dismiss the

pharmacologic rationale that the sponsor provided on the basis of the exposure multiples in the culture dish. We had many more questions, though, about things like were the cells viable at the end of the treatment and other things, as I mentioned in my talk.

DR. LE PICHON: As a follow-up to that, I'm just trying to understand how much to weigh the results on the extra evidence that was presented in the animal models since the drug was added to the water. Is it somewhat reasonable to assume, as I think you were just mentioning, that if anything, the animals got less drug than would have been expected in the study design?

DR. WEIS: I'm not sure we could answer that question because we don't know the exposures. I would assume that they got less drug. We did not see a correlation between in vitro outcomes and in vivo outcomes, so the same gene regulation changes were not observed in animals, so I don't think we can answer that question directly.

DR. LE PICHON: Thank you.

DR. ALEXANDER: I have a question for Dr. Stern, if we can go to slide 72. The last bullet, there is a trend. There's a relationship between exposure-response, but then you said it's not considered confirmatory evidence. I just wondered if you could expand on that because it is supportive, as you said, of drug efficacy, but why wouldn't you consider it confirmatory evidence in this case?

DR. STERN: Sydney Stern, the pharmacokineticist on this application. Whether there's an additive effect by these two drugs cannot be fully addressed. So the majority of patients are receiving miglustat. The data is supportive potentially of an effect of arimoclomol activity; however, the exposure-response analysis is specifically not considered strong evidence because the data comes directly from the pivotal NPC-002 study, which is the same endpoint and that the exposures are not due to a wide range of drug doses. Thank you.

DR. ALEXANDER: Thank you for that.

One more chance to ask a question of FDA?

DR. HONGSHAN: Again --

DR. ALEXANDER: Sorry.

DR. HONGSHAN: -- Li Hongshan, pharmacometrics reviewer. Actually, you asked a very good question. Beyond the exposure analysis, we did more analysis, multivariate analysis. We included exposure and also miglustat. We found the drug did show some efficacy because of the trend, not only the efficacy correlated with AUC, also correlated with miglustat, so that's consistent with all the observed data. The data suggest there is still some evidence from the exposure-response perspective.

DR. ALEXANDER: Okay. Thanks. Thank you for that.

It doesn't seem like there are any further questions. We will take a quick 15-minute break. Panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members during the break, and we will reconvene at 2:20. Thank you.

(Whereupon, at 2:03 p.m., a recess was taken, and meeting resumed at 2:20 p.m.)

Open Public Hearing

DR. ALEXANDER: Okay. Let's resume. We will now begin the open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the

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

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

So we'll start with speaker number 1. Please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are

representing for the record. You have 3 and a half minutes.

DR. BERRY-KRAVIS: Hello, everyone. My name is Elizabeth Berry-Kravis, and I'm a pediatric neurologist at Rush University Medical Center in Chicago, where I see many rare genetic neurological diseases and work on treatment translation for disease-directed treatments. As a result, I collaborate with at least 20 sponsors on trials to try to improve life for my patients with at least 8 rare diseases.

I've seen and cared for over 70 patients with NPC in the past 12 years in the process of running expanded access programs and trials of new agents for NPC and have been running the arimoclomol Early Access Program, enrolling 16 patients at my site over the past almost 4 years. I feel that the stability I've seen in patients clinically over 2 to 4 years in this program supports the trial data, showing slowing of disease progression in NPC. Stability here is the goal. That's a win. These patients also show

stability in the 5-domain NPCS Severity Scale with no change or just 1- to 2-point increases, which indicates the scale supports the clinical observations.

I believe this is a scale that experienced clinicians understand and can easily rate consistently with a scoring manual and anchors, which was provided to clinicians in the arimoclomol phase 2/3 trial and EAP. In fact, there's good inter-rater reliability on the scale in two studies conducted by Orphazyme and another company working in NPC.

The scale captures core features of NPC, and a 1-point change on the scale is obviously clinically meaningful, and a caregiver, clinician, or really anyone, can see just by looking at the items that a 1-point change would be clinically important, meaning if a person does not go up a point in the time frame when they might be expected to, based on natural history, this is meaningful.

The 4-domain scale discussed earlier is appropriate for shorter trials, but the 5-domain

scale, including cognition, which we have shown tracks with IQ, is very good for tracking long-term change over multiple years in NPC, as shown by NIH and others. I have now been running the arimoclomol EAP for a sufficiently long time, that the scale should be detecting change well and applies to my clinical impression of lack or slowing of progression in my patients.

Finally, I feel the data Zevra has shown, long-term stability in the LTE and also the natural history comparators to LTE patients over 48 years, is strong support for a treatment effect because treated and untreated patients when comparing to natural history are well matched, being weighted or matched on many more parameters that can ever be controlled in a small trial.

The reason these are helpful confirmatory data, even if post hoc, is that a trial in an ultra-rare disease with high heterogeneity and a small control group is very easy to randomize an unequal treated and control group and draw incorrect conclusions because of comparing groups

that are different from each other. In natural history, there is no randomization roulette. With detailed matching, one can choose a control group that is actually similar to the treated group, so this comparison can actually be stronger than the placebo comparison in a small trial.

One can also do more long-term comparisons in natural history than in the controlled trial to confirm that there is a long-term effect of the drug and make sure the treatment is sustained. Thus, to me, it is powerful that arimoclomol shows a similar, if numerical, benefit in the matched natural history comparison over a longer time than the trial.

Given the totality of the multiple analyses in the trial, the LTE and EAP, unmet need, and desperation of the community for one or better multiple effective treatments for this miserable disease, access to arimoclomol is critical. I would like to thank the FDA and the advisory committee for their attention and for listening to my impressions and thoughts.

DR. ALEXANDER: Thank you.

Could the speaker 2 come to the microphone? Please state your name in any organization you are representing for the record, and you have 3 and a half minutes.

MS. SAMUELSON: Good afternoon. I want to start by thanking the NNPDF for making it possible for us to be here in person today. My name is Krystal Samuelson, and I am the mother to 7-year-old Willow who has Niemann-Pick type C, who is here with us today. There's no financial gain for us in being here today. The hopeful outcome for today means more than money. It's priceless, and that is time, so let me explain.

In April of 2020, at the age of 3 and a half, during one of the most uncertain times not only for my family but for the world due to the global pandemic, Willow received her diagnosis of Niemann-Pick type C. While fighting for 2 and a half years for a diagnosis, Willow regressed quickly. She lost her ability to feed herself, to move independently around our house, and was

sleeping all day long. Five short but incredibly long months later, when we could finally get into the doctor, we were told that with how quickly Willow was regressing, that we needed to start making end-of-life plans for her.

One month later, in October of 2020, I made the decision to start Willow on arimoclomol, praying for just a little more time with her. I chose arimoclomol due to the ease of being able to administer the medication at home orally. By this point in Willow's life, she already had a tremendous amount of anxiety around hospitals and doctors since so much of our time had been spent there fighting for answers. Willow loved to be at home cuddled up by her family watching her favorite shows, so selecting an option I knew wouldn't disrupt her happiness made this decision easier for me.

When starting this drug, the doctor told us not to plan on Willow getting any of her lost abilities back but that the hope was to slow things down. After 30 days, I started noticing a

difference in Willow. She had more energy and no longer wanted to nap. She was wanting to get down on the ground and play with her sister and the light came back on in her eyes. I thought, "There's no way that this could be from the drug," and assumed she was just having a good week. Well, 30 days turned into 60, and then into 90, and I started to realize what arimoclomol had done for Willow with seemingly zero side effects. I had a portion of my little girl back that I never thought I would see again.

It's been nearly 4 years since we were told to make end-of-life plans. That's 1,460 days of memories I've been able to make with my beautiful daughter, and for that I'll be forever grateful. Willow is the happiest little girl, even with all she has gone through. She inspires me every day to not only be a better mom, but a better human. I made the choice when Willow was diagnosed not to dwell in sadness but to share and educate with others. I hope hearing a small portion of our story today gives you a glimpse into what

arimoclomol has done for our life. Thank you.

DR. ALEXANDER: Thank you.

Speaker number 3, could you please unmute, turn on your webcam? Please introduce yourself. State your name and organization you are representing for the record. You have 3 and a half minutes.

MR. KRAY: Good afternoon. My name is Alex Kray. Thank you for allowing me to speak this morning. I'm before you today strictly as the father of my 20-year-old son, Jasper, who has NPC type 1 disorder. I have no financial interest in Zevra Therapeutics or connection to any of its employees, management, owners, or affiliates.

The advisory committee should know that Jasper has been on arimoclomol for more than 7 years now and that our family's experience has been extremely positive. Given Jasper's severe rate of decline between mid 2014 and May of 2017, and the relative stability of his ataxia and actual improvement in dysarthria and dysphagia over the past 7 years since starting arimoclomol treatment,

I am convinced that, at least in Jasper's case, arimoclomol has greatly reduced the rate of progression of this insidious disease.

Within a month of diagnosis in March of 2015, we started treatment with miglustat; however, while the neurological decline became less precipitous, by early 2016, dysphagia and dysarthria began to set in. In May of 2017, we enrolled Jasper in Orphazyme's arimoclomol trial. Within 3 months of starting the trial, we noticed positive effects, namely an unambiguous improvement in dysphagia and dysarthria symptoms. Twelve months into the trial, dysphasia had become very uncommon, even with thin, clear liquids. We also observed improvement in smoothness of gait.

In 2016, Jasper was unable to stand still, even with feet apart, without constantly adjusting his stance. Eight years later, he's able to stand still with feet together for long periods of time. In terms of negative side effects, we've observed none. In addition to neurological improvement with respect to dysphagic gait and speech, the viscera

also benefited. Both the liver and spleen showed reduction in size, reverting to normal within 24 months of beginning treatment. Two key liver enzymes that are elevated in NPC patients, aspartate transaminase and alanine transaminase, reverted to norm from the highly elevated levels measured prior to initiation of arimoclomol treatment.

In April of 2015, Jasper's AST was at 51, 16 points above the upper reference limit, and his ALT was 23, just one point below the upper reference limit. By September of 2020, his AST was 26 and his ALT was 10. Arimoclomol appears to have significantly slowed Jasper's disease progression and has improved not just his quality of life, but our whole family's quality of life. Not having to worry about aspiration each time he eats, takes a pill, or drinks a glass of milk is priceless to us.

Taking into account Jasper's rate of progression prior to treatment with arimoclomol, I have no doubt he would be in markedly worse condition if not for this drug. For our family,

arimoclomol has not only greatly slowed disease progression, but has given us real hope for the future. Thank you.

DR. ALEXANDER: Thank you.

Speaker number 4, do you want to come to the microphone? Please state your name and any organization you're representing. You have 3 and a half minutes.

MR. SELLERS: Good afternoon, everyone. My name is David Sellers, and I'm from Framingham, Massachusetts. I have no financial interest in the sponsor of this drug or in the outcome of this hearing. I'm not being compensated for my time, but my travel is being assisted by NNPDF. I'm here this morning as parent to 16-year-old Gwyneth Sellers, who is a teenager living with Niemann-Pick type C, my baby, my pride and joy.

Gwyneth's journey has been an interesting one since birth. She arrived to us 3 weeks early, weighing only 3 pounds, underwent a miracle surgery on day 4, and fought hard in the NICU at Boston Children's Hospital for the first 6 weeks before we

could bring her home. Years later, a routine hearing exam revealed that Gwyneth had hearing loss and that she would need hearing aids.

Through it all, this tough, happy, go-lucky, smiling, mischievous ball of energy took everything in stride. Surely, we thought the surprises must be over, but concerns about the potential for additional hearing loss prompted us to do genetic testing at age 12. The call went to my wife, Carey [ph], at work at 4 p.m. on a Friday. The testing revealed that Gwen had NPC, and this information was given to my wife on the phone with no preparation and no additional facts provided.

There is no more devastating moment than when you research this disease and its related conditions. Your world stops and a constant sense of dread takes hold; however, in our case, it did not take us long to learn that we are among the lucky in the NPC community. We learned that so many are lost before being out of infancy, others never never reached their teenage years, and few, so precious few, survive through their 20s without

being devastated by the effects.

You tell your loved ones, and in the back of your mind you worry that they're going to treat her differently and that that alone is going to affect her trajectory in life. Your future, the milestones that you all look forward to celebrating, are all instantly in doubt, and a crushing despair takes hold. This is a three-sport athlete, a dancer, a girl who sings at the top of her lungs and brings so much joy into everyone around her, and now you live on the edge, always waiting for the other shoe to drop and for life as you know it to end.

To her credit, Gwen has been stoic from the very beginning. She chose to focus on the fact that right now she feels great, but you soon learn to recognize the science of NPC, and you watch the balance issues while ambulating; the strange gaze in her eyes sometimes; the terrifying things that you spot as a parent, shaky hands with fine motor activities. And now that you know them, you can't unsee them, and you see them getting worse, and

it's death by a thousand cuts.

Like many, we put her on miglustat because there was nothing else. News of the arimoclomol trial changed everything. For the first time in months, a glimmer of hope returned to our lives. Gwen has been stable while taking arimoclomol for the past 3 years, and her symptoms have showed improvement. She falls less often during sports, and she is more able to focus in school. She plays both soccer and basketball at the high school level and she passed her learner's permit test in June, and we're 5 hours into our driving lessons together.

Gwen is fortunate to have lived a mostly full, complete life. Arimoclomol doesn't just represent the chance to give her back things that she's lost, it can stop her from having to suffer in the first place. It is the difference between a life filled with gain and all of our lives being filled with only loss. Thank you for listening to me today.

DR. ALEXANDER: Thank you.

Speaker number 5, please unmute, turn on your webcam. Please introduce yourself. State your name and organization. You have 3 and a half minutes.

MS. GILMORE: I have no financial conflict to report. Hello. Cara Gilmore. I'm 45, and I live in Pittsburgh, Pennsylvania with my husband, Bradley. As an NPC patient, we need to have as many treatment options as a choice as possible. We're in desperate need, and there's no time like the present. I do support arimoclomol's efforts for FDA approval.

I was diagnosed with adult onset NPC1 at 39 after a misdiagnosis and 18-month diagnostic journey. NPC hasn't affected my cognition yet. I'm still able to work from home full-time, and most of my symptoms are ataxic. I use a rollator to get around and I talk a lot slower now. I no longer drive. I can no longer enjoy hiking, living, or cooking like I used to. I have many difficulties and ailments, mostly ataxic and fine motor skills.

Until there's a cure for NPC, I'm looking for therapies that can preserve the quality of my life, help me maintain independence, and have more time with family and friends. I joined the arimoclomol EAP 4 years ago and I don't tolerate my only other option. My speech and swallowing have improved, stabilized, or been prolonged. With NPC, even these things are small ones.

I've had no adverse side effects. Arimoclomol is easy and convenient to take in the pill form. The arimoclomol EAP and results have given me hope, hope to stay [indiscernible - 6:08:09], enjoy time with my friends and family for years to come, and live to see a cure for NPC. Again, I ask you to support arimoclomol's efforts for FDA approval.

DR. ALEXANDER: Thank you.

Speaker 6, do you want to come to the microphone and introduce yourself? Please state your name and any organization you're representing. You have 3 and a half minutes.

MS. LAZARUS: My name is Barbara Lazarus.

My travel here is supported by the NNPDF. I am the mother of two sons -- Daniel, 37, and David, 35 -- with adult onset NPC, and I am a speech and language pathologist of 44 years. I'm here to talk about the effects of arimoclomol in our family, as David has been in the Expanded Access Program since August of 2020.

After diagnosis in 2017, they both started miglustat, immediately experienced side effects they deemed unacceptable, and discontinued use. Originally, David's only physical symptom was related to swallowing and oral function. He demonstrated difficulty with drooling and open-mouth posture and gagging and coughing while drinking. We were devastated as we watched him struggle to drink without stopping to cough and gag, often wondering if he would require modifications at some point, such as a feeding tube to avoid aspiration.

His first modified barium swallow in 2018 showed mild aspiration with recommendations to closely watch for increased difficulties. As a

32-year-old man drooling, coughing, and gagging his way through a meal when dining out with relatives and friends, David became increasingly upset, embarrassed, and frustrated. After starting arimoclomol in 2020, we saw a significant improvement in his oral abilities. His drooling decreased and eventually stopped and his coughing and gagging all but disappeared. A repeat MBS in November of 2020 showed stability of skills with the same recommendation for caution.

Fast forward 4 years to June of 2024. David has been on arimoclomol alone, and his latest MBS shows no change and his oral feeding skills have remained stable. This stabilization indicates to me as a speech pathologist that this drug has shown tremendous benefit and is working to maintain David's quality of life and dignity in the best possible way.

David now enjoys his meals and he loves to eat without fear of choking, coughing, or drooling. From a speech perspective, he has maintained his speech intelligibility with only occasional mild

dysarthria and has no difficulty with articulatory quality. Although the NPC community is willing to accept risk when necessary, it is important to note that David has had no side effects from arimoclomol. Let me repeat that; zero side effects.

While this is the greatest benefit we have seen, David remains independent in walking and daily activities, and works part-time as a construction laborer. We truly feel he would not be able to maintain this skill level without arimoclomol. It has given him a quality of life that we all hope can be maintained. We are anxious to have our other son Daniel begin arimoclomol when it is approved. I ask that the FDA approve this treatment to improve the quality of life for all NPC patients and move this horrendous and fatal disease to a manageable stage. Thank you for your time and consideration.

DR. ALEXANDER: Thank you.

Speaker number 7, please unmute, turn on your webcam, and introduce yourself. Please state

your name and any organization you're representing for the record. You have 3 and a half minutes.

DR. WANG: Hello. Good afternoon. My name is Dr. Raymond Wang, and I work at the Children's Hospital of Orange County. I have no conflicts, financial or otherwise, to disclose. I'm a clinical biochemical geneticist who's been involved with the NPC community for 17 years. I've collaborated with specialists and researchers worldwide, including Dr. Berry-Kravis, to provide the best patient care, improve diagnostics, identify biomarkers, and enable clinical trial access for people with NPC. I also have the additional privilege to care for Willow, and I'm so proud of her courage and Krystal for telling their stories.

My site has facilitated arimoclomol EAP access for 8 NPC patients. One of our first EAP patients was enrolled at nearly 30 years of age. Her NPC diagnosis was made 4 years after she developed increasing unsteadiness and fall frequency. Her baseline 5DNPCCSS and R4DNPCCSS

scores were 5. After 2 years on arimoclomol, both scores have declined to 4. Though she is due for a 4-year follow-up very soon, I was overjoyed to find out last year that she had gotten engaged to and married the love of her life.

I would next like to present an NPC sibling pair. Sibling pair analyses provide superb insight into age of initiation effects of medication, as affected sibs share both genotype and environment. The older sibling was enrolled at 8.4 years of age with quite significant neurovisceral symptoms. His baseline 5-domain CSS was very high at 18. The R4DNPCCSS was 14. As soon as he was diagnosed, his younger sister was tested and was found to have NPC. At enrollment, she was 4 years old and had a 5-domain CSS of 2 with a revised CSS of 1.

Both siblings have been taking arimoclomol for slightly more than 3 years. I've graphed their 5-domain scores here. Arrows signify when the medication was initiated. Sibling 1 score was stable at 18 for about 2 years, then ticked upwards by 1 to 19 at last follow-up due to complete loss

of speech.

In contrast, sibling 2 score was reduced by 2 to a score of 1 after a year on medication, where she's now been stable for the past 2 years. Though she's not exactly at the same age that sibling 1 was diagnosed, there's still a drastic difference in her current clinical severity score, 1, compared to sibling 1's score at baseline, 18. She enjoys dancing and singing, an outcome I'm positive is due to early initiation of arimoclomol. In fact, among our 8 patients, all but one -- sibling 1 presented above -- experienced improved RD-N4PCSS within 2 years of beginning the medication.

DR. ALEXANDER: I'm going to have to ask you to finish up.

DR. WANG: Sure. I would just like to conclude my time by highlighting that the NPC patient community needs a win. Thank you very much for your time and consideration.

DR. ALEXANDER: Thank you.

Speaker number 8, please unmute and turn on your webcam, introduce yourself. Please state your

name and organization, if any, for the record. You have 3 and a half minutes.

DR. SANTRA: Hello. Good evening. I'm Dr. Saikat Santra. I'm a metabolic pediatrician at Birmingham Children's Hospital in the United Kingdom. These are my conflicts of interest, and I have no financial relationship with Zevra. At Birmingham Children's Hospital, we look after a large number of children with all metabolic diseases, including lysosomal storage disorders and have been one of the first sites performing the pivotal trial, NPC-002, of which you've heard today with some of our patients with the longest period of continued arimoclomol therapy.

We've had 7 patients under the age of 16 at the start of onset treatment of whom 5 remain on treatments, and the maximum period of follow-up for those patients is up to 7 years. Since the end of the trial, we've had 2 patients on expanded access who've been treated for up to 2 years. I can speak to the information you've received from other speakers so far today that we've seen no safety

concerns in any of those patients, even out towards over 7 years of treatments.

I can also speak to the experience you've heard from both patients and colleagues that some patients report improvements, and we've noticed that particularly in attenuated patients. We have one teenager who was a wicket-keeper at crickets. I think that would be the person that stands behind the batsman in baseball, and it's a very important skill to be able to move your eyes up and down in order to perform that skill properly, and that was something he found very difficult and was able to report significant improvements on that within 6 months of starting arimoclomol. Other patients have been unable to walk in a straight line and have been able to achieve that within 6 months of starting arimoclomol or have found it difficult looking up from the back of a classroom without moving their whole head, whereas they have been able to do on arimoclomol.

Anyone that works with Niemann-Pick C patients will know that from the natural history of

managing these patients over many years, improvement didn't worsen in the natural history at all, and whilst taking part in these trials, we never expected to see improvements, the fact that we see improvements is significant. All other patients we've managed have generally showed stabilization, or at least a slower rate of decline, apart from those with very high disease burden at the start of treatment.

In the United Kingdom, all patients were already receiving miglustat and have been receiving miglustat for many years in some cases before starting arimoclomol, and therefore, we feel confident that any observed effects from these patients was not explicable by the action of miglustat alone.

I would also agree with comments you've heard from other speakers that the abbreviated name, PC severity scale, really does capture the relevant aspects of decline. A 1-point change is, in our experience, significant in almost all situations. In the UK, our insertion practice for

G-tubes is different, and some patients will have moved to a swallow score of 4 as opposed to 3 purely because a planned G-tube was inserted rather than any actual change in dysphasia. But apart from that situation, I can't think of any reason why it would overestimate the climate. It certainly does not underestimate the climate; if anything, it overestimates.

Conversely, not everybody's improvement always leads to improvement in the NPC severity score, and it may be that, in fact, improvement is underestimated in some patients with the --

DR. ALEXANDER: You're going to need to finish up.

DR. SANTRA: That's all I have to say. Thank you.

DR. ALEXANDER: Okay. Thank you very much.

Speaker 9, please unmute and turn on your webcam, introduce yourself. State your name and organization, if any, for the record. You have 3 and a half minutes.

MS. KAMBHATLA: Hi. My name is Anna

Kambhatla, and I have no financial conflicts of interest, and I'm here with my son, Sanjay Kambhatla, who was diagnosed with NPC type C in April 2020. After Sanjay started college at age 18, we began noticing early symptoms of NPC. It took us 6 long years to finally diagnose the disease. During this time, Sanjay experienced a range of symptoms, including --

(Audio connection lost.)

DR. ALEXANDER: Go ahead, and don't rush because we'll give you a little extra time.

MS. KAMBHATLA: Sorry. My system rebooted.

We observed significant difficulty with balance and coordination before we started the medication. Six months after taking arimoclomol, Sanjay showed improvements in ataxia, speech, swallowing, and eye movements. You can see him walking here. Three years later, in 2023, this video, he is stable and continuing to improve with arimoclomol. His IQ has remained the same over the last 4 years.

MR. KAMBHATLA: Hi there. I'm Sanjay, and

I'm cognizant with walking up the stairs. I'm independent with organizing and taking 3 pills a day at home, at work, or while traveling, all without choking. I am motivated to run a race every year to push myself like everyone else at the Crossfit Gym and play pickleball with my family, and I am proud to have developed transferable skills through my internship at the County Human Services, and I'm hopeful about finding a place of permanent employment soon.

MS. KAMBHATLA: In conclusion, arimoclomol has shown incredible results, managing and improving symptoms with speech. You heard Sanjay speaking. It was not uncommon for us to ask Sanjay to repeat words every day before he started arimoclomol. Arimoclomol has also helped him in ambulation, swallowing, motor skills, and all other endpoints of NPC. Arimoclomol has not only halted decline but also brought about noticeable improvements in the quality of life for Sanjay. We are grateful for companies like Zevra for their dedication to advanced medicine, medical science,

through providing access to life-changing medications. Thank you for your attention and support.

DR. ALEXANDER: Thank you both.

Could speaker 10 come forward to the microphone and please introduce yourself? Please state your name, any organization you're representing for the record. You have 3 and a half minutes.

MS. STITES: Good afternoon. My name is Dawn Stites, and NPDS Family Services has supported my trip here today from Tampa. I am the mother of Cole, who has Niemann-Pick type C. In order to understand Cole's journey and the role arimoclomol has played in it, I need to explain to you what life was like before his NPC diagnosis.

Cole began playing T-ball at the age of 3. He would go on to play basketball, flag football, soccer, and golf, but baseball was his first love, and he found his place on the pitcher's mound. By the time he was 8, he was selected to participate in his Little League's All Star team, and would go

on to be selected every year he was eligible.

At the age of 12, Cole got to play in Cooperstown, an experience he still talks about with great joy. Tampa is filled with sports, and Cole loved attending games. He loved interacting with fans and could often be seen on the jumbotron at Buccaneers games with a big smile and some serious dance moves.

At the age of 13, Cole was rushed to the ER after a long and scary seizure. After a battery of tests, Cole was diagnosed with epilepsy, and he seemed to respond well to the medication, and life continued as usual. Three months later, Cole started to have breakthrough seizures. During this time, we started to see a difference in his walking and running. We also started to notice Cole was quiet and no longer had any interest in attending or watching sports. He seemed to be regressing cognitively, his speech was slowing down, he developed a hand tremor, and he had lost his spark. Our once extremely outgoing son was almost completely silent.

I will never forget sitting in the exam room while the doctor with tears in his eyes told us that Cole had Niemann-Pick type C and that it was progressing quickly. We were left with no hope when he advised us simply to take him home and make him comfortable. With the help of the NPC community, we were able to get Cole accepted into a clinical trial at Boston Children's Hospital. After visiting NIH to collect baseline data with Dr. Porter, Cole began arimoclomol in December of 2021. By February, we started to see changes, and by the summer of '22, we no longer saw any evidence of a hand tremor, his speech was much better, he enjoyed watching sports again, and most importantly, his spark was back.

In the 2 and a half years that Cole has been on arimoclomol, we've noticed no adverse side effects. What we have seen is a young man who enjoys traveling, meeting new people, making new friends, and cheering on all of the Tampa Bay teams. This past April, we visited NIH for our third visit to monitor Cole's progress. We were

excited to learn that his numbers were maintaining and some had improved.

Three years ago, we were given no hope. Today, Cole is able to participate in many of the things that he loves. He's an honorary member of the University of South Florida football team. He recently attended Sleepaway Camp for the first time, and he was invited to throw out the ceremonial first pitch at the Tampa Bay Rays game. Cole is part of the data that shows arimoclomol is effective. Please consider approving arimoclomol. All NPC families deserve to experience the hope that it's given our family. Thank you.

DR. ALEXANDER: Thank you.

Speaker number 11, please unmute and turn on your webcam, introduce yourself. Please state your name and any organization you're representing for the record. You have 3 and a half minutes.

MS. WALLACE: Hello. My name is Amanda Wallace. I do not have any conflicts of interest or financial disclosures. My background is in early childhood education. I have over 15 years

experience educating children in preschool through second grade; however, I am speaking to you today as a mother of two young boys, Brody [ph] and Owen , diagnosed with Niemann-Pick disease type C.

Brody and Owen were both diagnosed in March of 2020. Owen was only 1 month old and Brody was 20 months old at the time of their diagnosis. Owen had some complications in utero and had spent the first month of his life in the NICU with ascites, [indiscernible - 6:28:21] disease, did healthy feeding resulting in an NG tube, among several other medical complications. Brody did not have any symptoms other than a slightly enlarged spleen, so his diagnosis came as more of a shock to us.

After the boys were diagnosed, we immediately began researching not only this devastating disease, but the available treatment options to which there were none approved by the FDA and only a few investigational therapies enrolling patients. After much discussion and input from our medical team, we decided to begin the boys on miglustat and enroll them in

arimoclomol's Expanded Access Program once eligible.

We decided to pursue arimoclomol for several reasons, most importantly, the potential benefit and the lack of adverse effects reported. Brody enrolled in the EAP when he turned 2, and began taking arimoclomol in October of 2020. Owen followed suit, enrolling in the EAP, and began taking arimoclomol in May of 2022.

Our story is not an extremely compelling one, especially when compared to those you read about in the docket and may hear today. We don't have any miraculous changes to share with you, but that is due to the fact that our boys are doing so well. Our story is one of stability, a word that our doctors use quite often. Brody and Owen both are not only stable but thriving. They are from outward appearances your typical 6- and 4-year-old boys. It is very easy to forget that they do in fact have this horrendous disease.

Although it is hard to quantify the stability we see within our children, I am happy to

share that their lab work is within normal ranges and ultrasounds do not show any new concerning findings. Their liver involvement is quite stable and their gastroenterologist recently moved them from 6-month follow-ups to yearly follow-ups. Their fine motor and gross motor skills continue to develop on par with those peers.

Brody and Owen are essentially symptom-free children. Brody is learning to read and write, add and subtract. Owen is identifying letters, sounds, numbers, and learning to rote count fluently. They both love to swim, enjoy fishing, like riding their scooters, and are working hard to master riding their bikes without training wheels. Brody and Owen both play on their school's T-ball and soccer teams. They enjoy puzzles, crafts, books, Legos, and so much more.

We unfortunately know what the natural history and progression of NPC looks like, and we are so grateful that arimoclomol has essentially changed the disease trajectory for our boys. They truly are living their best lives right now. We

know they would not be able to participate in all of their activities, nor would they be as healthy as they are without arimoclomol.

Neither Brody nor Owen have had any adverse effects while taking arimoclomol. In our eyes, the reward is so much greater than any possible risk to which we see none. We urge the advisory committee to support the approval of arimoclomol as the first FDA-approved treatment for Brody, Owen, and all those living with Niemann-Pick disease type C. Thank you for your time.

DR. ALEXANDER: Thank you.

Could I ask speaker 12 to come to the microphone, introduce himself, and please state your name and any organization you're representing for the record? You have 3 and a half minutes.

DR. HOPKIN: I'm Dr. Justin Hopkin, Chief of Hospital Medicine at the University of Rochester. I'm speaking on behalf of the National Niemann-Pick Disease Foundation, the U.S. NPC advocacy organization, and NPDF assisted with the travel expenses of some of the OPH speakers through our

family services program, which is supported by several individuals and companies, including Zevra. As Board Chair Emeritus, I'm honored to share the perspectives of the foundation and the individuals and families living with NPC in the United States.

I'd like to thank the FDA for convening the advisory committee today. The NPC Committee has been privileged to engage extensively with several agencies to share insights about the lived experiences of NPC, the unmet need, treatment preferences, and risk acceptance. In these meetings, we convey that NPC is heterogeneous, relentlessly progressive, and neurodegenerative with a tremendous symptom burden. Losing the ability to walk, dress, write, speak, and eat is devastating. It has an impact on the quality of life for not only the individuals with NPC, but imposes a tremendous burden on their families and caregivers.

To clarify the NPC perspective, the community was surveyed leading up to the PFTD in 2019 to identify the most impactful symptoms, and

the results are shown here. These symptoms conveyed by our community mirrored those measured by the 5-domain NPCCSS. This isn't a coincidence since the 5-point scale was created both with scientific rigor, but also with input from NPC patients, clinicians, and researchers.

If you review the 5-domain scale closely, you'll see that any single point change in any domain is the result of a very significant and measurable change, while smaller changes are less likely to alter the score. By design, a single point change in the scale is relevant, and slowing of the loss of any single point is clinically meaningful, as shown in multiple peer-reviewed published studies that are seen on the next slide.

While we understand the concerns voiced today regarding the tool, that doesn't disqualify the tool, the science, or the data it produced. Like many research instruments, the 5-domain scale is not perfect, but it is the best tool we have today to measure the impact and severity of NPC and is being used for that purpose in multiple active

NPC clinical trials. Our committee continues to work to refine this tool. Please accept the results of the abbreviated 5-domain and rescored 4-domain as valid, reliable, and meaningful.

The NPC-002 trial was the pivotal placebo-controlled study for arimoclomol. Given the natural challenges of executing a clinical trial for NPC, including disease heterogeneity and an ultra-small patient population, a benefit was seen in the arimoclomol group at only one year, using an endpoint that measures direct clinical benefit, the 5-domain NPCCSS, the best measure available to assess how a person with NPC feels and functions.

Please accept the substantial clinical evidence is meaningful to our community, and if any uncertainty remains regarding the treatment benefit, please reflect on the totality of evidence, including the open-label extension data; the AP which includes nearly 80 U.S. patients; the patient and expert stories from our prior FDA engagements in the docket; and the community

response with a thousand signatures and family comments.

Listen to them. Each testimony is real-world evidence supporting the benefit of arimoclomol to treat the most impactful symptoms of NPC. Arimoclomol is shown to be incredibly safe and effective and an adequate and well-controlled clinical investigation. Leverage the data that you have seen today, and your vote that you will cast later on. Thank you for your time.

DR. ALEXANDER: Thank you.

Can I ask speaker 13 to come to the microphone? Please state your name and any organization you're representing for the record. You have 3 and a half minutes.

MR. ALVEY: Thank you. Good afternoon, everyone. My name is Garland Alvey, and with me here today is my daughter and real-world superhero, Abby. I'm here today as the Co-Founder and Executive Director of our nonprofit organization, AbbyStrong Fights NPC. I'm also a volunteer director with the National Niemann-Pick Disease

Foundation's board, and I want to thank them for the travel assistance to be here with you today.

I have no financial relationships with this applicant, but I know I speak for so many when I say how grateful we are for their commitment to the future of the NPC community. With your recommendation today, this bright future can now include our first FDA-approved treatment that showed safe and meaningful improvement. Arimoclomol has demonstrated through data and real-world evidence to be worthy of FDA approval.

I want to share with you just a small sample of what this 9-year-old superhero, Abby Strong, has done with the help of such an amazing and loving community around her. Abby fundraises and advocates at the local, state, and federal levels to help combat the challenges that ultra-rare disease communities like NPC face. Through this work, we've learned that our mission is clear. We join everyone in this room and in our communities to commit everything in our power to help meet the urgent unmet medical needs of the NPC community.

Together, we're stronger.

We're so proud of Abby and her work in Virginia to have Rare Disease Day and Childhood Dementia Day recognized in her school and all over the Commonwealth. Through our advocacy and education, so many people learned about the challenges facing small and heterogeneous patient populations like NPC. It's important to know that Abby is not the only person with NPC who's changing the world in spite of her disease, but we need effective treatments like arimoclomol to help extend their impact on our lives.

Everything we've done has been with the help of others. We're just one of many amazing family support organizations. This community rallies around those organizations, leading the way, like Hope for Marian Foundation; the Firefly Fund and NNPDF; and Ara Parseghian Medical Research Fund, just to name a few. These rare disease communities work tirelessly over the generations to get us to where we are today, right now.

More recently, we've celebrated a major

milestone while working hand in hand with lawmakers to include language in the fiscal year '24's agriculture appropriations bill. Many here are familiar with that, but there's some that may not be familiar with that language that included, "The committee encourages FDA to use its existing authorities and pathways to meet the urgent and unmet medical need of the current generation of NPC patients."

It goes on to say for the FDA to maximize its use of existing natural history data and real-world evidence contributed by the small patient population through existing and past clinical studies. Because of this language, we now have a future where we don't have to go make memories like they used to tell us after receiving an NPC diagnosis.

The science and regulatory landscapes have advanced to where this generation of NPC patients like Abby can now have treatments. The FDA can and should approve arimoclomol. The real-world evidence is right in front of us with solid and

confirmatory evidence from the applicant and so many comments from the NPC community, supporting this drug's ability to slow progression.

I want to thank the esteemed members of the advisory committee for their time today and for recommending the approval for the safe and effective treatment, arimoclomol. I also want to thank everyone in the NPC community for their commitment, courage, and sacrifice over this long journey. Thank you.

DR. ALEXANDER: Thank you.

Speaker 14, please unmute and turn on your webcam, introduce yourself. Please state your name and any organization you are representing for the record. You have 3 and a half minutes.

MS. MATHIESON: Good afternoon. My name is Toni Mathieson, and I am a patient advocate for Niemann-Pick UK, a nonprofit organization that has been supporting individuals affected by NPC since 1991. NPUK receives unrestricted grant funding from pharmaceutical companies, including Zevra.

Today, I'm pleased to share the perspectives

of Leighton [ph] and Holly, two UK patients with extensive experience of arimoclomol. Diagnosed with NPC at 5 months old, Leighton began losing skills at 18 months and experienced problems with mobility, swallowing, eye gaze, and concentration. Parents were told he would not survive past the age of 5; however, later this year, Leighton will celebrate his 18th birthday. They believe that a combination, miglustat and arimoclomol, which Leighton has received since the age of 10, has significantly slowed and has even improved some of his symptoms.

After 7 and a half years on treatment, he is still able to eat and enjoy the social benefits of shared dining. Leighton's school reported improved concentration, a noticeable improvement to his eye gaze, helping him to interact and retain focus. Leighton has also retained independent mobility and is able to support himself to retrieve items from across a room. At 17 years old, this independence is important to Leighton, as is the ability to verbally communicate, to hold a cup to take a

drink, or to feed himself.

Holly was diagnosed at 2 years old with symptoms causing emotional and social developmental delays and challenges with balance and coordination. Now 19, Holly and her parents feel that treatment with arimoclomol since 2013 has been transformative, with her clinicians reporting prolonged stabilization in her condition. They believe arimoclomol has been fundamental in maintaining Holly's physical well-being, swallow, and speech, improving balance and coordination, and most importantly, preserving her independence and quality of life.

Holly's ability to understand social cues and interact with her peers has also improved, reducing feelings of isolation and exclusion and enabling her to fully participate in mainstream education, achieving a diploma in performing arts. The consistency in Holly's physical abilities over 11 years, retaining mobility, calmness, or control in balance, has been noted by her physiotherapist as being remarkable. Physical stability has

allowed Holly to live a life not defined by her diagnosis. The non-invasive nature of arimoclomol has played a significant role in this, helping to independently and discretely manage symptoms and ensure daily routines are disruption free.

Given the lack of therapeutic options currently available for NPC, there is an urgent need for effective, approved, and accessible therapies, and it is encouraging to see two potential therapies under review this year. I therefore respectfully urge the committee to recognize the meaningful impact of arimoclomol on Holly and Leighton's lives, those of their families, and the wider international patients and clinical communities who consistently report similar benefits of arimoclomol as a monotherapy and in combination with miglustat.

This is not just about prolonging life, but about preserving quality of life and enabling patients to fully engage with the world around them, maintain their independence, and enjoy the simple pleasures of life that the rest of us take

for granted. Thank you.

DR. ALEXANDER: Thank you.

Speaker 15 wasn't able to make it today.

Speaker 16, could you please unmute and turn on your webcam, introduce yourself? Please state your name and any organization you're representing for the record. You have 3 and a half minutes.

MS. HAHN: Hello. My name is Caitlin Hahn, and I have no financial conflicts of interest with any NPC pharmaceutical companies. My husband and I [indiscernible - 6:43:26] in order to conceive Oliver, and we had a normal pregnancy, no significant issues besides high blood pressure. At 36 weeks [indiscernible - 6:43:35], we quickly identified that something was wrong. After a number of tests and procedures, we found that he was in end-stage liver failure due to NPC. The transplant board met about Oliver, and there was a good chance that he would not be eligible for a transplant due to his diagnosis. The genetics and metabolic team at Lurie Children's Hospital felt strongly that Oliver was a good candidate, as so

many advances had been made in this field. They felt that by the time he would begin to see decline, medications would be advanced enough that the transplant would in fact be beneficial to him.

Months old, he had the transplant. Because of that, he has labs every 3 months with more in-depth labs yearly, an ultrasound every year, and a biopsy every 5 years. At the 5-year mark, his biopsy identified that there were NPC cells present in the liver. The current medication he was on, miglustat, or Zavesca, was slowing the spread; however, it hadn't fully stopped it. After the biopsy and seeing the cells, we felt that it was time to consider the trial. This also makes sense because through kindergarten, he was also not quite at the same level as his peers for motor skills, strength, and coordination.

Since starting on arimoclomol, he's had no negative changes in his health or side effects. His labs have stabilized. He no longer fluctuates between good and bad. His enlarged spleen stabilized in size and it's no longer increasing.

We have noticed a stabilization and increase in his strength, improvement in his fine motor skills, and improved coordination. He's currently in a strength and conditioning class, as well as speech, occupational, and music therapy.

While he's been in therapies of different types for a majority of his life, he has never been able to make as much progress in them as he has the past 2 and a half years. He is currently a thriving 8 and a half year old kiddo, getting ready to start the third grade with his peers, which those of you familiar with NPC know is not a small feat. I credit much of this to the arimoclomol trials and its ability to stay stabilized and improve his overall function, while allowing both him and the rest of our family to live our best lives. Thank you so much for your time.

Clarifying Questions (continued)

DR. ALEXANDER: Thank you very much.

The open public hearing portion of this meeting has now concluded. I want to personally thank all our speakers, and we will no longer take

comments from the audience.

I'm going to offer Zevra the opportunity now to respond to clarifying questions that they needed a little more time to answer from this morning; so if you want to go ahead.

MS. HIMMELSTRUP: Thank you so much. For the first question from Dr. Lieberman, I will ask Travis Mickle to respond.

DR. MICKLE: I know, Dr. Lieberman, you had a very complex question. I believe the first portion of that was related to some distributions that may have been done with the various genotypes and phenotypes; and, no, we were not able to do that particular distribution. What we did see in the study was the various genotypes by the mutations. In fact, I think this does speak to the heterogeneity of the disease.

Of course, everyone knows about the three double functional nulls, as well as, in most cases, a double missense. The study itself has a total of 50 patients, and there was 27 with that particular type of genotype. Missense with a functional null,

there was 20 in the NPC-002 study. There was, I believe as well, a number of different new mutations that were identified as far as one or both of the alleles in that particular case.

Now, to go more specifically about what work we did related to the actual genotype -- and I'll go through this fairly quickly -- we have here, as you may have seen in some of the briefing materials --

DR. ALEXANDER: You're not presenting new data, are you?

DR. MICKLE: No. This is from the briefing material --

DR. ALEXANDER: Okay.

DR. MICKLE: -- just shown in the format with color. In this particular case, there's increased NPC protein, so we looked across the various genotypes representative of the missense. ER missense is probably the most frequent, and that's there on the extreme left, and then various genotypes for these patients. And you can see from this, various NPC protein concentrations that

increased in the presence of arimoclomol, anywhere from, in some cases, 100 up to the 400 micromolar concentrations.

With that, then we were able to identify the actual genotype on the far left here. Sorry. I brought up the wrong one. We could then narrow down to the 10 CLEAR network genes that we looked at in that particular case and we used in that example of looking across the different patient groups, finding one that responded well and see what else that would do for the various genes across the CLEAR network. Then, as you already know from the core presentation, we see then an increase in our in vivo models, both the mature form of NPC1 in the brain of the animals, as well as then the myelin basic protein. Thank you.

DR. ALEXANDER: Thank you.

MS. HIMMELSTRUP: Yes. The last clarification I want to make is on the endpoint. We had a little bit of discussion on the EAP data and the comparison to NIH, whether that was on the rescored or the scored. Two points to make here,

if we look at the original swallowing scale here, the revised swallowing methodology is based on the data that was included in the CRF. What you see here of the description, they were entered into the CRF, so there has been no re-recording of any data points from the study. Everything is from the CRF and then reclassified into a new scoring methodology, so no changes to original data.

For all the presentations of data we have provided on the primary endpoint, we have used the revised 4-domain swallow score, except for comparison to the NIH data because we did not have the granularity from the CRF to do the rescoring, so those analyses are on the 4-domain NPCCSS without rescoring. We did the same for the data on arimoclomol, so we are comparing apples to apples in those analyses.

Thank you for allowing us to clarify.

DR. ALEXANDER: Thank you.

Dr. Lieberman, did you have a quick follow-up or are you satisfied with the answer? You're ok?

(No audible response.)

DR. ALEXANDER: Okay. Good.

Alright. We will now proceed with the charge to the committee from Dr. Pilgrim-Grayson.

Charge to the Committee - Catherine Pilgrim-Grayson

DR. PILGRIM-GRAYSON: Before I start with the charge to the committee, I would just like to thank the patients, family members, caregivers, clinicians, and other advocates who spoke just now. Your perspectives and your experiences are really important for us to hear, and we're all here because of the patients, so it's always important for us to keep that in the front of our minds. So now I'll move to the charge to the committee.

As you have heard, Niemann-Pick disease type C is a rare and devastating disease with no approved therapies. Arimoclomol, proposed for the treatment of NPC, is a new molecular entity, the mechanism of action of which has not been fully elucidated. The applicant has provided data from one adequate and well-controlled trial, NPC-002, and additional confirmatory evidence.

As a reminder, the data from the pivotal trial, NPC-002, suggest that arimoclomol results in a slowing of disease progression; however, there remain concerns with the primary endpoint, the original 5DNPCCSS endpoint, and the rescore of 4-domain NPCCSS endpoint, which adds uncertainty to the persuasiveness of the results of the single adequate and well-controlled trial. Further, additional clinical and nonclinical evidence to support the effectiveness of arimoclomol is limited.

As I mentioned in the beginning of the day -- I just want to review our regulatory standard -- in the rare disease setting, just as in the setting of a common disease, we must have reasonable certainty about a drug's benefit. We recognize that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of a disease.

Today, we're asking you for your scientific

assessment of the data from the single randomized-controlled clinical trial and the additional clinical and nonclinical data to support a conclusion that arimoclomol is effective in the treatment of NPC. When you consider the questions that were posed to you, I will just provide this reminder about substantial evidence of effectiveness.

As you may remember, FDA generally will interpret that to mean two adequate and well-controlled clinical trials, but we may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence of effectiveness if FDA has determined that the data are sufficient to establish effectiveness. Confirmatory evidence, as you've seen, can be generated from multiple sources -- clinical, clinical pharmacology, animal data -- but the data must be of quality and quantity to establish effectiveness.

Per FDA guidance, we can apply flexibility in these situations such that the quantity of this

additional evidence can vary. If you have a strong, persuasive, adequate, and well-controlled clinical trial, then a less amount of confirmatory evidence may be necessary. Conversely, a less persuasive investigation may require a greater quantity of compelling confirmatory evidence to allow for a conclusion of substantial evidence of effectiveness.

I'll now turn to the discussion questions and the voting question. Question number 1 is, discuss your assessment of the efficacy results of Trial NPC-002. In your discussion, please comment on the 5-domain Niemann-Pick Disease Type C Clinical Severity Scale and the rescored 4-domain Niemann-Pick Disease Type C Clinical Severity Scale, and in particular, we're interested in your thoughts on the 4-domain. Also comment on your assessment of whether the trial results demonstrate a treatment effect of arimoclomol on Niemann-Pick disease type C.

Question number 2 is, discuss your assessment of the other data, specifically the

additional clinical and nonclinical data, with respect to support for the effectiveness of arimoclomol. We're specifically asking the committee to discuss these streams presented both by the FDA and the applicant, and as a reminder, if you need to see it, the clinical and nonclinical information is provided on FDA slide 7.

We have one voting question. We'll ask you to answer, do the results of Trial NPC-002 in concert with the other data, clinical and nonclinical in particular, support a conclusion that arimoclomol is effective in the treatment of patients with NPC? Provide a rationale for your vote, and if you vote no, provide recommendations for additional data that may support a conclusion that arimoclomol is effective.

I'll now turn the meeting back over to the chair, Dr. Alexander, to proceed with the committee discussion.

Questions to the Committee and Discussion

DR. ALEXANDER: Thank you, Dr. Pilgrim-Grayson.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. We will now proceed with the questions to the committee and panel discussions. We'd like to remind the public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

I'm not going to read this, for Dr. Pilgrim-Grayson has already read it. But let me first ask the committee if there are any questions or concerns about the wording of the question before we get into discussion. Anything that people would like clarified about the wording of the question?

(No response.)

DR. ALEXANDER: No. Okay.

So if there are no further questions or comments concerning the wording, we will now open the question to discussion. Just raise your hand if you want to jump in and start off the

discussion; otherwise, we'll just go around in order.

(No response.)

DR. ALEXANDER: No? No one's going to volunteer? Let's start with Dr. Fischbeck then.

DR. FISCHBECK: I didn't raise my hand --

(Laughter.)

DR. ALEXANDER: I know you wanted to.

DR. FISCHBECK: -- but I have expressed concerns about both the clinical trial, particularly the statistical analysis plan, and the preclinical studies. The main problem as I saw it was that it was a post hoc analysis. The clinical study was post hoc, and I think the standard for drug approval, or for knowing whether a drug works, is to do a study where you set the plan for statistical analysis before the clinical study starts, not afterwards. Doing it afterwards is like, well, such and such team won the World Series, but if we change the rule after the fact, maybe only allow doubles and triples, or something like that, then we get a different result, the

result we want. Changing the rules after the fact is not good, I think, in terms of having clear evidence that the drug is working, not just in individual patients, but it's working across the board in the study population.

Then with the animal studies --

DR. ALEXANDER: Let's just focus on the clinical trial because that's question 2 --

DR. FISCHBECK: I'm sorry.

DR. ALEXANDER: -- where we're going to get into the corroborating evidence.

DR. FISCHBECK: Okay.

DR. ALEXANDER: So do you have any more comments about the trial itself? You expressed your concern around the fact that these analyses were done post hoc.

DR FISCHBECK: Yes, it's a post hoc analysis, as encouraged by the FDA, but the applicant might have been encouraged in a direction that -- they could have been encouraged in a better direction. Okay.

DR. ALEXANDER: We'll get to the other thing

in question 2.

I've we'll get the other thing in question too.

Do you want to jump in, Dr. Ellenberg?

DR. ELLENBERG: Yes. Susan Ellenberg. I'm not as concerned about post hoc analyses. I think we often do post hoc analyses to help understand the results that we are seeing. Sometimes results are a little bit surprising. We're trying to understand why it might have turned out in a particular way.

It seems to me these are not post hoc analyses that the company developed because they did some fishing expedition. They were recommended by the FDA, not ones that they came up with. And in particular, the post hoc analyses with the rescoring of the swallowing, that was based on something that nobody could have figured out what would happen because it was a separate group of independent investigators who did the rescoring without knowledge of data. So I'm not as concerned about those analyses. I think they were

exploratory and helpful.

I do think there's certainly a suggestion of a treatment effect, and you might even say a strong suggestion. One concern I have is the potential interaction with miglustat. I think it's hard to say from these data whether this drug has an effect on its own or maybe only has an effect when given in combination with miglustat, and that presents a dilemma because miglustat isn't approved by the FDA.

If we knew for sure that there was this interaction and it was only effective in combination, I don't see how the FDA could make an approval and say you have to use this with this other drug that we haven't approved, so it's a little awkward. But I do think there's a strong suggestion of efficacy here.

DR. ALEXANDER: Thank you. I think FDA wanted to respond about the analysis question.

DR. PILGRIM-GRAYSON: Yes. This is Dr. Pilgrim-Grayson. I would ask Dr. Wonyul Lee to comment.

DR. LEE: Wonyul Lee, statistical reviewer for this application. First, I'd like to remind that the prespecified analysis for the primary endpoint actually met statistical significance, so our recommended analyses are just to evaluate the robustness of the observed effect in the prespecified analysis.

Regarding the interaction between miglustat and arimoclomol, we did perform some interaction tests, quantitative interaction tests and qualitative interaction tests. The quantitative interaction tests indicated some difference in the magnitude; however, the qualitative interaction test failed to reject the null hypothesis of null qualitative interaction, so I just wanted to add that information for you.

DR. ELLENBERG: I would just say that certainly tests for interaction are much lower powered than tests for effects, and in this case everything is underpowered because the study is so small. So I would not expect to see a significant interaction, but you certainly see something that

you would think, maybe there is such an interaction, such a qualitative interaction, but I certainly wouldn't expect to see a significant finding for that.

DR. LEE: Thank you.

DR. ALEXANDER: Dr. Coon?

DR. COON: Cheryl Coon. I'd like to address part A of this question, which is about the COA and my comments on it. We should not let perfect get in the way of good enough, and I think in this case, this is good enough. We can certainly get information out of this instrument as it's administered. There's a lot of room for improvement with this instrument.

I continue to be concerned about the response categories and the kind of leaps between categories that become a 2-point change, where clinically it sounds like truly it may be a 2-point change, but there isn't actual psychometric evidence to support that. When I looked across the data sources, it seemed like there might be enough data to be able to run IRT if you collapse across a

number of data sources, so in the future, that could be a fun analysis to do.

When I was looking through the briefing materials, I really wanted to see the information at the domain level , and I wanted to see it categorically, just descriptively; and I think that across the course of this day, I have seen that in the individual patient plots, where you can see some improvement, lots of stability, and some worsening.

When I look across those -- now this is me writing numbers down based on plots that are on the screen for about 20 seconds, so I may not have gotten these right -- the swallow domain, there was 77 percent that improved or were stable on therapy versus 69 percent on placebo; ambulation was about the same, 69 and 68 percent; speech, 85 versus 80 percent; fine motor, 85 percent versus 67 percent. So you can see some separation in some of those domains.

I thought it was interesting that -- who knows what piece of paper these numbers are on;

they're somewhere in here -- the 5-domain scale, it was somewhere in the the briefing documents that responder analysis, I think it was 50 percent versus 37 percent. When they moved to the revised 4-domain, it moved to 65 percent versus 40 percent. That's a lot of numbers, but visually I'm seeing some separation there, which to part B of this question, it does indicate there's something happening. It happens to actually hit significance on that primary endpoint, which is maybe surprising because you do have some error in the scores themselves and you have a very small sample. So that actually gives me a little bit more indication that there is something happening in terms of the treatment effect.

I think the challenge, which is what Dr. Ellenberg just mentioned, the concomitant medication that's going on in this trial, that is definitely increasing those percentages for the placebo arm, so it's hard to know what would happen if they weren't on that. So we are sort of evaluating this in a context that maybe is not what

the application is for; so the question about the treatment effect of arimoclomol on its own, I don't know that we have that answer, but there's definitely something happening with that therapy in this patient sample. Thank you.

DR. ALEXANDER: Thanks.

There are a couple things that came up during the clarifying questions related to the baseline differences and the early dropouts, and how that might impact the interpretability of the study, so I just would ask Dr. Ellenberg or Dr. Kryscio to comment on that, or anyone else who wants to comment on that. I think a couple people raised questions about the differences, the difference in baseline scores and also the fact that there were more dropouts in the arimoclomol group.

DR. KRYSCIO: Yes. Of course the problem is both floor and ceiling effects and the question about what are the assumptions, and there's definitely a ceiling effect here, and there's also an imputation effect. I think I agree with

Dr. Ellenberg that there seems to be some evidence that this therapy is working, and I also agree with Dr. Coon that it must be working in conjunction with a drug that's not approved, which is miglustat.

There are baseline differences, but I think the biggest problem is the dropout. The dropout is larger in one group than the other, than in the placebo group. It seems to me that the comments of the families, what they value most is stability rather than anything else and, if possible, some improvement, and that seems to be what the data is pointing towards.

DR. ALEXANDER: Dr. Ellenberg?

DR. ELLENBERG: Just to follow up on that, I noticed that even if you discount the 12-month data on those who dropped out before 12 months, you still had seven on the treatment arm who showed some level of improvement, some more than 1 point, and didn't have any on the placebo arm. Now, with 2 to 1 randomization, I doubt that 7 versus 0 is statistically significant, but it's still, to me,

an indication that something is going on.

DR. ALEXANDER: I'd just remind people to state their name before they start talking.

DR. KRYSCIO: Dick Kryscio again. Sorry.

DR. ALEXANDER: Yes, go ahead.

DR. KRYSCIO: One other in that is when we look at the baseline differences, one big difference is that three of the patients in the active arm had the worse disease and none of the patients in the placebo arm did, so that stacks the deck against the active arm. So we can debate about baseline differences, but I think it goes both ways.

DR. ALEXANDER: Thanks.

Dr. Mink?

DR. MINK: I actually have a slightly different view. This gets to the rating scale itself with the 2-point difference for some. Again, in a small trial, it depends on who's being enrolled and what their score is in enrollment because there are categories that are one degree different in terms of descriptor -- mild, moderate,

severe -- but the difference between mild and moderate is 2 points. So again, if you have a lot enrolled at a 2 and some get worse, they can't get worse by 1 point; they have to get worse by 2 points.

In addition, with the ceiling effect, if you have a cohort that is more severe, it seems to me that there's less likelihood for them to worsen to the same degree as those who have milder disease at the time of enrollment because, again, there's more likelihood of them going one category worse than if they're more severe. Similarly, there are some that are very near the ceiling with a score on the 4-domain scale of a 19 or even a 20, and I think that it's impossible, really, to determine whether there's any impact of the therapy on those individuals or not because they're going to show stability, but they're going to show stability at a highly disabled state.

So my concern is that the scale is one where in a small study like this, there is enough potential for an ascertainment bias affecting the

results that in a large study is probably going to wash out because these are all rank order for sure. But again, that discrepancy of a 2-point jump for one category descriptor is something I'm still concerned about. It's something that could be looked at, but we haven't seen any data about whether score at entry predicts how they're going to do, and I've tried to look for data about how the ratings field correlates even with age or disease duration, and I haven't been able to find anything like that.

DR. ALEXANDER: Robert Alexander. We heard from Dr. Ellenberg that she thought there was evidence of a drug effect. What's your view on that, Dr. Mink?

DR. MINK: My view is there's certainly some evidence for an effect, but I'm less convinced. I don't think it's particularly strong evidence. It's some evidence for sure, and statistically it does meet the criteria for statistical significance, but I think I have enough concerns that that result is influenced by the nature of the

rating scale and not necessarily by the interaction between the treatment and the disease alone.

DR. ALEXANDER: Thanks.

Dr. Kishnani, I'll let you jump in here.

DR. KISHNANI: Sure. In response to section A of the question, I think the 4-domain Niemann-Pick Type C Severity Scale has been carefully looked at, especially for the swallow component, and caution and care in getting experts, including speech pathologists, in, so I think for me that is very reasonable.

The biggest concern I have is what I think has also been shared earlier, is what does this treatment do as a stand-alone because it appears that it's an additive effect over and on top of miglustat, but what it does by itself is really not clear. The second concern is the ones who have the null mutations, it's a small number, but what we've seen from preclinical, as well as from clinical -- and I know we're not speaking preclinical here -- it's not completely convincing. So do we need more information so that we can learn

more about where the impact is most?

Those are really my concerns here, and I also agree about the ceiling effect and about the ascertainment bias that was just discussed. Thank you.

DR. ALEXANDER: Thanks.

DR. FISCHBECK: One other comment. I appreciate what Dr. Coon had to say, and in particular the comments and testimonials from the patients and family members were really striking. One thing I was going to mention, though, is ALS. Arimoclomol has been through phase 2 studies, which were indicative of some response to arimoclomol, and then just recently, just last month, there was published, a very well-done phase 3 study that showed no effect at all.

I think the same thing could happen here, that the good might get in the way of the best, or somewhat good might get in the way of what really works for this disease. Looking at this from a perspective across the board, other hereditary diseases, I think you've got a clear target for

further therapeutics development here. Anybody who's motivated to go after this pathway and to come up with a better drug that engages that pathway and has a a clear benefit and approval, at this point might get in the way.

DR. ALEXANDER: Dr. Berry, do you want to make a comment? And say your name when you start.

DR. BERRY: As a physician who has cared for many patients with this type of storage disease, we really want this treatment to work, but with regard to question 1 and in response to it, I think we danced around today talking about the ceiling and other things, but the truth of the matter is the response is not really overwhelming, and I don't know how we deal with that.

DR. ALEXANDER: Ms. Berggren, did you want to jump in?

MS. BERGGREN: Kiera Berggren. I would echo that as well. I have concerns around the scale itself. The swallow part in particular, I'm glad that it got revised. I think it's a cleaner tool. I think there are probably some questions around

standardization of administration questions and all of that. We know from other scales that anchors tend to be pretty easily identified, but the middle stuff can be really squishy, so I have some concerns around the 1-point minimally clinically important difference as you were speaking about.

I also would like to bring up the speech scale in particular because I think that scale mixes up speech, which is a motor speech movement, and communication, which is what I'm doing with my hands, my body posture, and things like that, and you can't have both of those in the same scale. I think it needs to be a clean dysarthria measure only, and if communication is an area of concern, then that should be a different scale.

DR. ALEXANDER: So it sounds like you still have some concerns about the --

MS. BERGGREN: Yes.

DR. ALEXANDER: -- primary endpoint.

Dr. Le Pichon?

DR. LE PICHON: Thank you. J.B. Le Pichon. I'm a child neurologist in Kansas City. So I'm

another one of those who see these patients, and I just have a few thoughts. The first one is, this study met the clinical endpoint and it was significant. This was both in the analysis of the FDA and of the company. The significance was an improvement in one point on average. It varied between 0.6 and 1.5 on the 5-domain Niemann-Pick Clinical Severity Rating Scale. On the 4-domain, the revision scale was, as I understand it, asked by the FDA, so it's hard to fault the company for having done that work.

A 1-point improvement in that clinical scale corresponds to approximately 6 months to a year of clinical worsening. That's significant, at least to me it is. If I look at my patient, and I am giving that patient 6 months to a year of continuing to function at the level they're at now, that is a big difference. It's a big impact in their life.

So the question is, is there enough data here for me, on question A, to trust that the 5-domain Niemann-Pick Disease Type C Clinical

Severity Scale and the revised 4-domain scale, do I have concerns about them? I mean, I think they're not perfect, but as we've heard from other people, they were devised from experts in our field. And the 5-domain has been around, if I remember correctly, for at least 17 years and has had multiple publications; so yes, I trust it. I acknowledge it's not perfect, but I trust it.

My assessment of the trial, at least as I hear it, is, yes, it's not perfect, but it shows an effect, and that effect is significant. And I think allowing the drug to move forward does not mean that we stop watching it. And it may be the only way for a disease that rare, to continue assessing its effect, is to allow it to progress, to move forward, and to move into a phase 4. Thank you.

DR. ALEXANDER: Thank you.

Did FDA want to comment?

DR. PILGRIM-GRAYSON: Hi. This is Dr. Catherine Pilgrim-Grayson. I really appreciate the discussion that we've been having and hearing

everyone's viewpoints. When people are answering the second part of the question, part B, about whether the trial results demonstrate a treatment effect of arimoclomol, I just want to remind you that we're looking at arimoclomol added on to background standard of care. So as you heard, 80 percent of people were taking miglustat, so focusing with that context in mind. Thank you.

DR. ALEXANDER: Thanks.

Yes, Dr. Chung?

DR. CHUNG: Hi. Wendy Chung. So the bottom line is my clinical intuition, seeing the data and hearing from the families, that there probably is a clinical effect with the standard of care that they have. This is rare diseases and it's messy. I am not happy how messy it is with the heterogeneity that we have across different mutations, different disease courses, but I do think it's an opportunity for us to do better in terms of our outcome measures because these are very blunt tools that we're seeing here, and I think that's what's leading to problems with the messiness.

I guess what convinces me is the consistency with the data going across. Unfortunately, I'm disappointed that we don't see anything with cognition and that it's noisy, and I don't think that's really acceptable because we should be able to do better with that. With the 5-domain scale, it looks like it's noisier than with the 4-domain scale, and again, in theory, we should have been able to see this with the 5-domain scale as a prespecified outcome measure.

But I guess what gives me greater confidence in this is the open-label extension, the natural history comparison, the expanded access, and with everything going in the same dimension, or in the same direction rather, with consistency within that I guess is what gives me the gut clinical intuition that there probably is something here. It is stabilization; it's not a cure in terms of this, but it does look like what I would consider clinically meaningful.

DR. ALEXANDER: Thanks.

Dr. Lieberman?

DR. LIEBERMAN: Yes. I just want to echo what Dr. Chung just said.

DR. ALEXANDER: Say your name.

DR. LIEBERMAN: Oh. Andy Lieberman. Sorry. I'm just going to echo what we just heard. I think that the clinical tool that is available and that was used in this study is really the best one available and is being used internationally in multiple trials for this disease. So it is not perfect, and I think the community needs to to think about how best to improve it going forward.

For me, the open-label extension data --

DR. ALEXANDER: Yes, we'll get to that. Just confine yourself to the study at the moment.

DR. LIEBERMAN: Yes. Okay. Fair enough. The stabilization of the disease over an extended period is compelling for a small effect, I think, and it's reassuring to hear comments from the FDA that we should view it in the context of what is currently the accepted standard of care, which would be miglustat, because evaluating on its own is I think really challenging.

DR. ALEXANDER: Thank you.

Dr. Kryscio?

DR. KRYSCIO: It's Dick Kryscio again. I want to go back to this issue of the floor and ceiling. We started with a 17-point scale and reduced it to 5, and then to 4. Shouldn't we be thinking about moving it in the opposite direction? It will put a lot more variability in there and probably avoid the floor and the ceiling. I'm just wondering if Dr. Coon or Dr. Tucker want to make a comment about that.

DR. ALEXANDER: Go ahead.

DR. TUCKER: Yes. A, they could do a much better job. We've all decided this measure is not perfect; it could be better. In any neurodegenerative disease, these are probably the five categories, so the fact that these are meaningful in NPC, I don't think is necessarily a surprise. What does surprise me, knowing a little bit about the CDER program, is that they could look at scale and variance, they could look at where gaps are in there, and they have person data, that

they could be looking at the measurement properties of this instrument, and that really has been pushed aside because this instrument is used so widely and all of that.

I don't know if it's the pharma company's job to do that, but this measure really needs to be stronger and better defined because that's why you're seeing ceiling effects. And we have no idea in the middle of the scale how much improvement there is because domains are also shared if they're shifting with fine and gross motor being defined in the same. In terms of the efficacy, I think Dr. Chung said it really well. I think there's enough, along with the standard of care, to believe that there is at least stability or some improvement in that piece.

DR. ALEXANDER: Yes. This is Robert Alexander. Just to respond to Dr. Kryscio's comment, we do have the results of the full 17-item in the briefing documents, so at 6 months, the difference was minus 1.69 has a p-value of 0.15, and at 12 months, minus 1.61 was a p-value of 0.21.

So the 5 and the 4 had a p-value, I guess, if you want to put it that way.

DR. KRYSCIO: This is Dick Kryscio again. I guess my memory is getting bad. But at least someone discussed the fact that maybe the swallowing instrument had to be split, or there was someone who said this earlier, that one of the scales should be split.

DR. ALEXANDER: Yes.

DR. KRYSCIO: So it's not just the 17 items. I'm talking about putting more noise in the system.

DR. ALEXANDER: I see. Okay.

Let's make sure we hear from everybody. Ms. Chamberlin, you want to comment?

MS. CHAMBERLIN: Sarah Chamberlin. I share the concerns that Dr. Fischbeck started out with in terms of the post hoc analysis, but I think if we look at part A, again, that analysis was requested and recommended by the FDA, and with the rescoring done independent of study data, it gives me more confidence in it.

I think also to Dr. Berry's point that

there's not an overwhelming evidence of treatment effect, we're not asked for overwhelming, we're asked for evidence of treatment effect, and I think we have seen that. Particularly to Dr. Coon's point, with the consistent separation between the cohorts when we pull the measures apart, it is not just the overall score that shows us that.

I think to everyone's point, we've said this is not a cure; this is good but not perfect. As these patients progress without treatment, we're going to get closer to the ceiling effect for this very small population, and it is going to be harder to determine whether we see treatment effect in future drugs because we have such a small population who, if they do not have something that inhibits progression of the disorder, are going to be more severe, and it's going to be more difficult to assess future treatments.

DR. ALEXANDER: Thanks.

Ms. Heinze?

MS. HEINZE: I'd just like to say that I think we heard from our community today and from

their testimonies that, to them, it is important to stabilize their patient, to stabilize their family member, and to give them hope. So that 1-point difference, to them, is a bonus on top of what they're really looking for, is a treatment to keep their family members from getting worse than what they are. So when we see that 1-point difference, to them that's like a celebration.

DR. ALEXANDER: Dr. Kraft?

DR. KRAFT: I'm thinking about this in terms of the framework of approval and through the pathway for a rare disease, which is a strong unequivocal clinical trial with weaker confirmatory evidence or an equivocal clinical trial and stronger confirmatory evidence. We will get to confirmatory evidence next, I understand, but my feeling is this is an equivocal clinical trial, well conducted, that shows, I think, effect, but a relatively small modest effect that is judged by the community on its face to be clinically relevant, and we can address the other part in our next question.

DR. ALEXANDER: Robert Alexander again. I think Dr. Ellenberg mentioned the data where there was a greater percentage of improved subjects in the arimoclomol group relative to placebo, so I just wondered what other people thought about that when interpreting the study, whether they felt that --

DR. ELLENBERG: I would also say that I've seen other studies in in rare diseases with small populations, and typically what they're doing is trying to show that they're slowing the decline, but you don't always see that some people are actually improving, and that's one of the things that impressed me here.

DR. ALEXANDER: You were impressed by that. You were struck by that, yes. You were impressed by that.

DR. ELLENBERG: By that there was actually some people who improved. It wasn't just slowing the decline.

DR. ALEXANDER: Dr. Le Pichon?

DR. LE PICHON: Thank you. J.B. Le Pichon,

a child neurologist in Kansas City. Just to follow up on that, I think that's a really good point regarding looking at each of the data points that was looked at individually. You quoted some of those numbers earlier with p-values that were in the 0.15, 0.3, but at that point, you start asking what is the meaning of a 0.05 value? Is that really relevant or are we looking for a trend? Are we looking for a trend that is indicating that the drug is effective? And in a small population, I would argue that a trend is enough to make a convincing argument that the drug is effective, and we don't need to go after this somewhat arbitrary 0.05 p-value for every single one of the measures that we're looking at.

DR. ALEXANDER: Thanks.

Yes, Dr. Coon?

DR. COON: Cheryl Coon. I have a lot of numbers that I stated earlier, and I did write down the improvement numbers as well. For swallowing, it was 6 individuals; speech was 6 individuals; fine motor was 2; and then overall, the 4-domain

score was 10. That's a lot of people in a small trial for a rare disease. Those are impressive numbers when we're talking about stability being meaningful and there are actually people who saw improvement. I would like to, remember what I was trying to say there. I can't remember, so I will go quiet now. Thank you.

DR. ALEXANDER: Thanks.

I was going to ask, is there anyone who believes that the study did not show a treatment effect, if they want to comment?

Go ahead, Dr. Fischbeck.

DR. FISCHBECK: I'm coming out as the minority here. It's a different disease but a similar kind of situation. With ALS, the last time I served on one of these committees, with adcom for Relyvrio -- there were two adcom meetings, actually. The first voted against and the second voted in favor of approval. If anything, there were more striking patient testimonials for that drug than we've heard today. It's hard to imagine, but there were a lot of positive anecdotal reports

of benefit both from the patients and from the clinicians who are taking care of the patients. The drug was approved, and the phase 3 study was published later that showed no benefit across the board.

So there still could be occasional patients, but there's so much variability in the disease, that I'm not sure that that is enough to warrant approval, but I'm in the minority. I particularly appreciated Wendy's comments, being on the front lines with these patients and what you'd like to see. I can understand that point of view.

DR. ALEXANDER: Dr. Le Pichon?

DR. LE PICHON: Very briefly, Dr. Fischbeck -- J.B. Le Pichon, child neurologist, Kansas City -- I appreciate your comment. The flip side of that would be a couple of drugs that were approved in my field just recently. I would remind people of omaveloxolone and trofinetide. Omaveloxolone was approved for Friedrich's ataxia and trofinetide for Rett syndrome, and frankly, the benefits of either of these drugs was on the order

of what we're seeing here with side effect profiles that were not nearly as good.

So I don't mean to introduce anything else, but you brought it up in talking about ALS, so I wanted to just highlight that.

DR. FISCHBECK: No, I agree.

DR. ALEXANDER: Any further discussion on this question? Anyone else want to make any points? I think we've heard from everybody, right?

Dr. Glasscock, did you want to make a comment?

DR. GLASSCOCK: Well, I guess my only comment would be, having worked in the rare disease field for 25 years, I'm not sure I've seen a program with certainty. So if certainty is what we're looking for, I don't think we're going to find it in this committee for anything that comes before it. I'm just echoing some sentiments that Dr. Chung shared earlier, but that would be the only thing that I'd like to emphasize here.

DR. ALEXANDER: Okay. Well, let me just take a shot at summarizing our discussion. It

sounds like the general consensus was that the endpoint, either the 5 or the 4NPCCSS, is fit for purpose, though imperfect, and could be improved, but it probably is adequate to the task of measuring improvement. It seems like there was an overall consensus that the study shows a treatment effect, but there was some difference of opinion in terms of the magnitude and importance of the treatment effect.

I would just say I seconded that. I think we saw an inclusion of data from just a couple patients that really moved things around a little bit. Then there was, I think, a number of people that were impressed by the fact that people actually improved on the study, which is something that's not so usually seen. So yes, I think that would be the overall summary of the discussion.

Feel free to add to it, Dr. Ellenberg.

DR. ELLENBERG: I'm not sure there was much of a difference of opinion about the magnitude of the treatment effect. I didn't hear anybody say, and I certainly don't believe that it's a big

treatment effect.

DR. ALEXANDER: Right, yes.

DR. ELLENBERG: If there's a treatment effect, it's incremental, but I think there are differences of opinion about how reliable it is. It's a small study, and there's a lot of variability.

DR. ALEXANDER: No, that's a great comment. I think most people said the treatment effect is small; the question is, was it really small or just small?

Does FDA want to make a comment?

(No audible response.)

DR. ALEXANDER: No? You guys are good? Okay.

Now, I think we'll move on to question 2 then. I'll read this one. Discuss your assessment of other data -- now we can talk about the other data --

(Laughter.)

DR. ALEXANDER: -- specifically additional clinical and nonclinical data, with respect to

support for the effectiveness of arimoclomol.

So let me just ask, are there any concerns about the wording of this question or anyone seeking clarification about the wording?

(No response.)

DR. ALEXANDER: No? Okay. We're good.

So just to make it a little more orderly, let's focus first on the additional clinical data, and then we can have a discussion around how supportive or non-supportive the nonclinical data is. Who would like to start?

I think I'm going to have to go to Dr. Fischbeck again.

DR. FISCHBECK: Because I have a particular role here. The clinical data, I think the main problem was the post hoc analysis. In the nonclinical data, we mentioned how it could have been done better, not putting the drug in the drinking water or if you're going to put it in the drinking water, have some way of measuring how much the mice were taking down with swallowing difficulties, if they had any. I've forgotten the

other one.

DR. ALEXANDER: For the clinical data, there were several lines of evidence, if you want to say that. There was change from Study 001, which was the observational study, to Study 002 in the arimoclomol group. There was the additional open-label extension data that they had and comparing the people that started on placebo versus the ones that had been on it in double-blind phase, and then comparing that data to the NIH natural history data.

What's your general sense of how much that data added or didn't add?

DR. FISCHBECK: I was just going to add, for the nonclinical data --

DR. ALEXANDER: Well, let's just focus on the clinical data first.

DR. FISCHBECK: Alright. Okay.

DR. ALEXANDER: How about Dr. Chung? Do you want to say --

DR. CHUNG: This is what I was alluding to before, and I guess I spoke out of turn when I put

that one I said before. But it's just consistent. It's all approximately the same. It was reassuring to me that we weren't seeing anything wildly different, and it was reassuring to me to see people on drug for longer periods of time and no new safety concerns. So for me, it was at least consistent internally.

DR. ALEXANDER: Dr. Mink?

DR. MINK: I certainly agree with the comment about safety concerns. Again, the effects are small, and looking at what was FDA slide 77, which was looking at the open-label extension, one way to look at this is at 2 to 3 years, if you actually start out with placebo and then cross to active drug, you do better than if you start with active drug and stay on active drug. So I think it just points out that the effects are small and there's a fair amount of variability that -- I think it's all consistent, but it's consistent with a small effect.

DR. ALEXANDER: Dr. Kraft? Say your name.

DR. KRAFT: Walter Kraft. What has been

striking is the safety profile, and a very safe drug is not an unalloyed good. We have a small molecule that is prepared to work through transcription factors that affect hundreds of genes. Small molecules are typically not well behaved, a lot of off targets. So the fact that we don't have side effects actually can be a little bit worrisome because we're wondering if it does good things, and it probably should be doing some bad things also. So that, in fact, has me a little bit worried in terms of the side effect profile that's remarkably stable.

DR. ALEXANDER: But maybe you could comment on how much weight you would put on this other data from outside the study, the transition from Study 001 to Study 002, or just the overall profile, the open-label or the comparison to NIH data.

DR. KRAFT: I think in terms of adverse effect reporting, I think we're pretty good at large dramatic effects, Hy's law --

DR. ALEXANDER: No, I actually meant in

terms of efficacy. Does this data contribute to your conclusion about the drug's efficacy?

DR. KRAFT: I would echo Dr. Chung's feeling. The general vector seems to be congruent with both effect size and the vector in terms of the clinical trial, so I would say yes.

DR. ALEXANDER: Dr. Berry, do you want to make a comment, an opinion about whether --

DR. BERRY: No. It's the data [indiscernible - 7:45:38] what I'm hearing here.

DR. ALEXANDER: -- this additional clinical data adds anything to your deliberation?

DR. BERRY: No.

DR. ALEXANDER: No? Okay.

How about Dr. Ellenberg? When you look at this additional clinical data, does that help you in terms of making --

DR. ELLENBERG: I don't think it helps me very much, but it doesn't detract from the sense that I got from the clinical trial. So looking at those to see whether there's anything there, that kind of undermines the conclusions from the

clinical trial, and then I didn't see anything.

DR. ALEXANDER: So you felt it was consistent with the clinical trial results?

DR. ELLENBERG: About as consistent as one could expect in this kind of a very small trial, very small patient population, I should say.

I guess I should have asked this before, but the company said there are 668 people who have been treated with this, who have had exposure to it, and I just wondered where they all came from because they weren't in the study.

DR. ALEXANDER: Well, I think some of them were in the compassionate use.

DR. ELLENBERG: Expanded access?

DR. ALEXANDER: Expanded access.

DR. ELLENBERG: So it was that many in expanded access, or are some of these phase 1 and normal volunteers?

DR. ALEXANDER: I don't know.

DR. GLASSCOCK: I think there were other diseases in there.

DR. ALEXANDER: Right. Yes, they had a

program in ALS also.

Dr. Kryscio, do you want to comment on the additional value of the additional clinical data?

DR. KRYSCIO: Well, basically for clinical data, we had the pretrial data and what was happening with the participants compared to what happened when they were actually on the drug during the trial, and then of course the open-label extension part. I just felt they didn't do much harm to the result that they obtained in the primary trial.

I thought it was kind of interesting that, basically, when they crossed the participants in the trial, the placebo participants, over to the active treatment and the open-label extension, they caught up with the people who are already on drug, and that to me was a positive.

DR. ALEXANDER: Yes. This additional data, that sort of increased your --

DR. KRYSCIO: I just said that when they intervened in this disease, it causes some stability. The decline --

DR. ALEXANDER: It sounds like you think this actually made you believe more in the effectiveness of the drug.

DR. KRYSCIO: Yes.

DR. ALEXANDER: Dr. Lieberman, do you want to comment?

DR. LIEBERMAN: Yes, I actually found the open-label extension and EAP data consistent with or supportive of the trial. I guess the comments that Dr. Berry-Kravis made in the discussion on Zoom about using the EAP data -- and I'm not the statistician to do this -- in finding comparators in NIH or other data sets, seems like a compelling way that could have been brought out, but I guess could be mined a bit more. But I think it's all consistent with a small effect in stabilization.

DR. ALEXANDER: Okay.

Dr. Kishnani?

DR. KISHNANI: I feel like the directionality was all in the same as in the clinical trial, and that was reassuring for me. What I've really appreciated is the long-term

safety; so for me that's a positive because at least it's not causing harm, and there was at least stabilization in the same direction.

DR. ALEXANDER: Thanks.

Does anyone want to comment specifically on the comparison to the NIH natural history data?

Dr. Le Pichon?

DR. LE PICHON: Yes. Just a couple of words I think are worth remembering, I don't think that was a fair comparison. I don't think it's a comparison that should have happened. The NIH natural history included patients who are in the cyclodextrin trial. It included patients who are actually on the drug at hand, and the patients were not comparable, as we've seen, in terms of age and in terms of advancement of the disease. So I don't find that part of the data to be compelling at all, and the overall scheme of the data that's being presented today doesn't bother me too much.

DR. ALEXANDER: Thank you.

DR. GLASSCOCK: Brad Glasscock. Just to reply to that last comment, I think they did do

some matching in that natural history comparison, so I'm not sure if that matching accounted for potential other investigational therapies. My understanding is that they did have some criteria to match upon and that they didn't just take everybody in the natural history data set, but only those that matched demographics and baseline characteristics of the investigational arm.

Maybe somebody from the sponsor could confirm.

DR. ALEXANDER: Okay. Any further comment on the additional clinical data?

(No response.)

DR. ALEXANDER: In that case, let's move to the nonclinical data. What were people's thoughts about how much that added to the assessment of the efficacy of the drug?

Dr. Lieberman?

DR. LIEBERMAN: Yes. Andy Lieberman. I think that there were a number of concerns in the mouse studies that made them not compelling, blinding, randomization, things that we are all

expected to do, PK analysis. The effects on survival from the drug alone were really small, less than 2 weeks universally, and not dose dependent. I think the compelling piece of data was the combined arimoclomol plus miglustat effect on survival, which is the piece of data that stood out for me; then maybe if that's what would happen with patients going forward, then I could sleep a little bit better than just trying to evaluate this drug on its own.

DR. ALEXANDER: So your general take on the value, or how much the clinical data adds to the --

DR. LIEBERMAN: Yes. I don't think it rose to the level of compelling confirmatory evidence for me because of all those issues, and similarly, the in vitro data, using a high concentration and 3 weeks to see an effect on filipin was concerning.

DR. ALEXANDER: Yes. I have to say I agree with you. There were a lot of issues in terms of the absence of actual PK measurements in the animal studies, I think was pointed out, and noted that in

the ALS program with the same drug, they also had a lot of preclinical data that provided the rationale for doing those studies. So I think the translatability of some of these in vitro and transgenic mice is a little bit uncertain.

Dr. Fischbeck?

DR. FISCHBECK: Just to reiterate what I said earlier, I think to put it positively, the preclinical, or nonclinical data, the mouse studies would be more compelling if they started the treatment after the disease manifestations, as we see in the patients.

DR. ALEXANDER: Dr. Kraft?

DR. KRAFT: Walter Kraft. I think the focus should be really on improving the preclinical package. For one thing, I think doing these trials is quite difficult, a small patient population, and I think we all acknowledge that. Secondly, in the contemporary era, without having a mechanism of action, it's difficult not only for that in itself to be the strong supplemental information to support a single trial, but it's also a mechanism

by which you could optimize your treatment.

So we would ideally understand the mechanism that could get us a therapeutic range that could optimize dosing, that could link to biomarkers that are both in the predictive as well as the causal pathways, all of which is a little bit weak at this point. So if there's money to be spent in the future, I think it would be in this domain.

DR. ALEXANDER: Thanks.

Just to remind people again to speak into the mic and say your name. I think there are a lot of people listening outside this room, and they're apparently having a little trouble hearing.

Dr. Chung?

DR. CHUNG: Wendy Chung. I want to just agree with a couple points that were just made. Without the mechanism of action, the in vitro studies were not helpful to me in terms of the cell-based studies. But I did want to bring up one of Dr. Fischbeck's points that really struck me in listening to the families' report, which is although for the individuals treated here, they

were symptomatic at the time, so the mouse really was not a comparator. In hearing their stories, it appeared to me with younger siblings and other things, there are individuals presymptomatic who now are starting treatment.

So it was interesting through that lens to see the data on the mice in terms of what might be going on in the future, but I agree with your original comment as well.

DR. ALEXANDER: Any further comments about the value of the preclinical data?

Dr. Mink, did you want to comment?

DR. MINK: I will comment it didn't really add much for me. Again, for all the reasons that have been stated, it didn't really add any strength to the argument for me.

DR. ALEXANDER: Go ahead, Dr. Le Pichon.

DR. LE PICHON: Dr. Le Pichon. Yes, I would agree with what's been said. The nonclinical data, the FDA did a really compelling job at showing that is, frankly, weak. The cell culture, it's hard to know whether the results that we're seeing in the

cell culture is a result of a stress response or if it's a true response. And in the mouse model, because of the limitations of the way the drug was given, you can try to make an argument, well, it was in the water, they probably got less of the drug. So it's probably doing something, but it's hard to be compelling, and it's hard to understand how dose -- well, I'll leave it at that.

DR. ALEXANDER: Do you want to comment further? No?

Does anyone have any additional comments about the value of the preclinical data?

(No response.)

DR. ALEXANDER: Okay.

So if I could sum up our discussion for question 2, it seems like there's a general consensus that the additional clinical data was consistent with the trial data. It was hard for me to say how much weight people were attaching to that, though. I didn't hear any real support that the preclinical data as performed really added to the confirmatory evidence of the drug's efficacy.

Does anyone want to expand on that summary or you're OK with that?

(No response.)

DR. ALEXANDER: Okay.

We'll now take a quick 10-minute break, and the same reminder to panel members that there should be no chatting or discussion of the meeting topics with other panel members during the break, and we'll reconvene at 4:40 p.m.

(Whereupon, at 4:29 p.m., a recess was taken, and meeting resumed at 4:39 p.m.)

DR. ALEXANDER: I think Dr. Pilgrim-Grayson would like to make a comment.

DR. PILGRIM-GRAYSON: Thank you very much. Catherine Pilgrim-Grayson at the FDA. So again, I wanted to thank you so much for all of the discussion that we've been having. It's really helpful to hear. I think when you move on to the voting question, thinking about what we've heard about the confirmatory evidence, when you've talked about the clinical evidence, we've heard you say that it tracks with the data, an adequate and

well-controlled trial, and with the nonclinical data, maybe it's not so strong. But I just want to make sure that you understand that we need the data taken together to be supportive of effectiveness. So just think about that when you are thinking about your vote, and I appreciate that. Thank you.

DR. ALEXANDER: Thanks.

We will now proceed to question 3, which is a voting question. We'll be using an electronic voting system for this meeting. Once we begin to vote, the button will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the voting is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO 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 continue in the same manner until all questions have been answered or discussed.

Question 3, do the results of Trial NPC-002, in concert with the other data, clinical and nonclinical in particular, support a conclusion that arimoclomol is effective in the treatment of patients with NPC? Provide a rationale for your vote. If you voted no, provide recommendations for any additional data that may support a conclusion that arimoclomol is effective.

Any questions about the wording of question 3 or anyone requesting any clarifications?

Dr. Coon?

DR. COON: Hi. Cheryl Coon. There was a clarification earlier from Dr. Pilgrim-Grayson that the consideration is arimoclomol added on to standard of care. Is that something that could be added to this question or is that just implied?

DR. PILGRIM-GRAYSON: This is Catherine

Pilgrim-Grayson. Thanks for the question. We just want you to evaluate the data as it happened in the clinical trial, which means that people were taking arimoclomol on background standard of care, and for most of the patients, it did include miglustat. Thanks.

DR. ALEXANDER: So if there are no further questions or comments concerning the wording of the question, we will 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. After you've made your selection, the light may continue to flash. If you're unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed. Go ahead and vote.

(Voting.)

DR. CHOI: For the record, we have 11 yes, 5 noes, and zero abstentions.

DR. ALEXANDER: Okay. 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.

Let's start with Dr. Kishnani.

DR. KISHNANI: Priya Kishnani. I voted yes. The reason is a clinical unmet need; a very good safety profile; trends towards efficacy; ultra-rare disease with nothing else available right now. Stabilization in this rare disease space is also considered really a remarkable improvement, and those were my reasons.

DR. ALEXANDER: Thank you

Dr. Fischbeck.

DR. FISCHBECK: Yes. I voted no. I thought that the new data that was presented was problematic, both the nonclinical data and the clinical data, for reasons we've discussed. I think it could be done better. I think there's a real unmet need in this disease, and I think this drug, or one like it, could be effective, but I haven't seen the data yet to make it a convincing case.

DR. ALEXANDER: Mr. Berggren?

MS. BERGGREN: Kiera Berggren. I also voted no, similar reasons to Dr. Fischbeck. I think the nonclinical data was really the linchpin for me. The clinical data is interesting and looks compelling with small values, but I think the nonclinical data, not knowing the mechanism of action, not knowing how the mice were dosed, things like that, were big questions in my mind.

DR. ALEXANDER: Dr. Berry?

DR. BERRY: Yes. Jerry Berry. I voted yes because I think that taking all the data together, it made sense that this is having a beneficial effect. And especially when you put it together with the beneficial effect that the families talked about, I think this may be something very good for the patients with this disease.

DR. ALEXANDER: Okay. This is Robert Alexander, and I voted no. First, I just wanted to acknowledge the testimony from the patients and their families and caregivers in the open public session, but I had to really rely on the data that

was in the controlled trial, and I didn't feel that it really rose to the level of substantial evidence of efficacy on its own. I also didn't feel that the additional clinical data that was reviewed really added much in terms of the assessment of efficacy, and certainly the nonclinical data did not in my mind.

Dr. Chung?

DR. CHUNG: This is Wendy Chung. I voted yes, and that was based on the consistency and totality of the data, the clinical data both in the trial as well as the additional data in the mouse in vivo data, although I didn't weight the in vitro data in the decision.

DR. ALEXANDER: Dr. Mink?

DR. MINK: Jon Mink. I voted yes, but it was a very reluctant yes. I found the effect size to be small and the strength to be weak, but overall, the bulk of the data favored a slightly positive effect. I think the unmet need is very clear. I'm not sure that this meets that need, but, again, on balance, I voted yes.

DR. ALEXANDER: Dr. Le Pichon?

DR. LE PICHON: I voted yes.

DR. ALEXANDER: Say your name.

DR. LE PICHON: J.B. Le Pichon. I voted yes on the basis of the double-blind, randomized-controlled trial that I think was compelling. It was not an enormous effect, but it was an effect that is clinically significant. The supporting clinical data, it was just that, supporting.

The nonclinical data I didn't rely on at all. I think that the nonclinical data is not convincing. Maybe I didn't follow directives. If I was forced to vote no just because the nonclinical data was not convincing, then I went against the rules, but this is where my clinical intuition was, and I am a clinician at heart.

DR. ALEXANDER: Ms. Chamberlin?

MS. CHAMBERLIN: Sarah Chamberlin. I voted yes. I think that the data from the clinical trial was compelling, and I think we saw a treatment effect for sure. I think the additional data,

again, showed an indication of effect. I think we all agreed it wasn't overwhelming. I think particularly the safety profile was also important, along with the testimony of the families. Those were bonuses.

I think in rare disease we're often asked, or patients and their families are often asked, to take on a large burden of safety or treatment burden, and the fact that this does show efficacy without side effects that largely impacted life, I think was significant. But it was largely based on the clinical trial data and the trend in the additional data that caused me to vote yes.

DR. ALEXANDER: Ms. Heinze?

MS. HEINZE: Elizabeth Heinze. I voted yes. I believe that the clinical data that was presented is very promising, very encouraging, that there were not large safety issues. I did take the natural history into consideration. I think it would have weighed heavier on me, the situation with the mouse trials, if there were more safety issues, but that made me think that we don't have

the adverse side effects, so the stabilization and even the improvements are very encouraging for a community like ours.

DR. ALEXANDER: Dr. Kraft?

DR. KRAFT: This is Walter Kraft. I voted no. The rationale was I took the perspective of a regulatory standpoint that is created for rare diseases, took that and applied it to this particular case, and I felt that it did not meet the evidentiary standards for approval. The vote no is not a vote against this continued development. I do worry about approval of drugs for which there is not unequivocal evidence of efficacy that is not without harm, also in terms of diversion of resources and activity within this space.

DR. ALEXANDER: Dr. Lieberman?

DR. LIEBERMAN: Yes. Andy Lieberman. This was a particularly difficult decision for me, but I voted no. I thought the clinical data were supportive of an effect, quite modest, but there wasn't compelling confirmatory evidence,

particularly in the mouse model, and that was quite significant for me.

DR. ALEXANDER: Dr. Ellenberg?

DR. ELLENBERG: I voted yes. I interpreted substantial evidence of efficacy in the light of flexibility for regulatory decisions and rare diseases. I felt that the additional data, if not compelling, were consistent, and therefore supportive of the clinical trial. I thought that a few patients did seem to have a substantial improvement, which impressed me. I think a clinical change of 1, and some of them seemed to have 2 points in improvement, that seems good. Even if it's a small proportion of patients, it's worthwhile trying, so that's why I voted yes.

DR. ALEXANDER: Dr. Kryscio?

DR. KRYSCIO: Richard Kryscio. I voted yes. I thought the clinical trial was reasonable. I wouldn't call it compelling, but it was reasonable, and when compared to the other clinical data, the non-randomized portions, it was very consistent, so that kind of swayed me in that direction.

As far as the nonclinical data, well, none of the animal studies talked about swallowing, which was something that took up part of the day; and of course animals don't speak. I do admit that the rotarod and the ring experiments conducted did not necessarily support the approval, but I still felt that the hardest to get is the clinical data, and it's based on small sample sizes, and it seemed to be consistent.

DR. ALEXANDER: Dr. Coon?

DR. COON: Cheryl Coon. I voted yes. Looking at the domains individually, there are patients who are benefiting from arimoclomol added on to standard of care, and this is while being well tolerated and easy to administer. The confirmatory evidence does substantiate the trial results through various clinical data sources, but I do agree that the nonclinical data sources were inconclusive.

DR. ALEXANDER: Dr. Tucker?

DR. TUCKER: Yes. Carole Tucker. I also voted yes, and I think it was a hard decision. I

think the additional data wasn't necessarily compelling, but I think the consistency, the long-term safety, and really looking at this as added on to standard of care made a difference for me versus thinking about arimoclomol on its own.

DR. ALEXANDER: Okay. We have a request for those of us who voted no to provide some input on what additional data they would recommend. I can start. I think what would be helpful in this case is a confirmatory trial, another trial.

Dr. Fischbeck?

DR. FISCHBECK: Yes. For nonclinical, I think a better-done mouse study would be helpful, and another clinical study, larger if possible, importantly, with a prospective statistical analysis plan that's adhered to.

DR. ALEXANDER: Okay. Dr. Lieberman?

DR. LIEBERMAN: I think nonclinical data that addresses the concerns that I raised earlier about PK and blinding randomizations.

DR. ALEXANDER: It's a little hard to hear.

DR. LIEBERMAN: I'm sorry. Addressing the

concerns about the animal studies would be quite helpful to show efficacy.

DR. ALEXANDER: So some additional nonclinical studies.

DR. LIEBERMAN: Yes.

DR. ALEXANDER: Dr. Kraft?

DR. KRAFT: This is Dr. Kraft. I would say probably less a focus on another clinical trial -- I think it's just difficult to do given the size and the nature of the disease -- but more on the preclinical space, particularly around mechanism of action, as it's linked to biomarkers, and an effect size, an exposure-response size that will assist. That's easier said than done, and I understand that this is a very difficult lift.

DR. ALEXANDER: Ms. Berggren?

MS. BERGGREN: Kiera Berggren. I agree with my colleagues on the panel here that I think the nonclinical stuff could be bolstered a lot more. Rare disease space is really challenging to do research in, and there is not a perfect tool to assess any of the rare diseases that any of us work

with. So I think we're seeing some differences there, but I think it's the nonclinical part that really needs to be bolstered up, the mouse studies in particular.

DR. ALEXANDER: Thank you.

I ask Dr. Glasscock, as our industry representative, if you have any comments.

DR. GLASSCOCK: Yes. Just to the point on the regulatory standard and the totality of evidence, I would say that it's not usual in the rare disease space that we're looking at data from a gold standard trial design, randomized, placebo-controlled, double-blind study. I think the confirmatory evidence from the additional clinical work was compelling, and certainly is within, I think, what FDA has previously deemed substantial evidence of effectiveness for other ultra-rare, relentlessly progressive, neurodegenerative conditions primarily affecting children, in this case, with a median age death of 13. So I think you would be well within your previous precedent to grant approval for this

product.

DR. ALEXANDER: Thanks.

So before we adjourn, are there any last comments from the FDA?

DR. PILGRIM-GRAYSON: Thank you. This is Dr. Catherine Pilgrim-Grayson. So, good evening. I started with good morning, and now we're at good evening already; it's been a long day. I just want to thank all of you so much for the robust discussion and your insightful comments. It's been really helpful, and a special thanks to you, Dr. Alexander, for chairing. Again, I also want to thank the patients, and families, and caregivers, and clinicians who commented in the open public hearing. Thank you.

Adjournment

DR. ALEXANDER: Okay. So we will now adjourn the meeting. Thank you.

(Whereupon, at 4:59 p.m., the meeting was adjourned.)