



U.S. Food and Drug Administration

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE

Thursday, May 6, 2010

8 o'clock a.m.

The Inn and Conference Center
University of Maryland University College (UMUC)
Marriott Conference Centers
3501 University Blvd East
Adelphi, MD

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Diem-Kieu H. Ngo, Pharm.D., BCPS, , Designated Federal
Official

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Ying Lu, Ph.D.

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PERIPHERAL AND CENTRAL NERVOUS SYSTEM
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FDA PARTICIPANTS (Non-Voting)

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Russell Katz, M.D.
Norman Hershkowitz, M.D.
Philip Sheridan, M.D.

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P R O C / E E D I N G S

DR. NGO: Good morning everyone. I would like to first remind everyone to please silence your cell phones, BlackBerrys, and other devices if you have not already done so. I would like to also identify the FDA press contact for today, which is Mrs. Ayse Yeaton.

Thank you.

Call to Order and Introductions

DR. ANDERSON: Good morning. I am Britt Anderson and, as is usual, we will begin the meeting by going around the table and allowing everyone to introduce themselves and their sort of affiliation or purpose for being at the meeting, and maybe this time we will start on the left here with Dr. Katz, if you would begin, please.

DR. KATZ: Hi. Russ Katz, Director of the Division of Neurology Products, FDA.

DR. HERSHKOWITZ: Norm Hershkowitz, Medical Team Leader, FDA.

DR. SHERIDAN: Philip Sheridan, Clinical Reviewer, FDA.

DR. GORMAN: Rich Gorman, Clinical Associate Professor, University of Maryland.

DR. SNODGRASS: Wayne Snodgrass, Pediatrics, University of Texas Medical Branch.

DR. DURE: Leon Dure, pediatric neurologist, University of Alabama at Birmingham.

DR. MIZRAHI: Eli Mizrahi, Chair, Department of Neurology, Baylor College of Medicine, child neurologist.

DR. PEARL: Phillip Pearl, Division Chief, child neurology, Children's National Medical Center, George Washington University here in Washington area.

DR. KHATRI: Pooja Khatri, University of Cincinnati, neurologist.

DR. FRANK: Sam Frank. I am a neurologist at Boston University, and the Acting Consumer Rep.

DR. KHANNA: Prerna Mona Khanna, University of Illinois, College of Medicine, and former member of the Risk Communication Advisory Committee under the FDA.

MS. VEGA: Good morning. My name is Marielos Vega, and I am a research nurse at the Department of Family Medicine and New Jersey Medical School, and I am also a former member of the Risk Communication Advisory Committee for the FDA.

DR. GREEN: Mark Green. I am a Professor of Neurology and Director of Headache and Pain Medicine at Mount Sinai School of Medicine.

I am Britt Anderson. I am a neurologist. I am currently at the University of Waterloo in Ontario, Canada.

DR. NGO: Lieutenant Commander Diem-Kieu Ngo, the Designated Federal Official for this meeting.

MS. KANDELL: I am Ellen Kandell. I am an attorney and a recovering litigator, and the Patient Representative for epilepsy.

DR. LESAR: Timothy Lesar, Director of Clinical Pharmacy Services, Albany Medical Center in Albany, New York.

DR. GARDNER: Jacqueline Gardner, Professor of Pharmacy, University of Washington, Seattle.

DR. CRAWFORD: Stephanie Crawford, Associate Professor, College of Pharmacy, University of Illinois at Chicago.

DR. CHAPMAN: Kevin Chapman, pediatric neurologist, Barrow Neurological Institute in Phoenix.

DR. CLANCY: Robert Clancy, Professor of Neurology, Children's Hospital of Philadelphia.

DR. FELNER: Eric Felner, Associate Professor of Pediatrics, Pediatric Endocrinologist at Emory University, Atlanta.

DR. AOKI: Tom Aoki, Professor, Division of Endocrinology and Metabolism, University of California at Davis.

DR. van BELLE: Gerald van Belle, Professor of Biostatistics at University of Washington, Seattle.

DR. LU: Ying Lu, Professor of Biostatistics, Stanford University, and also Director of Cognitive Studies Program Center, Palo Alto VA Health Care System.

DR. COHEN: Jeffrey Cohen, Vice Chairman, Neurology, Dartmouth Medical School.

DR. TODD: Jason Todd, private practice neurologist from Cornelius, North Carolina.

DR. TWYMAN: Roy Twyman. I am with Johnson & Johnson. I am the Industry Rep.

DR. ANDERSON: Thank you, everyone. There are some things to read here.

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

meeting will be fair and an open forum for discussion of these issues and that individuals can express their opinions without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. 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 please take care that their conversations about the topic at hand only take place in the open forum of the meeting.

We are aware that members of the media may be anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until the meeting is concluded.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or at lunch.

Thank you.

Now we will have a reading of any conflict of interest.

Conflict of Interest Statement

DR. NGO: The Food and Drug Administration is

convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the Committee are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

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

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

her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this Committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting, expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves discussing supplemental New Drug Application 22-432, H.P. ACTHAR Gel, repository corticotropin injection, 80 USP units per mL by Questcor Pharmaceuticals, proposed for the treatment of infantile spasms. This is a particular matters meeting during which

specific matters related to H.P. ACTHAR Gel will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Eli Mizrahi for a research grant to his employer, awarded from the National Institutes of Health. The grant is to further develop the tetrodotoxin animal model of infantile spasms. Dr. Mizrahi has no involvement with this grant. The NIH funding for this study is between \$100,001 to \$300,000 total, and H.P. ACTHAR Gel is being provided by the sponsor.

The waiver allows this individual to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver document, which are posted on FDA's website at www.fda.gov/ohrms/dockets/default.htm. Copies of the waiver may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of this statement will also be available for review at the registration table during this

meeting and will be included as part of the official transcript.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

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

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

FDA encourages all other participants to advise the Committee of any financial relationships that they may

have with the firm at issue.

Thank you.

DR. ANDERSON: All right. Then, at this point, we will proceed with Dr. Katz's introductory remarks to why we are here today.

FDA Introductory Remarks

DR. KATZ: Thank you, Dr. Anderson, and good morning to everyone. I would like to welcome the Committee members, the members of the PCNS Committee, and, in particular, I would like to welcome our other invited guests. You have all heard them introduce themselves. We have quite a distinguished group here on the panel today, consisting of members of other FDA committees, academics, practitioners, academics across a wide range of relevant fields, so I appreciate very much your taking the time out to help us with this application.

In particular, let me welcome the members of the public who have signed up to make statements in the public session later this morning. We know it can be a difficult thing to come and speak about personal matters in front of a group like this in such a large public setting, so we very much appreciate the effort that you have made to come and

tell us your personal stories.

So, as you know, we are here to talk about supplement to NDA 22-432 for the use of H.P. Acthar Gel in the treatment of patients with infantile spasms. I think actually, this application presents us with two sort of unusual situations we don't typically find ourselves in.

The first is that we are actually considering a treatment or potentially approving an indication which actually has become the standard of care for the past 50 years or so in patients with infantile spasms. That is obviously a very unusual position for us to be in.

It is an interesting fact that I point it out really to I think make clear to remind ourselves that that fact alone really can't I don't believe inform our decision about whether or not we think the application ought to be approved.

We really have to decide whether or not--and we want to know what you think about--deciding whether or not the application stands on its own with the evidence, the safety and effectiveness of it as submitted to us by the sponsors. So, the fact that it has been standard of care I really think is something to sort of, for the most part, put

in the background as we deliberate on the application today.

The other unusual feature of the application is that none of the data submitted, whether it's the effectiveness trials or the safety data, were prospectively gathered or conducted under the auspices of the sponsor, which is, of course, in a typical case for an NDA, the sponsor performs the studies or designs, and conducts and has oversight of the studies.

All the data generated in the application that we will be considering today was generated by practitioners or academics, whether it's the controlled trials, or whether it is the safety data that we will talk about in depth.

As far as we know, none of those practitioners or academics ever contemplated the fact that their data would be used to support a new drug application.

So, I think the fact that these studies, these data, were generated in an atypical setting I think will raise questions about the reliability of the data, the interpretability of the data, and whether or not you think it supports an application. So these I think will be issues that we want you to discuss.

I just want to take a minute or so to talk about

what the standards for approval are, particularly the standards for determining whether or not a treatment is effective.

There are two paths forward from the point of view of the law as to how we might consider whether an application and a treatment is effective. In either path, we have to determine if we are going to approve an application, that there exists something called substantial evidence of effectiveness and, in the typical case, substantial evidence consists of adequate and well-controlled clinical investigations, plural, and that typically means at least two independent sources of evidence that the drug is effective.

But the law also defined substantial evidence as possibly arising from a single adequate and well-controlled trial and something called confirmatory evidence. This latter approach has been used even by us in a couple of cases, but it's not the typical way we proceed.

If we think about that, the latter standard, the one study plus confirmatory evidence, it's typically applied in situations that are serious or life threatening, and in which, for a variety of reasons, a second independent trial

can't be conducted.

So, what is confirmatory evidence? Well, it's really in the eye of the beholder, but some of the sort of typical types of confirmatory evidence that we have seen come from that single trial very often--in other words, a very low p-value, or multiple centers in a multi-center study standing alone by themselves as being statistically significant, or multiple subsets, different outcome measures all being positive, all moving in the same direction in that single study. But confirmatory evidence can be something else.

It may even be--for a variety of reasons, it may even come from smaller studies that, in themselves, actually don't achieve statistical significance, but for various reasons, might be considered to be confirmatory of the finding in that single well-controlled study.

Today, of course, one of the critical questions we will ask you is whether or not you think that the sponsor has submitted substantial evidence of effectiveness, and if you do, it will be very important for us to understand which of those two paths towards substantial evidence of effectiveness do you think has been met, and why, of course.

Very briefly, with regard to the question of effectiveness, the sponsor has submitted data from three controlled trials. This was done as you know if you have read the booklets, in conjunction with the Agency, we had discussions about how to move forward with this application. We decided that if they could obtain the primary data from several controlled trials, that would be useful. That would permit the sponsor, as well as our statisticians, to perform independent analyses of the data.

Again, these were all widely different in design, performed by academics. So in an attempt to sort of analyze the studies in a sort of consistent way, since one of the issues with regard to these studies is that they weren't detailed statistical plans prospectively laid out for analyzing them the way a typical drug company sponsor's NDA would have it.

So, in an attempt to analyze these studies in a consistent way, the sponsor looked at a comparison between drug and control, the proportion of responders on ACTH and control. The primary category of responder was overall responder, and they looked at this in all three studies, and overall responders were defined as patients who had complete

cessation of spasms for some period of time, as well as having resolution of the typical hypsarrhythmic pattern on EEG.

So, the primary evidence of effectiveness was performed by Dr. Baram in a study of 29 patients randomized to Acthar Gel 75 U/m² given twice a day or prednisone 2 mg/kg per day, each for two weeks, followed by two-week titration. The parents and treating physicians were aware of the treatment assignment, but the primary outcome measure, which was video-EEG, was performed at two weeks and was read by a blinded reader.

In this study, they were highly significant between treatment, the differences on the overall responder rate, as well on the proportion of patients who were spasm-free and the proportion of patients whose EEG resolved.

The second study, referred to as Study 04 in the application, was first published by Hrachovy, et al., and that compared Acthar Gel 150 U/m² given once a day to Acthar Gel 20 units/day, so it's sort of a high dose/low dose comparison.

It was a very complicated study. The patients on high dose got treatment for three weeks, followed by a nine-

week titration off drug. The low-dose patients got treated for two weeks, followed by a two-week titration. The primary outcome measure, video -EEG, again was assessed after 12 weeks in the high dose and after two weeks in the low dose, a very complicated study and then, if patients didn't respond, there were various other complicated treatment algorithms to follow.

There were no statistically significant differences between treatments here although one subset under certain analyses was nominally statistically significantly positive.

The third study was also published by Hrachovy, and this was a study of Acthar Gel 20 U/day versus prednisone 2 mg/kg/day for two weeks and, if patients didn't respond to that, they got an additional four weeks of the original treatment. If they didn't respond to that, they were crossed over to the other treatments, very complicated.

So, the latter two studies were, as I say, complicated in design, very difficult to understand how to interpret them in a valid way. In any event, they both failed to achieve statistical significance on the primary outcome of overall responders.

The sponsor argues, nonetheless, that these studies are supportive of effectiveness, largely because the response rates in the treatment groups in those studies were considered to be much greater than would have been expected based on based on published rates of spontaneous improvement in these patients.

Some of those rates came from the placebo group of a previous controlled trial with another agent, others with sort of an observational data approach. So, of course, comparisons to historical controls are fraught with trouble, and so we are eager to learn whether or not you think that these comparisons of the published historical response rates or published placebo response rates are particularly compelling.

Another issue that we think is very important for you to address is the questions of the persistence of any effect. The general practice is to treat with ACTH for a brief period of time, and then the presumption is that patients' spasms are controlled for some significant duration after the fact, that relapsed patients can be treated again with a very short treatment course.

The studies that were presented in the application

attempted to obtain some follow-up data, but there was no, in our view, systematic attempt under rigorously controlled conditions to see what the long-term potential persistent effects were.

So, we need to know whether or not you think that the sponsor has presented adequate evidence to support, first of all, the dosing regimen that they have proposed--in other words, the specific amount of drug, as well the specific duration of two weeks--and whether or not you think that the sponsor has presented any reliable data that that regimen actually does protect patients out in time for some reasonable duration.

There is also a view expressed in the literature, and the sponsor tries to make the case, that control of spasms is, in fact, associated with a better outcome in other ways in terms of neurodevelopmental outcomes and in terms of the onset of other different seizure types.

As I said, none of the studies that were submitted were designed to obtain systematic prospective assessment of these developmental or other seizure type outcomes, and we are very interested to know whether or not you believe any of the data presented do support the claim that control of

spasms and control of EEG, resolution of the EEG picture, actually does predict an improvement in outcome of these other measures.

Turning to the question of safety, again, the safety data that are presented were obtained under basically normal practice conditions of various physicians, and the sponsor has gone back and obtained the records that were kept, and they were contemporaneously recorded records of patients treated at various centers by various physicians.

I think there is about a total of close to 320 patients, safety data for about 320 patients, presented, 122 of whom received a dose that they are proposing to recommend, an additional 37 received the same daily dose, but given once a day.

The sponsor has also made some efforts to look at the postmarketing reports--again, the drug has been on the market for 50 years or so--in children to see what the adverse events might have been.

The adverse events seen, and you will hear about this in great detail, were those that were more or less expected to be seen with ACTH but, again, the extent and the nature of data capture in these databases is unknown. In a

typical drug company-sponsored study, a prospective cohort is followed, everything that happens after drug that is adverse is written down whether anybody thinks it is related to treatment or not, and then we look at those adverse events.

Here, of course, we don't really know whether or not these practitioners actually recorded all the things that we might think of as adverse events reliably.

Of course, we are all familiar with the limitations of adverse-event data generated from spontaneous postmarketing reports.

So, for these reasons, as well as the fact that the safety database is quite small, we are interested to know if you think that we can conclude that the safety of the proposed regimen in this population has been adequately described.

I think those are the main issues we would like you to discuss. There is a list of questions and topics that we specifically would like you to address, and a few of them we have designated as those it is very important for us to have you actually vote on. So that is important for us.

Of course, if we have left anything off that list

that you think is important for us to consider, of course, we are very eager to hear what those issues are.

So, with that, I think I will say thank you for the work you have done in preparation and for the work you will do for the rest of the day, and again welcome, and I will turn it back to Dr. Anderson.

DR. ANDERSON: Thank you, Dr. Katz.

At this point we proceed to the sponsor's presentations, and coordinating that is Dr. Young.

INDUSTRY PRESENTATION

Background

DR. YOUNG: Good Morning, Dr. Anderson, Dr. Katz, and members of the Advisory Committee, members of the FDA review team, ladies and gentlemen.

[Slide.]

DR. YOUNG: My name is David Young. I am the Chief Scientific Officer for Questcor Pharmaceuticals. I will be serving as the facilitator today during this meeting.

[Slide.]

We appreciate the opportunity to be here to discuss Acthar Gel, as Dr. Katz said. The recommended

dosage regimen, as Dr. Katz mentioned is 150 U/m² divided into twice daily doses of 75 U/m².

Today, we will also be calling that 75 U/m² BID, the duration of treatment of two weeks followed by gradual tapering.

[Slide.]

As you know, infantile spasms is a disorder with devastating consequences. It is an orphan disorder with an incidence of 1,000 to 2,000 infants per year.

At the present time, three of the most commonly used drugs to treat IS are: Acthar, which is used off-label, and presently the standard of care as the most widely used drug; vigabatrin, which is the only U.S.-approved drug; and prednisone, which is also used off-label.

[Slide.]

Acthar is a purified preparation of the naturally occurring corticotropin polypeptide ACTH that is obtained from porcine pituitary, consists of all 39 amino acids associated with ACTH, and is administered as a modified-release formulation.

[Slide.]

In 1952, Acthar was approved for multiple

indications, none of which were IS.

It was first used for IS in 1958. Since that time, approximately 30,000 infants with IS have received Acthar and, in the past two years, more than 40 percent of the infants with IS have been treated with Acthar off-label.

[Slide.]

Over the last 52 years, there have been many different regimens used for Acthar. We can group these regimens into three categories; the 75 U/m² BID regimen, which is our recommended regimen, and the two others as you see on the slide.

The duration of treatment of these regimens has varied from weeks to months.

Given the wide variety of dosage regimens used, being able to provide guidance on a safe and effective dosage regimen is one reason Questcor is seeking approval here.

[Slide.]

There have also been many response measurements in IS. The endpoint most widely accepted is the cessation of clinical spasms and resolution of hypsarrhythmia confirmed by a prolonged video-EEG. We will refer to this endpoint as

overall response or no hypsarrhythmia, no spasms.

[Slide.]

In order to evaluate this NDA today, it is important to understand both the use and regulatory challenges that have been associated with off-label Acthar use.

From 1996 to 2000, an Acthar shortage existed because of manufacturing and stability problems. FDA and Aventis, the previous owner of Acthar, met to determine what could be done to keep Acthar available for IS patients.

Given the limited supply, Acthar was rationed to IS patients through the National Organization of Rare Diseases, or NORD. As you can appreciate, this was a public health issue for infants and families who needed the treatment of Acthar.

[Slide.]

In 2001, Aventis stopped manufacturing Acthar, and Questcor acquired the product. Questcor agreed to modify the production process per agreement with the Food and Drug Administration and to increase supply and distribution.

[Slide.]

In order to ensure that Acthar would be available

to all infants who needed it, in 2006, Questcor submitted a supplemental NDA to FDA. We wanted to make sure that physicians and patients had a dosing regimen with documented safety and efficacy, and that safety, efficacy, administration guidance, and counseling information would be available to physicians, nurses, and caregivers.

[Slide.]

In 2007, FDA issued a non-approvable letter regarding this NDA. The primary reasons for not approving Acthar at that time were that the safety and efficacy was based on a meta-analysis of Acthar and other corticotropin polypeptides, and the FDA required source data to support the efficacy and safety.

[Slide.]

In our desire to ensure availability, Questcor met with the FDA at the end of 2007 to define what was required to obtain approval. At this meeting, FDA agreed that the treatment goal for IS was to have complete cessation of spasms and resolution of hypsarrhythmia or overall response, that conducting a prospective clinical efficacy study would be extremely difficult, and that prior investigator-initiated RCTs, not sponsor-initiated studies, might be

sufficient to support the efficacy portion of the NDA.

[Slide.]

To meet this agreement with the FDA, we looked at the ten publications which had Acthar efficacy study information. The top four represent RCT studies, and the bottom six are non-RCT studies.

We obtained data from the first three studies highlighted in yellow, because they were the RCTs that had this overall response endpoint. These studies will be discussed further by Dr. Trapnell.

[Slide.]

In terms of safety, given 52 years of use of Acthar, FDA agreed that Questcor could perform a prospective analysis of retrospective data to support the safety of Acthar. This meant that Questcor could obtain data from clinical charts and the RCT study charts. These three studies on the slide comprise the integrated safety database which Dr. Trapnell will discuss later on.

[Slide.]

We will demonstrate today that infantile spasms is a devastating disorder with few therapeutic options. Other approved IS treatments are needed.

Acthar is effective in IS as demonstrated by a single adequate well-controlled study and additional confirmatory evidence. Acthar AEs and SAEs at the recommended dosage regimen are typical of the steroid class of drugs and clinically recognizable, and lastly, that the benefits of Acthar outweigh the risks.

[Slide.]

In our agenda today, Dr. Shields will be talking about infantile spasms. Dr. Trapnell will talk about the sNDA efficacy and safety studies. Dr. Shinnar will be talking about additional evidence to support the efficacy and safety of Acthar.

Dr. Duchowny will be talking about the potential limitations in sNDA studies and current treatments. Dr. Pellock will come in and summarize.

I would like to now hand this over to Dr. Shields.

Infantile Spasms

DR. SHIELDS: Thank you and good morning.

[Slide.]

My name is Don Shields. I am the Director of the Pediatric Epilepsy program at UCLA.

[Slide.]

My disclosures are listed here. I have no financial interest in the outcome of this meeting.

[Slide.]

For those of you who may not be familiar with infantile spasms, I will give a brief overview of this unique pediatric disorder.

I will discuss the disease background of infantile spasms including the characteristics that make it such a distinctive disorder, a brief overview of the etiology, and the prognosis for the unfortunate children who develop infantile spasms.

[Slide.]

What are the distinct features of infantile spasms? Dr. West first described infantile spasms in 1841 in Lancet, and I have included excerpts from his report here because it characterizes the age, the semiology, and the outcome of a patient who was, in fact, his son.

In his son, the seizures began at four months of age, and to quote, "The child had slight bobbings of the head forward. These bobbings increased in frequency and strength. These would be repeated at intervals of a few seconds and repeat from 10 to 20 or more times at each

attack." This is an excellent example of the seizure semiology, typical clusters that occur.

By one year of age, the consequences became quite clear. "He neither possesses the intellectual vivacity or the power of moving his limbs of a child his age. Yet, his hearing and vision are good. He has no power of holding himself upright or using his limbs and his head falls forward without support." This is the typical developmental outcome of the child whose seizures persist, clearly devastating.

[Slide.]

Now, we shall see the subtle appearance of the spasms belie the significance to the child. These things can occur hundreds of times a day, and if you look at this, you wouldn't think this is something to be terribly afraid of, often misdiagnosed.

However, if this was a child who started having spasms at around five months of age, the typical age, he probably would be sitting, starting to roll over, would be smiling, and social. But if he was typical within a month of starting the spasms, these developmental milestones would have declined substantially.

They are a little more obvious, as you can see, when he is sitting up, but the very characteristic spells, often misdiagnosed. In some sense, infantile spasms can be considered a variation on a theme of dementia, but one that has the potential for recovery in at least some of the infants.

[Slide.]

The EEG for patients with infantile spasms is clinically distinct. This is an example of an EEG from a child with spasms. This is hypsarrhythmia during sleep. For those of you who may not be familiar with EEGs, this is an exceedingly abnormal, highly disorganized, very high voltage EEG, and when we see this pattern of hypsarrhythmia, the child almost certainly has infantile spasms.

As noted, hypsarrhythmia often occurs during sleep. This is a normal EEG during sleep for comparison. You don't have to be an electroencephalographer to see the difference between them.

This highly abnormal EEG prevents the child from attending to his or her environment, which I believe leads to cognitive decline or delay. Just as the clinical response means that there are no spasms, an electrographic

response means that the hypsarrhythmia resolves. Resolution of the hypsarrhythmia appears to be essential for improving the developmental prognosis and, as soon as I see a patient in the clinic with infantile spasms or a physician refers that patient to me, I admit the patient to the hospital for evaluation and initiate treatment as soon as possible.

[Slide.]

Fortunately, infantile spasms is an uncommon disorder with on 1,000 to 2,000 cases per year in the United States. Although overall it is uncommon, it represents about a quarter of epilepsies in children under a year of age, not including neonatal seizures or afebrile seizures.

The seizures in the EEG for this, as we have seen, are distinct from virtually all other seizure disorders. Unfortunately, in many cases, the seizures are difficult to control, and as I mentioned, if they are not controlled, the associated cognitive delay is virtually inevitable.

Another unusual feature of spasms is that most of the standard anticonvulsants are not very effective.

[Slide.]

Many disorders are associated with spasms and we generally define two categories. One is cryptogenic where

we cannot identify a cause after careful history, physical exam, and appropriate laboratory tests. This is about 30 percent of spasms cases, and cryptogenic patients generally have a better developmental prognosis.

The remaining 70 percent comprise the symptomatic group with an identifiable etiology. They generally have a poorer developmental prognosis although the prognosis is still heavily dependent on the specific associated etiology.

[Slide.]

With regard to outcome, there are significant consequences associated with infantile spasms. There is a high mortality rate reported between 6 and 33 percent by age 3. I think the lower rate is more accepted these days, and mortality is most commonly due to the underlying neurologic disorder associated with the spasms.

The results are quite substantial morbidity especially in the cognitive area. About 70 to 90 percent of patients are intellectually developmentally delayed, most commonly with IQs in the 30 to 50 range. About a third eventually are diagnosed as autistic.

The key issue is that children who eventually have normal intelligence were the ones whose spasms were

controlled, and the time to initiation of treatment and controlled spasms appear to be significant factors for improved developmental outcome.

[Slide.]

Uncontrolled infantile spasms typically disappear by one to two years of age, but may evolve to other catastrophic seizure disorders such as Lennox-Gestaut syndrome. These patients generally have a poorer prognosis for development.

In some patients whose spasms are controlled will later develop partial seizures, such as patients with tuberous sclerosis. However, children with partial seizures that have not evolved directly from the infantile spasms generally have a better prognosis than those whose spasms were not controlled.

As I mentioned, infantile spasms typically resolve by the first or second year of life, and a spontaneous remission rate has been difficult to estimate because Acthar has been used for treatment for more than 50 years, so the natural history is not really very clear.

However, in 1991, Hrachovy and colleagues looked at patients who were not initially treated with hormonal

therapy and assumed that patients treated with other medications generally not considered to be effective represented the spontaneous remission rate, and this is a graph from their paper.

During the first three months of infantile spasms, the spontaneous remission rate appears to be only about 2 percent. Over the course of any two- to three-month period, during the first year of life, the maximal spontaneous remission rate is around 10 percent.

For purposes of comparison, we will assume that the maximum spontaneous remission rate for any given three-month period that would be part of a study, would be 10 percent. Given the spontaneous resolution of the spasms, the developmental consequences are still significant if the resolution does not occur early, and as the slide indicates, early spontaneous resolution is uncommon.

[Slide.]

There are two outcome issues regarding infantile spasms. One is control of the spasms, and the second is developmental outcome. These are separate, but related, issues meaning that, if you control the spasms, the child has a better chance at a positive developmental outcome.

In some cases, even when the spasms are controlled, the development may not be good if the child has an underlying disorder that precludes it. However, even in those cases, from the family's perspective, control of the spasms is a worthwhile outcome for the child even if the development is not substantially improved.

[Slide.]

Certain factors are recognized to have an important influence on outcome. Factors with a better outcome are cryptogenic etiology, initiation of effective treatment within one month leading to 100 percent control of spasms, and resolution of hypsarrhythmia.

Factors recognized as being associated with a less favorable outcome are symptomatic etiology. However, some symptomatic etiologies may still have a favorable outcome and early onset, which means usually less than three months of age because many of these infants have cortical developmental abnormalities that may preclude a good developmental outcome regardless of what happens with the spasms.

[Slide.]

However, there are two factors here that are

amenable to change. Early recognition of the fact that the child has spasms, preferably before it is apparent that there is a developmental delay or regression, and similarly, a delay in the initiation of effective treatment.

[Slide.]

As discussed, patients with infantile spasms are at risk for significant morbidity and mortality, and the consequences clearly extend beyond the patient. We haven't really discussed this much, but you can imagine watching your own child having several hundred seizures a day and regressed developmentally. The consequences for the family are quite substantial.

Untreated or inadequately treated infantile spasms is associated with a higher risk for mortality and morbidity. Early, effective therapy may provide the child with an increased probability of the best possible cognitive outcome.

Patients with infantile spasms require treatment options that have the highest probability of stopping 100 percent of the spasms and that normalize the EEG.

[Slide.]

To conclude, this is a review paper I wrote a few

years ago entitled "Little Seizures, BIG Consequences."

This title emphasizes the disparity between the nature of the seizures, which are seemingly minor, and the nature of the consequences which can be major. The abstract makes the point, "However, early recognition, a careful diagnostic evaluation and proper treatment may allow some children to attain seizure control and to achieve a normal, or at least much improved, level of development. Thus, there is the opportunity to have an important impact on the lives of these unfortunate children and their families."

Thank you.

Dr. Carol Trapnell will now discuss efficacy and safety of Acthar.

sNDA Efficacy and Safety Data

DR. TRAPNELL: Good morning.

[Slide.]

I am Carol Trapnell, the Chief Medical Officer at SAJE Consulting. I am here today to discuss the Questcor efficacy and safety data submitted to the FDA to support the approval of Acthar for the treatment of patients with infantile spasms.

[Slide.]

For disclosure, I am a paid consultant to Questcor and I have no financial interest in the outcome of this meeting.

[Slide.]

Questcor's goal from the onset was to determine if Acthar is efficacious to treat children with infantile spasms, and if so, then, to determine an effective and safe dose and dosing regimen.

[Slide.]

As reviewed by Dr. Young, in discussions with FDA, the primary endpoint was the overall response, which is spasm cessation together with hypsarrhythmia resolution on prolonged video-EEG as an all-or-none response. Questcor also assessed the secondary endpoints of spasm cessation alone, and hypsarrhythmia resolution alone.

In addition, Questcor agreed to contact investigators to obtain source data from previously published, randomized controlled trials that used the overall response as the primary study endpoint.

Once these data were obtained, we assessed whether it could support Acthar's efficacy in support of an NDA application. As Dr. Young reviewed, there were ten

published clinical trials of Acthar in patient with infantile spasms, four of which were randomized controlled trials.

The three studies highlighted here were selected because each used the overall response as the primary endpoint. These studies became NDA Studies 01, 05, and 04, respectively. Studies 01 and 04 compared Acthar to prednisone. Study 05 compared two different doses of Acthar. Note that, when possible, I will show all Acthar doses as U/m² to keep the units consistent during my presentation.

[Slide.]

The three randomized controlled trials had the following methodologies in common. All were investigator-initiated and published in the medical literature. All patients were diagnosed with infantile spasms based on spasms and hypsarrhythmia, had no prior treatment with the study medications, and had either cryptogenic or symptomatic etiology of their disease.

The source data were obtained from either study charts, investigators' databases, or both. We developed CRFs, or case report forms, to standardize data collection,

as well as developed independent statistical analyses plans for each study.

[Slide.]

The endpoints for the studies were as follows. The spasms response was the complete cessation of spasms. This was documented by prolonged video-EEG. The EEG response was the complete resolution of the hypsarrhythmic pattern on the prolonged video EEG.

Finally, the overall response endpoint was a composite endpoint determined from the outcomes of both the spasms response and the EEG response endpoints. This was our primary endpoint for all three studies.

[Slide.]

Studies 01 and 05 were single-blind, randomized controlled trials. The interpretation of the EEG was done in a blinded manner. Study 04 was a double-blind, double-dummy, randomized controlled trial.

Studies 01 and 04 allowed patients who failed their initial treatment to be treated with the with the alternative study therapy. It is important to note that none of the three randomized controlled trials were designed to assess relapse, as Dr. Katz mentioned earlier. However,

we did an exploratory analysis for relapse in patients in Study 05, which I will discuss later.

[Slide.]

I will first discuss Study 01, which was a randomized controlled, single-blind study of Acthar compared to prednisone in patients with IS. This study was conducted in the early 1990s at the Children's Hospital of Los Angeles by Drs. Baram and her colleagues. The results were published in 1996.

The study objective was to compare the efficacy of Acthar 150 U/m²/day given in two divided doses, which I will refer to as 75 U/m² BID, to prednisone at a dose of 2 mg/kg in divided doses, which I will refer to as 1 mg/kg BID.

Those drugs were administered for two weeks with a 2-week taper for the treatment of IS patients. The Acthar dose used in this study is the Questcor-recommended dose for approval.

To provide context, we were only able to obtain the data in database form, because access to the source data was denied by the IRB through the HIPAA regulations.

[Slide.]

This study had a very straightforward design.

Following randomization, patients were treated with either Acthar or prednisone. Response was determined after two weeks of treatment with a prolonged video-EEG as noted here.

Responders were then tapered over an additional two-week period. Non-responders after two weeks of study treatment were offered treatment with the other study therapy.

[Slide.]

Twenty-nine patients were enrolled into the trial, 15 of these patients were randomized to receive Acthar, while 14 patients were randomized to receive prednisone. Of note, the study prospectively planned to enroll 16 patients per arm.

[Slide.]

The demographics of the patients enrolled in Study 01 are shown here. The median age of the patients in this study was six months. The study enrolled more females than males, and the majority of the patients in this study had an IS etiology considered to be symptomatic. This is consistent with the natural history data presented by Dr. Shields.

[Slide.]

Here, we see the efficacy results from this study. The primary endpoints and the two secondary endpoints all showed a highly statistically significant difference in favor of Acthar. Of note, 87 percent of the Acthar patients achieved an overall response, as well as an EEG response.

In addition, 93 percent of the Acthar patients achieved complete spasm cessation as noted by the spasms response. This slide also contains a dashed line at the 10 percent response rate. As Dr. Shields noted, this represents the approximate spontaneous remission rate that would be expected for these patients.

I will include this reference line in other slides in my presentation where appropriate.

[Slide.]

Here is the disposition for the patients who were non-responders to their initial treatment. The two patients who were non-responders to Acthar were treated with prednisone. Of the 10 patients who did not respond to prednisone, nine were treated with Acthar. We only had outcome data for eight of these nine patients.

[Slide.]

This slide shows the overall response for these

patients that I have just discussed. As you can see, for those patients who subsequently received Acthar, 87 percent who initially failed prednisone achieved an overall response after two weeks of Acthar treatment.

These results are comparable to the overall response rate for patients who initially received Acthar in this study.

[Slide.]

In conclusion, for Study 01, the data demonstrate that Acthar is efficacious for the treatment of patients with IS when compared to prednisone for all three study endpoints, the overall response, the spasms response, and the EEG response.

The p-value for each endpoint was highly statistically significant in favor of the Acthar treatment. In addition, as per the last slide, seven of the eight patients, or 87 percent, who failed initial treatment with prednisone had an overall response to Acthar treatment.

This single adequate and well-controlled trial provides convincing evidence that Acthar is efficacious at the Questcor-recommended dose of 75 U/m² BID for two weeks for the treatment of IS patients.

[Slide.]

I will now discuss Study 05, which was a single blind, randomized controlled trial comparing 2 doses of Acthar in patient with IS. This study was conducted and published by Dr. Hrachovy and colleagues in 1994. The study objectives were to compare the effectiveness and safety of Acthar administered 150 U/m² once daily to Acthar 50 U/m² once daily in the treatment of patients with IS.

[Slide.]

I want to make additional comments specific to this study methodology. We obtained redacted copies of study charts and case report forms were designed to facilitate data capture from those charts.

An independent verification of the data transcription process was performed to assure capture of all available data into the CRFs.

[Slide.]

This slide shows the design of Study 05. Patients were randomized to receive either Acthar 150 U/m² once daily or Acthar 50 U/m² once daily.

Patients randomized to the 150 U/m² group received this dose for three weeks, followed by a nine-week taper.

Patients were assessed with a prolonged video-EEG after this 12-week period as shown here.

Patients randomized to the 50 U/m² group received this dose for two weeks, at which time they were assessed for response by a prolonged video-EEG as shown here. Responders were tapered off treatment over one to two weeks. Non-responders after this initial two-week period of treatment had the option to have their Acthar dose increased to 75 U/m² daily for an additional four weeks of treatment, followed by a one- to two-week taper. A final prolonged video-EEG was performed after the taper was complete.

[Slide.]

Study 05 enrolled 59 patients. Thirty patients were randomized to the 150 U/m² group, and 29 patients were randomized to the 50 U/m² group.

[Slide.]

Four efficacy populations were defined for the analysis of the study data. I will present the mITT population, which was the primary analysis population, as well as the ITT population which was requested by the FDA.

The mITT population included all patients randomized who received more than 1 dose of Acthar and could

be evaluated for overall response. Fifty-one of the 59 patients randomized into the study met this definition and were included in this population. The ITT population included all 59 patients randomized to study treatment. The ITT population was used for a sensitivity analysis. Worst case scenario rules were applied for this analysis for patients with missing data, such that patients randomized to the 150 U/m² dose with missing data were classified as treatment failures.

Patients randomized to the 50 U/m² dose with missing data were classified as treatment responders. The other two populations we defined are discussed further in the briefing documents.

Also, as you may have noted from your briefing documents, 13 patients withdrew from the study prior to study completion. However, these patients were included in the efficacy analyses when appropriate.

[Slide.]

Key demographics for the ITT population are shown here. The median age was approximately seven months, which is similar to the median age in Study 01. Overall, approximately two-thirds of the patients were males and, as

in Study 01, the majority of patients in this study had symptomatic IS.

[Slide.]

The results for the mITT population are shown here. As you can see, the spasms response was significantly different in favor of the Acthar high dose used in this study, and while there were no significant differences in the overall response between the two doses, there was a modest difference in this endpoint between these two doses in favor of the 150 U/m² dose.

[Slide.]

This slide shows the results of the same analysis, but using the ITT population. In this population, with the sensitivity analysis rules applied, the spasms response was nearly statistically significant in favor of the high-dose group.

[Slide.]

As you saw on the results of the mITT population, 15 of the 24, or 63 percent, of the patients randomized to the 150 U/m² group achieved an overall response, while 13 of the 27, or 48 percent of the patients randomized to the 50 U/m² group achieved an overall response.

As I mentioned previously, Study 05 allowed non-responders in the 50 U/m² group to escalate their Acthar dose to 75 U/m² daily.

This slide shows the overall response categorized by the final Acthar dose received by the patients in the mITT population. As shown on the right-hand portion of the slide, 26 percent of the 27 patients initially randomized to receive Acthar 50 U/m² daily responded to this dose.

The difference in the 63 overall response rates seen in the 150 U/m² group compared to this 26 percent response rate is statistically significant in favor of the Acthar 150 U/m² dose.

Finally, 18 of the 20 patients who did not respond to the 50 U/m² were dose-escalated to 75 U/m² daily. Six of those patients subsequently responded to this higher Acthar dose. Thus, the overall response for patients initially randomized to the 50 U/m² group was 48 percent.

[Slide.]

Finally, as I mentioned at the beginning of my talk, we also did an exploratory analysis of these data to assess the relapse rate in patients classified as overall responders in the mITT population.

These data show that the relapse rate between these two treatment groups is similar at a rate of between 15 and 20 percent.

[Slide.]

To conclude Study 05, the data show that Acthar is efficacious in the treatment of patients with IS. The overall response rate for the two treatment groups was between 50 and 65 percent, compared with the expected spontaneous response rate of only 10 percent.

Acthar 150 U/m² daily had more biologic activity compared to the 50 U/m² daily dose. The spasms response rate was greater in the high-dose Acthar group. Importantly, there was a statistically significant difference in the spasms response in mITT population, and a nearly significant difference in this endpoint in the ITT population.

This study provides confirmatory evidence of Acthar's efficacy for IS patients.

[Slide.]

I will now discuss the third randomized controlled trial submitted in the NDA, Study 04, which was a double-blind clinical trial comparing Acthar 50 U/m² daily to

prednisone 2 mg/kg/day in patients with IS.

This study was conducted and published by Hrachovy and colleagues in 1983. The study objectives were to compare the effectiveness and safety of Acthar 50 U/m² daily to prednisone 2 mg/kg/day in the treatment of patients with infantile spasms.

Similar to Study 05, we obtained redacted copies of the study charts, and CRFs were designed to facilitate data capture.

[Slide.]

This slide shows the study design for Study 04. Patients were randomized to either Acthar or prednisone. Patients assigned to Acthar received 50 U/m² once daily for two weeks, at which time a prolonged video-EEG was performed.

Patients who responded were tapered off Acthar over a one- to two-week period. Non-responders again had the option of having their Acthar dose increased to 75 U/m² once daily, and if so, were treated for four weeks at this higher dose.

For prednisone, the study design was similar except for non-responders at two weeks could received

prednisone at the same dose of 2 mg/kg/daily for an additional four weeks.

In addition, non-responders of either two or six weeks of either treatment could choose to be treated with the alternative study therapy.

[Slide.]

For Study 04, 24 patients were randomized into the study. Twelve were assigned to each group.

[Slide.]

The demographics for the Study 04 patients are shown here. The median age of study patients was approximately eight months. Slightly more than half the patients were male, and there were more symptomatic IS patients.

These are similar to the demographics of the patients enrolled in the other two randomized controlled trials that I presented earlier.

[Slide.]

This slide shows the results for the overall response, as well as the spasms and EEG responses. There were no differences between the two treatment groups for any of these three endpoints.

[Slide.]

In conclusion for Study 04, both treatments exceeded the expected 10 percent response remission rate. However, there was no difference in the efficacy between the Acthar 50 U/m² daily and the prednisone 2 mg/kg daily doses.

[Slide.]

I would now like to summarize the results of the three efficacy studies presented. This slide shows the comparison of the primary endpoints overall response by study. As you can see, the data demonstrate an apparent dose-response across the studies.

The Questcor-recommended Acthar dose in Study 01, as shown in the left-hand column, achieved the highest overall response rates of 87 percent, with 150 U/m² daily dose from Study 05 showed an overall response rate of 63 percent, while the 50 U/m² dose from Studies 05 and 04 showed a 48 percent and 42 percent overall response rate respectively.

[Slide.]

Again, for perspective, this slide has the expected spontaneous remission rate of 10 percent. All three of these studies demonstrate that Acthar greatly

exceeds this remission rate.

[Slide.]

Likewise this slide shows the data for the spasms response endpoints. These data again show a dose-response with the Questcor-recommended Acthar dose as shown in the left-hand column, achieving a 93 percent spasms response rate.

[Slide.]

In conclusion, these data show that Acthar is efficacious for the treatment of IS based on the primary endpoint of overall response, and the secondary endpoint of spasms response.

The Questcor-recommended regimen of 75 U/m² BID for two weeks with a 20-week taper is the regimen that provides the best observed efficacy. These data, particularly the data from Study 01, which was a randomized, well-controlled trial, support approval of Acthar for the treatment of IS patients.

[Slide.]

I will now move into a discussion of the safety data submitted in the NDA.

[Slide.]

The data submitted to support the safety of Acthar in patients with IS come from the following sources. The integrated safety data include data from Study 02, Study 05, whose design I discussed previously, and the retrospective study.

The safety data from Study 04, which I had previously reviewed for efficacy, will be presented. These data were not integrated because it was difficult to assess Acthar-specific adverse events from the data due to the study design.

I will also review data from the postmarketing surveillance database.

[Slide.]

The safety data were obtained from either clinical-care or study chart, or from study-specific forms completed from clinical-care charts. None of these captured adverse events as would normally be done in prospectively design, industry-sponsored clinical trials.

The case-report forms were designed to capture all available safety data. The CRF collected traditional adverse events, parent-reported adverse events, physical exam findings, and laboratory abnormalities.

These adverse events will be shown according to these categories. It is important to note that, in some cases, there was duplicate reporting of the same adverse events across one or more of these CRF pages.

Therefore, it is not possible to obtain overall numbers for each adverse event by simply adding across these data. For example, irritability may have been reported by the parents as an adverse event, and then recorded as part of the physician assessment.

[Slide.]

I will first summarize the methods for Study 02, which was a retrospective analysis of adverse events associated with Acthar treatment for patients with IS.

[Slide.]

Study 02 was a retrospective chart review of all children at the Children's Hospital of Los Angeles admitted or cared for with a diagnosis of infantile spasms between 1990 and 2006, and 2006 and 2008.

Of note is that the Study 01 patients were treated at the same institution during the first time interval. However, as discussed earlier, we were unable to access the source records due to IRB and HIPAA issues. It is therefore

presumed that the safety data for the Study 01 patients are included within the Study 02 safety data.

The clinical charts contain data from routine clinical care of these patients. The investigators developed study-specific forms containing data fields of interest. Available safety data were then entered into the forms from the investigator's review of the clinical charts.

Data from the study-specific forms were then transcribed into standardized CRFs for data analysis.

[Slide.]

The investigators collected data on 159 patients, 84 of whom received Acthar as their initial IS treatment. Sixty-four patients were treated between 1990 and 2006. These patients were included in the previously cited publication from 2007. Twenty patients were treated between 2006 and 2008.

[Slide.]

I will now move on to discuss the retrospective study. Questcor developed a protocol to perform a retrospective chart review to determine the adverse-effect profile for patients with IS treated with Acthar.

[Slide.]

This protocol was developed by Questcor and reviewed by FDA as a special protocol assessment. The protocol described desired safety data to be collected from clinical charts of patients with IS who had been previously treated with Acthar at four U.S. sites.

The available data were then transcribed into CRS. Every effort was made at each site to identify all charts for IS patients treated with Acthar.

An independent assessment of the data collection was performed so that we could be sure that all of available safety data had been captured and, like Study 02, the CRFs were designed to collect for additional adverse events, parent-reported adverse events, and physical exam and laboratory abnormalities separately due to the nature of the source data.

[Slide.]

In order to summarize the safety data, we grouped the Acthar dosing regimens as shown on this slide based on the highest dose received by each patient. We had five dosing groups; the Questcor recommended dose of 75 U/m² BID with the other four dosing groups as shown here.

[Slide.]

In total, we had 319 patient in the integrated safety summary from the three studies. 122 received the Questcor recommended dose. A total of 159 patients received a total daily dose of Acthar of 150 U/m².

All of the tables in the briefing document show the safety data for all of these groups shown here. However, for the purpose of this morning's discussion, the subsequent slides will show the data for the Questcor recommended dose, the 150 U/m² once-daily dosing group, the low dose group of less than 80 U/m² daily, in all 319 patients.

[Slide.]

The key demographics for the integrated safety population are shown here. The age at start of treatment, the gender ratio, and the IS etiology are similar to the demographics from the previous study.

[Slide.]

This slide shows the traditional adverse events by MedDRA Preferred Term. The most common adverse events were infection, irritability, Cushingoid appearance, and hypertension. These are known steroid class adverse effects of Acthar.

Convulsions were the most frequently reported seizure-related adverse event in these patients. It was not possible to distinguish worsening IS from progression to other forms of epilepsy. It is believed, however, that these convulsions were not directly related to Acthar administration.

As you can see, there appeared to be more adverse events in the 150 U/m² once-daily group when compared to the Questcor recommended dose and dosing regimen including the four highlighted here. These findings may be due either to the fact that these patients received a higher single daily dose or they received Acthar for a longer duration of time.

[Slide.]

This slide shows the parent-reported adverse events in the integrated safety population. The majority of patients had at least one parent-reported adverse event with the most common being irritability, excessive appetite, and infection. Again these are known steroid class adverse effects of Acthar. Again, the differences seen here between the Questcor recommended dose and the 150 U/m² daily dose may be a function of the higher single dose or the longer duration of treatment in the latter group.

[Slide.]

The abnormal clinical laboratory tests with an elevated white-blood-cell count being the most common abnormal lab test, any abnormal physical findings were all consistent with the known steroid class effects of Acthar.

In addition, the muscular abnormalities were due to the underlying diagnoses.

[Slide.]

Now, I will focus on the serious adverse events or SAEs. First, it is important to note that Questcor used an expanded definition of SAEs in the safety database. The Questcor SAE definitions include the clinical situations shown in orange on the right-hand side of this slide.

These four clinical situations were actually labeled as severe adverse events by the investigators for Study 02, but were subsequently classified as serious adverse events during the data transcription process. These expanded SAE definitions were also carried over to the data for Studies 05, 04, and the retrospective study.

Well, having an infection that requires intravenous antibiotics is an SAE. The other three severe adverse-event definitions, outlined here by the box, would

not necessarily meet the standard definition for an SAE. Therefore, there may be over-reporting of SAEs in our safety database.

[Slide.]

With that background, this slide shows the SAEs by MedDRA Preferred Term in two or more patients in the ISS population. Overall, 66 percent of patients on the recommended dose had no reported SAEs. The three most commonly reported SAEs were convulsion, infections, and hypertension.

The cases of hypertension were treated with antihypertensive therapy, observation, or drug discontinuation. While convulsions were the most commonly reported SAE, it was not possible from the data to distinguish worsening of IS from progression to other forms of epilepsy.

As I have mentioned previously, in this integrated safety summary, convulsions may also have been incorrectly classified as serious adverse events. It is important to recognize that all of the reported SAEs are well known to be associated with Acthar therapy and are clinically recognizable.

[Slide.]

I will now discuss the two deaths reported in our integrated safety data. Neither of these patients were treated with the Questcor recommended Acthar dosage regimen.

In the retrospective study, a four-month-old patient in the 80 to 135 U/m² Acthar dose group with a complex medical history including severe hypoxic, ischemic encephalopathy, frequent gastroesophageal reflux, and aspiration pneumonia died two weeks after completion of an Acthar taper of aspiration pneumonia.

The patient received Acthar at a dose of 66 U/m² daily for five days, then 132 U/m² daily for 12 days, followed by an 18-day taper.

A three-month-old patient with a history of IS, microcephaly, and severe developmental delay was enrolled in Study 05. This patient received Acthar at a dose 50 U/m² for two weeks, which was escalated to 75 to 100 U/m² for an additional six weeks. The patient died after developing respiratory failure with documented RSV infection.

[Slide.]

I will now summarize the safety data from Study 04. First, all reported adverse events were consistent with

the integrated safety data for Acthar as described by the ISS population.

SAEs were reported in four patients, two patients who received Acthar alone developed hypertension and weight gain. Two patients who received prednisone and then Acthar developed hypertension and Herpes simplex. There were no deaths reported.

[Slide.]

Questcor had 76 patient reports from its postmarketing surveillance data in the NDA submission. Thirty-three reports were considered serious. There were eight deaths reported including the death from Study 05.

There are additional details about the postmarketing data in your briefing document.

The reported AEs are well known to occur with Acthar, particularly with prolonged drug administration, which was the case for many of these patients.

[Slide.]

To conclude the safety overview, the adverse-event data demonstrate that Acthar, when administered at the recommended dose, has an expected adverse-event profile consistent with the steroid drug class.

Adverse events are common and some may progress to more serious problems if not clinically recognized.

[Slide.]

Finally, in summary, the data presented today, in particular the results of Study 01, a randomized controlled trial, demonstrate the efficacy of the Questcor-recommended dose and dosing regimen of Acthar 75 U/m² given BID for two weeks with a two-week taper. These data are supported by the data in the confirmatory study 05.

In addition, the safety profile of Acthar includes clinically recognized adverse events associated with the steroid class of drugs.

When taken together, the efficacy and safety data support the approval of Acthar for the treatment of patients with IS.

I would now like to turn the podium over to Dr. Shlomo Shinnar, who will provide additional confirmatory evidence of Acthar's efficacy and safety.

**Additional Evidence to Support the Efficacy
and Safety of Acthar**

DR. SHINNAR: Thank you. Good morning.

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I am Shlomo Shinnar. I am a child neurologist. I am the Director of the Epilepsy at Montefiore Medical Center and the Albert Einstein College of Medicine, and I will discuss additional data from the published literature.

[Slide.]

I am a consultant to Questcor and other companies as shown here. I have no financial interest in the outcome of today's meeting.

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In 2004, the Academy of Neurology and the Child Neurology Society issued a practice parameter on the treatment of infantile spasms. It concluded that ACTH is probably effective for the short-term treatment of infantile spasms and in the resolution of hypsarrhythmia.

The practice parameter review, which I was privileged to be part of, was based on the view of 14 studies of ACTH therapy. This included five randomized controlled trials, which used no spasms and no hypsarrhythmia confirmed by video-EEG as the endpoint, and three of those, which are the three that Dr. Trapnell has described, used Acthar. And there were also nine open-label case series, six of which used Acthar.

[Slide.]

This slide, which you have seen before, summarizes those studies. The three RCTs have already been discussed by Dr. Trapnell. The Dreifuss RCT used an endpoint of reduction in spasm frequency, which we don't consider anymore to be a useful parameter for this disorder, so will not be discussed further.

The six non-randomized trials are the ones I would like to further discuss, and three of them at least used the no hypsarrhythmia/no spasms endpoint confirmed by video-EEG.

[Slide.]

These two studies shown on this slide were performed by Dr. Snead and colleagues, and they were the initial studies actually to utilize the recommended dose of 150 U/m² per day divided BID, and they used no spasms/no hypsarrhythmia confirmed by video-EEG as the criteria.

The results from this dosing regimen are remarkably consistent with that from the RCT by Baram; namely, in the retrospective analysis from 1983 and the 30 children with Acthar, 97 percent responded in the no spasms/no hypsarrhythmia criteria compared with 50 percent on prednisone.

In the subsequent study, which was a prospective single-arm, unblinded study, using the same criteria of the 15 children, 14 of 15, or 93 percent, had a full no spasms/no hypsarrhythmia response.

[Slide.]

The other four non-RCTs are more difficult to interpret because they have different dosing regimens and all but one, namely, the Hrachovy study of 1980 which had five subjects but which did use this criteria, but all these studies do show quite high spasm response rates.

[Slide.]

This study summarizes all the RCTs which Dr. Trapnell showed and the non-RCTs which used the stringent endpoint of no spasms/no hypsarrhythmia confirmed by video-EEG. What emerges is a remarkable consistent story at the dose of 150 U/m² per day divided BID.

All three studies show a response rate 87 percent and higher, with a total number now of 60 patients at this dose providing additional confirmatory data to the randomized trial which had 15.

In the lower dose ranges, you will see that, at the lowest doses used, response rate, as described by Dr.

Trapnell, in the 42 to 48 percent range, was somewhat intermediate for the higher doses, but not the recommended regimen.

[Slide.]

All these response rates are much higher than the remission rate, which Dr. Shields has previously described, and, as she mentioned, waiting for spontaneous remission is fraught with difficulty as there are significant consequences when these patients are left untreated.

The response for Acthar in all these reports are well above what can be expected based on natural history and placebo, and I would like to now show you one of the placebo trials.

[Slide.]

This is the data from Appleton, et al., which was one of the pivotal trials submitted for the vigabatrin infantile spasm approval. It's is a similar population of children, and I would like to focus on the placebo arm, which would have a mixture of cases with valuable time to diagnosis, which are quite comparable from the published literature.

You see that the placebo response rate for just

spasms is 10 percent, but for the more stringent no spasms/no hypsarrhythmia, it is only 5 percent, well below any of the Acthar dosing. I would add that if one looks at the vigabatrin rate, which was just approved, it is 25 percent for the no spasms/no hypsarrhythmia, and the other pivotal trial in the package insert showed 15 percent response rate for the high dose, 7 percent for the low dose, all substantially lower than these Acthar response rates.

[Slide.]

What about relapse? So, the randomized clinical trial, as re-analyzed by Questcor did not permit, except for one study analysis of relapse, but those data are published in the literature for these studies, as well as the non-RCTs.

What we see is across all published studies that looked at the strict remission criteria--because if you don't, you have a higher relapse rate because they were not truly in remission--the relapse rate is 15 to 20 percent. This is regardless of which regimen of Acthar was used, and, in fact, regardless of whether Acthar or prednisone, if you get these patients into remission, no spasms/no hypsarrhythmia, there is a 15 to 20 percent relapse rate,

and that is similar to what is reported with other drugs when you achieve this remission.

[Slide.]

Acthar therapy in the literature is associated with favorable outcomes, with a high response rate, a lower incidence of later epilepsy, and improved cognitive outcome, although none of these data are going to be from randomized clinical trials, but all from cohort studies.

Acthar is the only drug treatment for which long-term outcome measured in decades are available and have been published from the Finnish Infantile Spasm Group.

IS patients treated early have a higher rate of response and a lower rate of relapse and subsequent epilepsy in the cohort studies that have examined it, although these are not RCTs since we do treat as soon as they arrive, so these are really intra-cohort analyses of response rate based on time to treatment.

Finally, in cryptogenic cases treated early, there is a high rate of long-term normal outcomes defined as no epilepsy and normal intelligence in later life with five or more years follow-up.

[Slide.]

What about adverse events? Well, the reported adverse events are really representative of the steroid class. There was hypertension in variable rates. If you give Acthar long enough, a very high proportion will develop hypertension. Irritability is very frequent. Infection occurs in a significant minority, and again longer treatment times with all steroid class preparations and certainly including Acthar will result in a higher rate of infection.

If you give this drug long enough, eventually they will all look Cushingoid, which reverses when treatment is discontinued.

Finally, on imaging studies an appearance of brain shrinkage has been reported, which reverses when the drug is withdrawn. This is not thought to be atrophy, but thought to be changes in water content of the brain, resulting in this picture. It is not unique to Acthar. It is seen with steroids as well, and not unique to infants with infantile spasms. It has been reported with patients treated for renal disease and other causes with steroids.

With over 50 years experience, while the adverse events of steroids in general, and Acthar in particular, are certainly not to be dismissed, there are no unexpected side

effects, and these side effects are known and recognizable by clinicians.

[Slide.]

In conclusion, in the United States, Acthar was and continues to be the clinical standard of care for the treatment of IS based on more than 50 years positive experience and the literature with both randomized clinical trials and cohort studies supporting a high level of efficacy.

The best reported efficacy results for Acthar in RCTs and cohort studies is with the regimen of 150 U/m² per day divided BID. This regimen was also well tolerated in the RCT, the two cohort studies and the safety studies, and has the additional advantage of being one of the shorter proposed regimens which we would think would minimize adverse-event potential for this type of medication.

Thank you.

I will turn over the podium to Dr. Michael Duchowny, who will be discussing potential limitations.

Thank you very much.

Potential Limitations in sNDA Studies

and Current Treatments

DR. DUCHOWNY: Good morning.

[Slide.]

My name is Michael Duchowny. I am a practicing child neurologist and Director of the Comprehensive Epilepsy Center at Miami Children's Hospital.

I have been involved in the care of children with epilepsy for almost 30 years, and working at a tertiary children's hospital, I have personally treated over 100 children with infantile spasms.

My role today is to present my perspective on the potential limitations of the sponsor's NDA for Acthar in infantile spasms.

[Slide.]

These are my financial disclosures. However, I have no financial interest in the outcome of this meeting.

[Slide.]

As most of you know, there are well-accepted criteria for demonstrating adequate efficacy. There must be a replicated, well-controlled or single well-controlled study with confirmatory evidence, and the pivotal efficacy study should utilize methodology as shown here.

While most of these points have been

satisfactorily addressed today, three are underlined. Each represents a potential limitation in the NDA submission. Let's talk about them.

[Slide.]

Regarding the potential limitations related to efficacy, there is only one well-controlled clinical study using the recommended regimen.

Secondly, with regard to study size, the pivotal study enrolled only 29 patients, 15 on Acthar, and 14 on prednisone.

Lastly, in relation to treatment duration, patients were evaluated only once at two weeks after the onset of therapy.

We will focus first on the issue of a single clinical trial.

[Slide.]

From a clinical perspective, Study 01 was a straightforward parallel-designed study. As was stated in the FDA briefing documents, Study 01 should almost be considered double blind.

It should also be emphasized that the pre-defined sample size had no dropouts throughout the duration of the

study.

Thus, in my opinion, Study 01 was an adequate and well-controlled pivotal trial.

[Slide.]

Furthermore, the confirmatory studies provide additional evidence for efficacy. Study 05 is a supportive efficacy study, and there are two non-RCT cohort studies by Carter Snead that confirmed the response rate of 87 percent reported in the pivotal trial.

We can add other supportive literature as presented by Dr. Shinnar and the long-standing off-label experience confirming that Acthar is effective.

[Slide.]

With respect to the size-limitation issue, the efficacy findings in pivotal Study 01 can still be considered robust. In terms of the overall response and the cessation of infantile spasms and hypsarrhythmia, all were highly statistically significant, and the treatment difference was very large.

Furthermore, the Acthar response rate in prednisone non-responders and steroid-naive patients was similar. I would add that the 87 percent of response rate

in Study 01 was remarkably similar to the response rate in other non-RCT studies with an almost identical dose of Acthar.

[Slide.]

Turning to the issue of treatment duration, I believe that the choice to measure efficacy at two weeks is both reasonable and clinically justified. An earlier measurement could miss therapeutic response, whereas, a later measurement could allow the spasms and hypsarrhythmia to continue and jeopardize quality of life.

Furthermore, there is no difference in relapse rate with different Acthar treatment regimens, and the rate is similar to other drugs. Although we do not have long-term follow-up data, the prognosis of both treated and untreated infantile spasms is well known to clinicians, and all existing data supports the need for prompt intervention for a favorable, long-term prognosis.

[Slide.]

There are also commonly accepted criteria to demonstrate adequate safety. A safety database should include an adequate number of patients and have a prospective process to capture all adverse events. It is

optimal that a portion of the safety data should be derived from blinded studies.

[Slide.]

Potential limitations in the safety data that Dr. Trapnell presented today are that it is retrospective based on data from clinical practice charts and includes only 122 patients at the recommended dosing regimen.

There are also few patients from blinded studies.

[Slide.]

However, although the data was retrospective. Information was collected from all possible parties including physicians, parents, and caregivers, the physical examinations, and laboratory values.

[Slide.]

Although only 122 patients were studied at the recommended 75 U/m² twice daily dosing regimen, there is safety data available from the entire integrated safety-summary population of 319 patients.

The dataset reveals a similar profile across all dosing regimens, and is consistent with my own safety experience, as well as other clinicians who have treated patients off-label during the drug's 50-year history.

There are also no differences in the safety profile of Acthar and other steroid classes of drugs.

[Slide.]

Admittedly, there is no data from blinded studies as the safety data was collected from unblinded chart reviews.

[Slide.]

However, when discussing limitations, it is important to also present the full clinical picture of infantile spasms as there are also significant limitations in treatment options.

Vigabatrin is the only presently approved agent for infantile spasms, and in my clinical experience does not successfully treat all patients. There is still an important unmet need for additional therapies.

[Slide.]

Finally, I think we should ask ourselves what are the limitations of not having an Acthar label for infantile spasms. The benefits of labeling include the provision of a dosing regimen based on safety and efficacy to physicians and patients, and providing information about Acthar efficacy, safety, and drug administration to all health-care

professionals and parents and caregivers.

[Slide.]

So, in conclusion, there are clear limitations in the safety and efficacy data from the existing studies. However, in my opinion, this devastating orphan disorder needs as many treatment options as possible.

Given the existing data, the limitations of existing treatment options, the advantages of placing drug on label, and the potential negative consequences of infantile spasms, it is, in my opinion, a drug that needs to be approved for infantile spasms treatment and placed on label.

I will now turn the podium over to Dr. Jack Pellock, who will conclude today's presentation.

Thank you.

Summary

DR. PELLOCK: Thank you, Mike.

Good morning.

[Slide.]

My name is Jack Pellock. I am Professor and Chair of Child Neurology of Virginia Commonwealth University.

I am here today to summarize today's presentations

regarding the treatment of infantile spasms with Acthar.

[Slide.]

My disclosures are listed here with the most relevant being in print. I have worked with nearly all companies that have developed therapies for epilepsy or anti-epileptic drugs, all monies going to the University. I have no financial interest in the outcome of this meeting.

[Slide.]

As Dr. Shields discussed, infantile spasms is a rare but devastating disorder. There is significant morbidity and mortality, which includes cognitive and physical developmental delays, of mental retardation, autism, and epilepsy.

In fact, 50 to 70 percent of these patients develop by their seizure types, but the majority developing refractory epilepsy, and 50 percent being truly catastrophic epilepsies. This is a life-threatening disorder. The mortality rate in infantile spasms is up to 31 percent with the majority, perhaps 33 percent, occurring at age under three.

[Slide.]

Acthar is the gold standard for treatment of

infantile spasms. Acthar has been used since 1958 in approximately 30,000 infants with infantile spasms. Acthar is the standard of care for infantile spasms. The AAN/CNS designation probably effective is the highest rating given to any treatment for spasms.

Acthar is presently given off-label to greater than 40 percent of infants with infantile spasms. There are no instructions, no guidance for physicians, and minimal caregiver counseling and education. Thus, although it is the standard, physicians have employed multiple treatment protocols when using Acthar.

[Slide.]

As you know vigabatrin was recently approved for treatment of IS. In my clinical experience, not all patients respond to this therapy. It also has significant adverse effects, some of which are irreversible. This is why physicians and patients need additional approved effective treatment options.

[Slide.]

As shown today, Acthar is clinically effective in eliminating spasms and hypsarrhythmia. There is a positive response in 87 percent of patients with IS.

Efficacy is defined as all or none, cessation of spasms and of hypsarrhythmia. High dose and short duration of treatment is recommended. 150 U/m² per day in divided doses of 75 U/m² given BID for two weeks followed by gradual tapering.

[Slide.]

The safety of Acthar is well characterized. As you have heard, adverse events are characteristic of steroid-class adverse events, such as irritability, Cushingoid changes, hypertension, and infections.

These symptoms are known and clinically recognizable. Adverse events are typically reversible after Acthar treatment is completed. Acthar adverse events are anticipated as with any high dose steroid regimen. They are rarely life threatening and short duration of treatment minimizes the exposure risk.

[Slide.]

In reviewing the benefit-risk balance, infantile spasms is a neurologic emergency that must be recognized and treated rapidly and effectively.

Acthar effectively eliminates spasms and hypsarrhythmia in 87 percent of patients. Best patient

outcomes follow early and effective treatment. Adverse events are clinically recognizable and expected.

I think it is fair to say that many child neurologists today would agree that Acthar benefits outweigh the risks of drug and the consequences of inadequate treatment.

[Slide.]

In conclusion, Acthar has an important therapeutic role in the successful management and treatment of infantile spasms, a devastating and catastrophic form of epilepsy.

Approval of Acthar for the treatment of infantile spasms one, provides an effective and safe recommended dosing regimen. It mitigates potential safety concerns through label directions, provides a benefit to patients that far outweighs both the risk of the drug and the consequences of inadequate therapy, increases the probability for a long-term successful outcome.

This is a rare, but devastating child-neurology emergency, an emergency to physicians, child neurologists, an emergency to parents, but most importantly, an emergency to the children afflicted with this disorder.

I ask you, the panel, to consider approving Acthar

today.

Thank you.

I will turn the podium over to Dr. David Young, who can address clarifying questions.

Clarifying Questions

DR. YOUNG: Thank you. I would like to thank the Committee for being involved in this effort, looking at Acthar for the NDA commission, and pass it back to Dr. Anderson.

DR. ANDERSON: At this point, we have the opportunity to ask the sponsor or any of the presenters for questions regarding clarification of the presentation or other issues. We discuss the questions before us later on in the afternoon, so this is our chance for people to get additional information or clarity on aspects of the sponsor's presentation would be helpful to them.

Dr. Crawford.

DR. CRAWFORD: Thank you, Mr. Chairman. To the sponsors, thank you.

Dr. Young, a few clarifying questions for anyone who could answer. I heard both yourself and Dr. Pellock say that--and probably others--that ACTH was the gold standard

for infantile spasms. Dr. Shinnar said it's the clinical standard of care, as did Dr. Pellock.

The clarification question I have is as we were shared the AAN/CNS Practice Parameters, it said probably effective. One of the latter speakers said that was the highest rating given for spasms. That is still lower than effective.

So, could you please clarify that?

If I may, a second clarifying question. As I heard Dr. Trapnell's presentation and Dr. Duchowny. Study 05, we heard in Dr. Trapnell's presentation was single-blind, yet Dr. Duchowny said it could be considered double-blind. Please help me clarify that one.

I might have the study number, I have to look at the exact one because I noticed that you didn't underline that single-blind was a problem--I am sorry, Study 01. You said it could be considered double-blind.

DR. YOUNG: What I would like to do first is can I split this in half, have two people come up, because there are two different areas here.

I would like first to ask Dr. Shinnar to come up and talk about the AAN probably effective, and then Dr.

Trapnell will follow after that, talking about the single-blind, double-blind issue.

DR. SHINNAR: The AAN has very stringent criteria in its rating of the drugs. Basically ACTH received probably, vigabatrin possibly, and prednisone has insufficient evidence for efficacy.

The rationale for probably was that the Baram trial, although considered Class I for efficacy because of the interpretation of the EEG, was by a blinded reviewer, was not considered blinded from the point of view of adverse events because the parent reporting them knew the treatment.

The rational, of course, with difficulty giving sham injections in babies for ethical and other reasons.

So, that was the reason why, in its criteria, it was probably effective because the safety data was not considered blinded.

DR. YOUNG: Dr. Trapnell.

DR. TRAPNELL: The Study 01 was a single-blind trial in its design and that the EEG reader, as Dr. Shinnar just said, was blinded. The reference to the double-blinding was actually from language used in the FDA's briefing document to describe the study, saying that because

the infants themselves did not know what they were receiving as far as treatment, but the patient classically was double-blinded even though the caregivers and the patients and the parents were not.

DR. GARDNER: Dr. Young, a good case has been made for early identification and early initiation of treatment, and I wondered if you could tell me what the sponsor's strategy would be beyond clarifying guidance in the approved labeling to improve recognition and early initiation of treatment.

Who would be the targeted audience for messages and how might you go about that given the rarity of the condition and the geographic spread?

DR. YOUNG: We actually will be targeting multiple populations. This is our preliminary plan in terms of physicians and nursing and health care professionals. So our desire is to make sure that the health care professionals understand the diagnosis, understand how to diagnose it, et cetera.

So we will be providing brochures, monographs, speaker programs, et cetera, and this will be for a wide variety of again physicians and nurses and caregivers.

But besides that, something that is also important, of course, is the parent. So, we will have a program for parents, and again this would be documents that would be given to parents, handbooks, et cetera.

But I think really what you are asking is how is that parent who sees their child have these things occur, all of a sudden is going to know what this is.

So, part of that educational process has to be involved with making sure that there are websites, the websites are appropriate. Nowadays, we always go to the Internet and look at what has happening to our children.

That has to occur, and we will have programs in that type of area. So, that is one way. The other way, of course, is again, when they go to pediatricians, we will have the websites and active information, which they then can refer and understand more about the diagnosis and treatment.

DR. KATZ: I have a lot of questions, but I will ask one now. The determination of spasm free and, of course, resolution of the EEG were made at specific points in time in the study or various points of time in the various studies.

So, it is sort of a snapshot at a particular moment. I am wondering, was there any attempt to capture spasms by the parents or the caregivers during the trial either before or after the initial video-EEG? Were there diaries kept at all, or is all the information we have about spasm occurrence only at the point in which the video-EEG was done?

DR. YOUNG: Dr. Trapnell, could you address that, please?

DR. TRAPNELL: In Study 01, parent diaries were kept on a daily basis, so we have that information only from the publication. We were not given access to that source data. We do know from the data that we did obtain that there were data in what we received showing what the parent response was.

In general, it was between about three and seven days for the patients who were treated with Acthar and with prednisone who did respond to treatment.

We do not have any parent information data following the two-week assessment in that study.

In Studies 05 and 04, we do not believe there were parent diaries although we do know from the clinical charts

and from the study charts there are notes from the parents where that is reported and recorded in the chart. But that was not collected in a systematic way.

DR. KATZ: Just a follow-up. So, in Study 01, where there were diaries, how did the response, the spasm count by diary jibe with the response on the Video-EEG?

DR. TRAPNELL: In the parents who responded that the patient had stopped having spasms, I believe all of those were confirmed by video-EEG. I would have to go check that to be sure that is 100 percent correct, but I believe that is correct.

DR. ANDERSON: Keep signalling if you want to ask a question and we develop a list. So I try to go a little bit in order as people sort of raise their hands. So, Dr. Lu.

DR. LU: I have several questions, I hope that's okay. First of all, I have a question about all the review is based on the published literature, and the drug has been used since 1958.

Is there a mechanism that is actually tracking all possible trials, because we all know that when, you know, published in the journal, oftentimes it is positive studies,

and get better chance to be published, as well as maybe the first time of those kind of studies. So, for that, we usually phrase publication bias.

So, if we base only on published data, where it self, we have a biased population, and how does the company address that?

The second question is you mentioned it is almost impossible to conduct another prospective, well-controlled clinical trial. I would like to get more information on that because right now you tell us that average is 600 to 700 patients on this active drug based on last two years' data, and you claim the response rate is about 86, 87 percent. We know even vigabatrin, an approved drug, and you claim that is between 15 to 26 percent response rate and it has been in the market.

So, for sure and that is the case, I can't see why it's so hard to conduct another prospective trial against vigabatrin and for the total response. So, maybe you can elaborate a little bit more for that.

Now, the other question also is more technical question. For the Study 01, do you have the original protocol, what was the original design, and the sample size

calculation, what was the original hypothesis where the results actually confirm their hypothesis or the result was just different, because I can't find from your material.

There is also another study by Toronto. It's open-label, but it's a randomized study. It's very small sample size. Out of one Acthar, three patients received Acthar, one of them have total response, and vigabatrin, they have six patients receive and have three responders.

So, the result is 2006, and it is not listed in your material, but it was listed in the FDA's material.

So, I wonder how do you comment on that?

So, the last question is for the safety data.

DR. ANDERSON: Dr. Lu, I will let you ask your questions, but so that we can kind of keep track of them, as well, maybe we can take them sort of a little bit more step by step, so we don't have to remember each of them in order.

The first one was what the sponsor had done in terms of tracking unpublished negative studies, because of the publication bias. So, let's take that one first.

DR. YOUNG: I am going to have to be calling different people up here, so you are going to notice I am going to be moving around here.

With regards to the publications, I am going to ask Dr. Shinnar, who knows much of the publications, involved a lot of reviews of publications, as well as knowing a lot of the studies to address that one.

DR. SHINNAR: Although the drug has been around since '58, Video-EEG, which is what we use typically now to confirm really dates to the '70s, so earlier case reports and stuff, we don't necessarily include.

We do believe we have captured all the RCTs. It is a rare disease, and to do something with Video-EEG is costly and expensive, and within the child neurology community, which is fairly small, you would at least hear about it.

In fact, the lack of the study against the low dose Acthar, this is prednisone, was published as a negative study, so we do believe that there are no other studies. The study you referred to in Toronto was actually a synthetic formulation. It is the Ascalan study, which Dr. Young has already mentioned. We only included Acthar studies as I noted also in my review, and not the synthetics.

DR. ANDERSON: So, then we had another question

regarding what would be the challenges of doing an additional study given the large number of individuals treated every year, perhaps with vigabatrin as a comparison group.

DR. YOUNG: What I would like to do is ask Dr. Pellock to come up and address that one, please.

DR. PELLOCK: I think the formidable challenge in designing that trial would be sham injection. I don't think any of us would want to or could get that through an IRB. I really think that would be an unethical trial.

In order to do a truly double-blinded trial, the design would have to include that, I would believe.

The other thing is your total numbers of spasms that present per year, and might be treated with Acthar, not all of them are treated that way, and comparative trials, although clinicians find them very useful, I think for registration purposes are usually not sufficient.

So, that is why I certainly believe, and having participated in trials where, in fact, other drugs have failed, this is a really, really, really tough population, and if you can get one child enrolled every couple months with multiple, multiple centers going, perhaps up to ten,

you are doing a very good job.

So, this would be many, many, many years. The design is very difficult, and the ethics of treating people with what you might not think is the best therapy is a challenge.

DR. ANDERSON: We will take one of the other questions and then I would like to give some of the other people a chance, and then maybe come back to your subsequent questions, but there was one other one which was addressing the 01 protocol, original sample size calculations from the original protocol.

DR. TEMPLE: Could I just correct one thing? A comparative trial in which you beat the other drug is a perfectly successful trial for registration. Don't have any illusions about that. Non-inferiority trials are difficult, but winning in a comparative trial works just fine. So, don't worry about that.

DR. YOUNG: Thank you.

Dr. Trapnell.

DR. TRAPNELL: When we got in touch with Drs. Baram and Mitchell about Study 01, the original protocol was no longer able to be found, so what Drs. Baram and Mitchell

both did is they sat down with us and reiterated the protocol to the best of their recollection, so that we could at least document that for use in our analysis.

Their planned study size was 16 per arm. I do not know what their statistical hypotheses were to justify that number.

DR. ANDERSON: I am going to keep going with the question session until about 10:15. Then, we will take a 15-minute break, and then we will have more chances for clarifying questions after we come--actually, I guess we will go until about 10:30 before the break, but then we will still have more chances for questions if people feel like they are not getting an opportunity.

I just want to let everyone know what I am doing here. So Dr. Dure is next on the list.

DR. DURE: Thank you.

I have a question about the dosing regimen, and a number of references have been made to the CNS/AAN Practice Parameter where it pretty clearly states that the evidence is insufficient. So I am curious to know why the dosing regimen is being so strongly proposed especially in light of the fact that the other studies, the Hrachovy studies were

once a day dosing, and those are considered confirmatory.

From what I read here in the briefing documents, the pharmacokinetic data from Snead suggests that there is a fairly short half-life here. So, I wonder why we are not considering a study to look at dosing regimens. It is not clear to me that this has been adequately explored.

DR. YOUNG: Let me answer part of that and I will ask Dr. Shinnar to come up some of it, too.

With regards to the half-life, the half-life with the modified release dosage form is approximately five and a half, six, hours. We know that giving the drug twice a day versus once would result in a different accumulation. The twice a day would result in a more sustained concentration both in the plasma, as well as the tissues, et cetera., so there is definitely a difference of what occurs between the once a day dosing versus the twice a day dosing.

DR. DURE: Right, but it is not so much that, I understand that part, but does it have to be 75 U/m^2 . I don't think that has been adequately addressed in terms of twice a day.

DR. YOUNG: With regards to the dose twice a day, what Shinnar showed was again that we had the highest

response rate in an experimental study, RCT, and I will let him talk further about that.

DR. SHINNAR: The AAN Practice Parameter has some very strict guidelines and. in order to make the statement that you know something, that requires a double-blind RCT. So, since the recommended dose has not been compared head to head--it was compared to prednisone, shown effective, but not compared head-to head--to another dose. From the point of view of a Practice Parameter, the AAN, one could not make the statement that you have defined.

What our statements were based on, including my own, is that you do have one positive against a comparator, and that the reported efficacy rates for the recommended dose are consistently higher than those for other dosing.

A comparative efficacy trial, when something is 50 percent effective versus 80 or 90 percent effective, will require a very substantial sample size because they are both effective drugs. But if you are talking about which dose you would recommend, the highest observed dose-response rate that came out of the positive pivotal trial is often what is used. But are there randomized clinical trials demonstrating clearly this dose against all other doses?

No, there are not.

DR. YOUNG: Could I add to that? Questcor does not want to put forward that this is the best optimal only dose that is effective and safe. That is not what we are trying to do, and we don't believe.

What we are trying to say here is that this dosage regiment is effective and safe. It is an effective, safe regimen.

DR. ANDERSON: Ms. Vega.

MS. VEGA: Yes. My question is regarding the prospective study where you look at retrospective data to look at the safety.

How was this data collected? Did you have--I know two people reviewed the medical charts, the doctors, but were they collecting data in the same charts, or was there inter-rater reliability done, or a pilot period phase to see the data before you went into the full study? What was the prevalence of missing data or, for that matter, missing charts?

I am not sure if this was electronic medical records or paper charts.

DR. YOUNG: I will let Dr. Trapnell address that

one.

DR. TRAPNELL: So, at each site, there was, first of all, a very significant effort to identify the charts. They were looking at the diagnoses codes, pharmacy records, clinic records, any access, any data or ways that the investigators could identify the charts was done, so we feel that was a very thorough look to make sure we had all the charts to start with.

Once we got the charts, there was a very extensive effort to look at all sources of the data from clinic notes, hospital records, emergency records. We really tried to get a comprehensive set of data for each patient and then, once that was done, those data were gone through to try to pull out as much data as we could identify.

We are very confident that we did get as much of the safety data that we could find. We are particularly confident that we clearly identified all SAEs and any patient deaths in those data that we had for the patients.

DR. ANDERSON: Did that get your question about the reliability and comparing the raters, and those sorts of things?

MS. VEGA: No.

DR. ANDERSON: I think that was also part of the question was the actual mechanics of the review.

DR. TRAPNELL: You know, it was a challenge obviously, because it was from clinical-care charts, and it was from data that was not collected in a systematic way for each patient. You know, it was basically how the patients were care for.

So, again, we did everything we could to be sure we got all of the data that was available, but it was certainly different amounts of data on the patient-by-patient look.

DR. ANDERSON: So, when you say "we," do you mean your employees were doing that, or you mean the physicians were doing it and then giving it to you?

DR. TRAPNELL: Right. It was the investigators. They had staff that were entering the data into CRFs, just like you would traditionally do for a study, and then that data was confirmed by a monitor, and then a second monitor confirmed that data, as well.

DR. ANDERSON: Dr. Khanna, you are next.

DR. KHANNA: Thank you.

What is the presumptive mechanism of action of

Acthar to relieve or ameliorate infantile spasms?

DR. YOUNG: We actually don't know the exact mechanism of action. That is unknown. There is a lot of hypotheses, different hypotheses, but we don't know the exact mechanism.

DR. ANDERSON: Dr. Pearl.

DR. PEARL: Thank you.

I have a couple of points, if I could, of clarification from the sponsor. I think it was Dr. Trapnell who said that the IRB did not allow access to the source data for Study 01. Could you clarify that that only applied to that study, and how did that affect, in your opinion, your collection and analysis of the data? Are there are corrective strategies that might need to be entertained because of what data was available to you?

If I could go on to my other points, which are short? If you could clarify the tapering schedule. There was something in the documents, that I think the plan was to go from 150 U/m², after two weeks rapidly to 30, and then going down every three days, if that could just be clarified, and what is the rationale for that.

The third thing is, in reality, hypsarrhythmia is

not always a definite call, and Calloway and Hrachovy and Colleagues defined at least six forms of modified hypsarrhythmia. Is there going to be any attention paid in the potential labeling from the company and education for physicians about inclusion or classification of the various forms of hypsarrhythmia?

DR. YOUNG: I will ask Dr. Trapnell to address a couple of these, but let me address the last one in terms of what the company plans to do.

Within our educational material, we realize we are going to have to make sure that in terms of diagnosis that every physician understands what we are talking about, and so within the educational material, yes, there will be.

Within the label, that is a little harder to do within the label, but within the educational material, we definitely will be doing that.

With regards to the first two questions, I will ask Dr. Trapnell to address the first two questions.

DR. TRAPNELL: So, the HIPAA and IRB issues affected two studies: Study 01 and Study 02. Both were from the Children's Hospital of Los Angeles. Please know that we asked several times if we could try to get to the

source data, and were told no each time.

The IRB was unwilling to give us access because, from their perspective, these studies were not designed to be reviewed by a drug company, and so, therefore, they felt that was not the appropriate thing to have done, so that is why we couldn't get it.

So, the data that we had from 01 was actually from the Investigator database. It included some of the key demographics, the outcome responses, and some of the other study information, and that is what we had to use for the analysis.

Study 02, we actually had the study-specific forms that had been designed by Drs. Partitian and Mitchell. They designed the forms and they were the ones who then pulled out the data from the clinical charts onto these forms that were anonymous as far as patient identifiers, and those were endpoints of safety that were of interest to them, and they are patients who they treated with IS.

That was the data that we had in order to do our analysis. So, we actually did, we felt, the most we could do with the data that we had for both of those two studies for the analysis of those.

DR. YOUNG: In terms of the other studies, 04 and 05, we had study charts.

Was there another question?

DR. PEARL: A clarification on the taper and rationale.

DR. TRAPNELL: The taper that is being recommended is one of the possible tapers in the proposed label. It is actually the taper that was used in the Baram 01 study.

DR. ANDERSON: Dr. Green.

DR. GREEN: I would like to know how far out in any source or form do we have objective relapse data.

DR. YOUNG: Are you talking about within all the literature?

DR. GREEN: In any form, any source. Objective relapse.

DR. YOUNG: Dr. Shinnar, could you address that?

DR. SHINNAR: The Finns actually were the first to use Acthar, and Dr. Liukkonen has published outcome 20 and 30 years out in a cohort of over 100 children with IS. There are no late relapses to spasms, so children can develop partial seizures several years later. Other cohort studies are followed for up to five or six years including

the Lombroso one. So, they are not from the RCTs, but there is extensive literature in the population-based manner and from Finland on the natural history of the disease.

DR. GREEN: Yes, but the question is how does that relate to treatment. Do we have any late recurrence data following treatment?

DR. SHINNAR: I am talking about children who were treated. These were all treated with Acthar.

DR. GREEN: Okay, I am sorry. Thank you.

DR. SHINNAR: Just not an RCT.

DR. GREEN: Gotcha.

DR. ANDERSON: We will get to everyone. We are up to Dr. Frank now.

DR. FRANK: Thank you.

I have two questions. The first is that Acthar is derived from porcine tissue and so from a safety perspective, can you address what is being done to minimize risk of any porcine-related diseases like retrovirus or minimize immunogenic porcine proteins in terms of transmission to humans?

The second question I have is that a once daily dosing usually means morning, twice daily, morning and

evening. But there is an endogenous circadian rhythm to all hormones and steroids.

Is there any benefit to BID not being morning and evening in terms of side effects or efficacies, or any data to suggest that timing of Acthar may have an impact on safety or efficacy?

DR. YOUNG: With regards to the first question, the manufacturing procedure that we have in place now is one that the FDA has looked at and looked at the GMP issues, as well as agreed on the process, et cetera.

With regard to the specifics of viruses, et cetera, can I get back to you on that? I am not the CMC person. I will have to talk to somebody with regards to that what processes are taking place.

The second question was timing of dosing I believe with regards to circadian rhythm and things like that. That actually hasn't been studied in RCTs or studies that is not well established, so we do not have any information on that.

DR. FRANK: And timing in the studies that were presented, was that looked at, or is it not documented well enough?

DR. YOUNG: Well, we didn't look at it to analyze

it differently. It's documented, but we did not analyze the timing issue; no, we did not.

DR. ANDERSON: We have come to you, Dr. Clancy.

DR. CLANCY: I would like to pick up on a question that Dr. Pearl touched on regarding the EEGs. I will make my clarifying question in a second.

The EEGs play a central role in all of these studies. They define who is admitted into the study, and they define what success is, and yet the two key studies have very different variables for the EEG.

For example, in the Baram study, to get into the study there was 24 hours of EEG, and in Rick Hrachovy's it is up to 24 hours, it is not really clear. That's a difference.

In Dr. Baram's, there is one reader who is blinded, but we don't know if the reader knew the sequence. This is pre-treatment and post-treatment.

There is no statement in Dr. Hrachovy's study of who read the EEGs and were they blinded, did they know the sequence.

Dr. Baram admitted patients with hypsarrhythmia and variants, and Hrachovy only said hypsarrhythmia. The

most key problem that I have is that what does it mean to have resolution of hypsarrhythmia? Were there criteria? Were there voltage numbers? Was it fewer spikes? We don't know that. We also have no idea how much agreement there might be between a reader in Texas and a reader in California, so there has to be a lot of skepticism about how comparable these two trials are.

Now, I know Dr. Hrachovy covets, loves his EEGs. Those tests may still exist. My question was, was there any attempt to resurrect those recordings and independently review if someone else felt that yes, indeed, this was hypsarrhythmia, and yes, indeed, there was improvement or resolution of the hypsarrhythmia.

DR. YOUNG: Dr. Trapnell.

DR. TRAPNELL: Unfortunately, in most cases, and most to Dr. Hrachovy chagrin, all of the EEG tracings were lost in a flood during Hurricane Agnes. The only thing we have are the actual reports of the EEGs which, if I am remembering correctly, they were all signed by him, so I am assuming he was the reader of most of the EEGs for the two studies from his site

DR. CLANCY: Do you know if he was blinded or not?

DR. YOUNG: He was blinded.

DR. TRAPNELL: Yes, he was blinded to what he was reading as far as treatment, yes.

DR. ANDERSON: Dr. Mizrahi.

DR. MIZRAHI: I have a question concerning the request for indication. The request is to reduce or eliminate spasms and hypsarrhythmia. All of the data suggests an all or nothing response.

So my question is why ask for an indication for reduction of spasms and hypsarrhythmia rather than just elimination, which is one of the options requested.

DR. YOUNG: That is a very good point, and in some sense when we first put this together, we viewed the elimination as a form of reduction to zero. But that is a very good point. It just as easily could be an elimination versus a reduction.

DR. MIZRAHI: Because I guess just reduction would be considered a treatment failure.

DR. ANDERSON: I don't want to let your other question jump the queue, but do you want to respond to this one, Dr. Katz?

DR. KATZ: Yes, from the point of labeling, I

think we have to decide what we think is the critical outcome to be measured and by which we will assess whether or not the drug is effective or not, and I think there is sort of general agreement that is the sort of all-or-none criterion

So, typically, in an indication were this to be approved, we would say something like it is approved for the treatment of infantile spasms. We wouldn't particularly mention in the indication what the particular parameter was that was used to determine that.

We would describe what was one else in labeling, but the indication for a condition is typically this is the treatment for infantile spasms in this case. So, it is likely not to--if it were to be approved, the outcome is likely not to be mentioned in the Indication section.

DR. ANDERSON: Dr. van Belle.

DR. van BELLE: Thank you.

This is a very unusual case as far as I am concerned. I have questions about both the context and the content of the application.

With respect to the context, the applicant mentions a Type 3 meeting with the FDA. I would like to

know what was discussed at that meeting and, specifically, was there agreement with the FDA about what would constitute the primary endpoint for the re-analyses. I am just trying to get my handle on what was really agreed to by the Agency and by the sponsor.

Thank you.

DR. ANDERSON: Maybe that is a question for the FDA.

DR. KATZ: I think you mentioned it or someone mentioned it, do I think we agree that looking at the proportion of overall responders as defined by complete cessation of spasms and resolution of the EEG.

I think we agreed to that based on the perception in the field that that really is what counts for a treatment for a spasm. Reducing spasm wasn't really what people wanted or felt was particularly useful in this condition. People thought that complete cessation of spasms and resolution of the EEG was what really would be the standard by which you would judge a treatment to be effective.

DR. ANDERSON: And you had a content as well as context question?

DR. van BELLE: I will only ask one question at a

time.

DR. ANDERSON: Well, go ahead, take your second one here. You have earned it. A lot of other people took two. Do you want to go ahead and get your other in?

DR. van BELLE: No.

DR. ANDERSON: Dr. Snodgrass.

DR. SNODGRASS: Hello. Thank you.

I do have a couple of questions. One is very sort of basic pharmacology. Is there any data available to compare, when you are comparing ACTH dose 150 per day or 35 BID to the 2 mg/kilo prednisone, is there any data to compare, let's say, the area under the curve for the glucocorticoid effect or the ACTH--that is, the rise in cortisol to--let's say, the prednisolone levels and its cortisol-like effect in terms of actual--since there seems to be a difference at this dose of 75 BID in efficacy compared to the efficacy of the prednisone, are there equivalent glucocorticoid effects meaning that there is some other mechanism for the ACTH. So that is one question.

The other relates to if this were to be approved, is consideration for postmarketing ideas regarding stratification of patients--this has been alluded to by

others--if it's not classic hypsarrhythmia, but it's some variant, how would those be classified, and should there be some postmarketing efforts to look at the difference in response or some other biomarker or maybe there is genetic data that might be available.

DR. YOUNG: For the first question on the glucocorticoid effects, I would like to ask Dr. Miller to step up and address that one, and then the second one, I will ask Dr. Shields to address that one.

DR. MILLER: Good morning. My name is Walter Miller. I am Professor of Pediatrics and Chief of Endocrinology at the University of California/San Francisco.

With respect to the profile of cortisol after the administration of ACTH, there are extensive data for Cortrosyn, the synthetic intravenously administered form. There are no data showing 24-hour profiles after the administration of Acthar.

The question essentially presumes that the mechanism of action of Acthar is glucocorticoid mediated. In fact, we know is that when you administer ACTH, it will stimulate a wide variety of steroids from the adrenal cortex, and we have no reason to presume that it is cortisol

as opposed to any one of 50 other steroids that may be emerging from the adrenal.

Similarly, it is entirely possible that the ACTH is working centrally as well as via the adrenal.

If I might return to one of the previous questions about the administration BID versus once a day, I would wish to point out that in infants, the diurnal rhythm of ACTH and cortisol is typically not established until about nine to 15 months of age, so it is not nearly as germane an issue as it would be in adult practice.

Thank you.

DR. YOUNG: With regard to the stratification arm, I will ask Dr. Shields.

DR. SHIELDS: The issue of hypsarrhythmia is a difficult one, and kind of presented as though it is some kind of monolithic thing, which it clearly is not. It is a much more complex issue than one we would have time to present here.

But I think the way to look at this is infantile spasms is a clinical and electrographic diagnosis, and you need to see the clinical symptoms and then electrographic diagnosis. Hypsarrhythmia incursion may be two-thirds of

the patients, but there is some variation on the theme in the other one-third of patients.

Most of us think of patients that come in--even if they have one of the variations, we think of them exactly the same way as far as treatment is concerned as if they had, you know, the classical hypsarrhythmia pattern, so I don't really think of them in a different way. They get the same approach, the same treatment, the same evaluation.

DR. ANDERSON: But I think the implication of the question was whether the company had any intention of sort of surveying or postmarketing monitoring to try to determine whether those different categories might, in fact, respond differently to the therapy.

DR. YOUNG: At this time, we have not considered that, but, of course, would be amenable to discuss that and absolutely consider whatever is necessary that the FDA feels we need to do.

DR. ANDERSON: We will get the FDA's comments on this and then I will have us take a brief 15-minute break, and then we can cycle through another round of questions after we come back.

DR. TEMPLE: I just had one question. Is it known

whether peripherally administered ACTH actually gets into the brain?

DR. YOUNG: There is a publication in the late '70s that states that approximately 1 to 2 percent does get into the central nervous system, yes.

DR. TEMPLE: So, that's not much to be part of the mechanism, is it? But who knows?

If you will all look at your watches, we will resume again in 15 minutes for some more clarifying questions.

Clarifying Questions (continued)

[Break.]

DR. ANDERSON: Before we begin with general questions, the sponsor has informed me that they do have a specialist here who could address questions in terms of the company's approach to some of the hypsarrhythmia and hypsarrhythmia variant questions.

The question I have for the Committee, do we want them to address that further, those who raised questions regarding variability? Okay.

So, Dr. Young, could you bring up your speaker, please.

DR. YOUNG: Dr. Duchowny.

DR. DUCHOWNY: As someone who is board certified in EEG interpretation, I just wanted to respond to several questions from Dr. Pearl and Dr. Clancy about the diagnosis of hypsarrhythmia and the EEG.

I would like to make three points in response to the questions.

The first is that from an EEG standpoint, the pattern of hypsarrhythmia is one of the most clear-cut EEG patterns that we have. This is a highly abnormal EEG and in most laboratories, it would be diagnosed as hypsarrhythmia by EEG by people trained in the interpretation of EEG.

Secondly, it is true that not every EEG of a patient with hypsarrhythmia or with infantile spasms has all of the features of hypsarrhythmia and, as a result, other terms, such as pre-hypsarrhythmic or modified hypsarrhythmic EEG have arisen.

From a clinical standpoint, once the infant is having infantile spasms, I think it's a clinical judgment whether to initiate treatment. But we have all seen that EEG pattern evolve from so-called pre- or modified hypsarrhythmia in a very rapid period of time and, given the

devastating consequences of the disorder and not applying prompt therapy, it's a clinical judgment. But I think most clinicians would probably elect to initiate treatment.

Thirdly, with respect to the sampling time at two weeks, it is possible that, if you don't sample subsequently, in theory, you could miss a hypsarrhythmic EEG that recurred. In practice, the hypsarrhythmia return is almost always associated with infantile spasms, and this would be occurring in families who now are quite educated on what the clinical appearance of infantile spasms are and the importance of prompt treatment.

DR. ANDERSON: I think the next person who hasn't had a chance yet is Dr. Chapman.

DR. CHAPMAN: My question is sort of more of a practical question. Whenever I start patients on ACTH, I always sort of put them on GI prophylaxis, because of placing children on steroids.

Is that something that your company is going to recommend or going to discuss at all? It's not in the safety data, because--I mean don't think children tend to get them very often, but I know I have always placed them on it, so is that something you are going to recommend?

DR. YOUNG: Could I have Dr. Shinnar address that issue.

DR. SHINNAR: This has been a valuable clinical practice even within our own institution. I personally don't. The clinical trials have not utilized it. In reality, if you look at this clinical context of utilizing steroids for a short period of time, the incidence is extremely low, and I think this would be one of those that we would consider clinical judgment rather than evidence based support either way.

DR. ANDERSON: Dr. Cohen hasn't asked a question yet. Why don't we go to Dr. Cohen?

DR. COHEN: I promise only one question, no follow-ups.

As an adult neurologist, but early in my career I, probably to your chagrin, did pediatric neurology as well and it was always my take on things that the treatment of infantile spasms with ACTH is really not that people do deviate kind of from the dosing recommendations that you are making.

So, I guess what I am trying to say is postmarket, is this too restrictive what you are doing, will this change

over time postmarket and just some discussion of that.

DR. YOUNG: What we are proposing is a regimen that we have documented through an RCT efficacy and safety. So, that is what we are proposing. We realize that physicians may deviate depending on their clinical practice and their clinical evaluation of the patients.

We understand that and that happens with all medications. So, we are not too concerned about--we don't have any desire to take that out of the hands of the physician. But in terms of our submission to the Food and Drug Administration, we believe that this is a regimen that works, is effective and is safe. That is our approach here.

DR. ANDERSON: I am going to keep going with questions up until 11 o'clock, but at that point we have our outside speakers, our open speakers scheduled, and I don't want to delay them, who have made arrangements to come. So we could then resume later on any remaining clarifying questions, so I will keep going up until 11:00.

Dr. Twyman is next on my list.

DR. TWYMAN: On the same track, you know, given the catastrophic nature of inadequate treatment, and with guidance through labeling could be quite helpful with regard

to trying to point to an effective dosing, do you have an idea, at least currently and in practice, what doses are actually used and what dosing paradigm and over what treatment period is actually being used today?

DR. YOUNG: We do have some information on that. There have been surveys done where we have information of what people are using. But everything we have is survey anecdotal, no formal investigation type of work. The dosing regimens, categories that Dr. Trapnell put up there, those general categories, is the general types of doses and regimens that are being used.

DR. TWYMAN: Yes, but is it typically in the 75 BID range, or is it lower, and is it typically less than two weeks or greater than two weeks?

DR. YOUNG: It varies across institutions, training, et cetera. Dr. Duchowny might be able to touch base briefly on some of the things that he has seen throughout.

DR. DUCHOWNY: On personally surveyed members in two pediatric neurology departments that I have been part of about their practice of treatment of infantile spasms, and what is remarkable is that the range even within the same

institution is really quite variable.

I think the positive benefits of having at least a clear indication in terms of a treatment regiment is definitely a positive, because I think the range is really too variable to make any statement about what is common practice.

That is one of the major issues that exists today.

DR. ANDERSON: I will get Dr. Lesar next and then Dr. Katz, and then we will take our speakers, so Dr. Lesar.

DR. LESAR: This is a question about the patients in 01 and 05. There was an imbalance in the male to female ratio by my count. In the two studies, 16 out of 39 receiving the recommended dose were male, and the opposite ratio for those receiving the comparator.

I wonder if further analysis was done and if there is anything to inform us on those, that imbalance and its potential effects on the outcomes of those studies.

DR. YOUNG: I am sorry, I am hearing an echo over here.

DR. ANDERSON: I think the question had to do within 02 and 05, if you looked at the two different

treatment groups, there was a difference in the male to female ratios between the two different treatments, sort of between, for those two studies, and if we could have some additional comment on the implications of that gender imbalance or whether there was an implication.

DR. YOUNG: Dr. Trapnell, could you address that, please.

DR. TRAPNELL: Yes, we did note the same imbalance. We don't think that has any clinical significance. We did analyze the 01 study by gender, and the results are shown here on this slide.

[Slide.]

The overall response. Again, as you can see on the green bars, that is the overall response for all patients, and the females and males are shown for the Acthar, 75U/m² BID on the left, and on the right, for the prednisone 1 mg/kg BID dose.

So, again, these are the results by gender for Study 01, which is the primary study in the NDA.

DR. ANDERSON: Dr. Katz, do you want to ask another question?

DR. KATZ: Yes, thanks. I want to follow up on a

question that Dr. Green asked and Dr. Shinnar responded to briefly. I don't expect--we have a minute until the open session--so I don't expect an answer now, but maybe it's something the sponsor could work on maybe over lunch, and we can talk about it in the afternoon.

It has to do with relapse. I think Dr. Shinnar said, well, you know, the Finns have long-term information on relapse, but I think it would be useful to hear some of the specifics.

The sponsor is proposing a two-week treatment regimen. The implication is that for some period of time after that--at the moment I don't know what the period of time is--that the spasms are eradicated. I don't know if that is supposed to be for six months, a year, two months, so, information about what the actual relapse response is in some reasonable period of time after a two-week treatment.

I know this data doesn't exist in the controlled trials, but if there is data somewhere that speaks to the specific regimen that is being proposed, and in the near term--and useful in the far term, too--but in the near term what actually is the relapse response rate, and some specifics about what those data are I think would be useful

to us certainly.

So, I don't expect an answer now, but maybe we could, in the afternoon, get some more details about that.

DR. YOUNG: We will do some homework at lunch.

Open Public Hearing

DR. ANDERSON: We are going to begin moving into the open public hearing session. I have some text that I am supposed to read to begin this.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or

other expenses in connection with your attendance at the meeting.

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

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 are a variety of opinions. One of our goals today for this open public hearing is 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 Chair.

Thank you for your cooperation.

DR. ANDERSON: We have slightly over 20 speakers today, and so for each of you, that is why we have had to sort of limit the time a little bit. So we will appreciate

it if you can help us stay on track with the three minutes of allotment.

At this point, our first speaker is Molli Salzman.

MS. SALZMAN: First of all, I would like to thank you for the opportunity to speak today on behalf of my son. My name is Molli Salzman, I am from Morris, Illinois, and I am the proud mother of Charley. He has lived quite a journey in his two and one-half years of life. Charley has taught everyone around lessons that are irreplaceable, leaving people touched and amazed.

Charley was born into a household of craziness. He is the youngest of three boys. Between work and two other boys, and myself finishing nursing school, my husband and I had to be on a full plate. At six months old he started to bang his head into his exerciser chair. He would cry in between them, so we knew he could control it.

When first presented to the doctor, it was passed off as him being tired and drifting off to sleep and dropping his head, but then the episodes became more and more frequent. He then started to change. He was slipping away slowly, his smiles were gone, he was miserable all the time. He slept the day away. At one point, I wasn't even sure he

knew I was his mom. He just had these vacant eyes.

Something was seriously wrong. My mother's instinct was in full drive. The one thing I would like to stress is how real "mommy instinct" is. Something was not right. I could not sleep until we had answers.

We got our answers on March 26, 2008. That is the day when Charley was diagnosed. After research, we realized how serious this was, in fact, the most devastating form of epilepsy on his developing brain.

We were in shock. It is funny how your body handles a traumatic situation. Having a relatively healthy family and very few deaths, it was a blow like no other, and when it is your child, you are left gasping for breath, as if someone sucked punched you from behind, but hoping to keep it together. It was too much.

After being sent to the hospital, the neurologist said that we had a pretty grim outcome. Roughly, there was about a 80 percent chance he would be delayed whether it was physically, mentally, socially, or all the above.

In the first three years of life, the baby's brain goes through incredible growth and development. This specific type of epilepsy, if left uncontrolled, would not

allow for his brain to complete these milestones.

We started Charley on ACTH injections within 48 hours of hospital administration. I prayed that this would rid him of his uncontrolled epilepsy. After six injections his seizures stopped. We slowly tapered down over three months and watched him come out of the fog. He rolled over within ten days of starting ACTH. He started to focus, smile, and play. He crawled around 11 months and walked at 15. He hasn't stopped since.

Charley is now two and a half. The last seizure medication that he was on was ACTH. There have been no other antiseizure medicines. What a miracle. He speaks simple sentences, plays well with others, and has a typical two-year-old attitude. He has the best manners in the house, and has two of the best older brothers that anyone could ask for.

He is very inquisitive and always asks a lot of questions. We are so lucky to have him teach us at the small age of two what is most important--family.

Today, we are grateful to tell his story.

Thank you.

DR. ANDERSON: Thank you very much, Ms. Salzman.

Next, we have Eric Hargis.

MR. HARGIS: Thank you.

First, by way of disclosure, I have not received any compensation or travel support to be here today. Questcor was one of the many corporate sponsors of the Epilepsy Foundation's National Walk for Epilepsy, providing \$20,000.

The Epilepsy Foundation is a \$90 million voluntary health agency and all medical positions are determined by an independent board of medical advisors.

As discussed this morning, infantile spasms is a rare but devastating pediatric epilepsy. Infantile spasms sometimes occur hundreds of times a day, and can lead to long-term developmental delays and intellectual disability. As you can well imagine, parents facing this condition are desperately seeking ways to end their child's suffering and prevent irreversible damage.

In treating infantile spasms, for years now pediatric neurologist have used Acthar and it is recognized by the American Academy of Neurology as an effective treatment. However, since Acthar is difficult to manufacture and not FDA approved for this indication, there

is a very long history of continuity of supply problems.

In 1996, the sole provider of Acthar experienced manufacturing problems, and later, in '98 and '99, it limited its production because of the difficulty of making the drug and the limited size of the market.

The Epilepsy Foundation alerted the FDA of our concern about patient care and physician concerns about resulting access problems.

Recognizing that Acthar is one of the frontline treatments for infantile spasms, the FDA worked with that manufacturer to help patients obtain this much needed treatment. A program was established with NORD to continue to make the product available even while the manufacturers of Acthar changed.

Unfortunately, problems of access have resurfaced periodically and in each case, the Epilepsy Foundation and experts have had to work with the Shortage Branch of the FDA of ensure continued availability.

The Epilepsy Foundation is here today because it is our hope that an FDA approval of Acthar for infantile spasms may help resolve the chronic supply issues. We also hope that the difficulties families have encountered with

insurance coverage including the cost of coverage for a product that is necessary but off label for use in infantile spasms will be resolved should the FDA approve Acthar for this use.

I should note that there are a number of existing medications for infantile spasms, and the Epilepsy Foundation does not endorse any specific treatment option. However, because there are many treatment options does not mean that Acthar is no longer needed.

To the contrary, our advisors tell us that this product remains necessary for the treatment of infantile spasms. As Acthar has been widely used by pediatric neurologists for many years, it is recognized by the AAN as an effective treatment and one that the FDA itself has worked to ensure is available to patients. We believe the FDA approval for the treatment will be beneficial for families dealing with this devastating condition.

I would like to thank the member of the Committee for facilitating this process and the opportunity to share comments with you today.

DR. ANDERSON: Thank you, Mr. Hargis.

Our third speaker is Emily Kather.

MS. KATHER: Hi. I'm Emily Kather. I just wanted to disclose ahead of time that Questcor did pay my travel expenses, but I am here representing myself and my son.

My child's name is Benjamin. This is his story as far as his battle with IS. The first six months Ben was born full-term, healthy, developmentally appropriate to advance in all areas.

He was a happy, healthy, and affectionate baby, as you can see from the pictures. I like pictures because they are worthy a thousand words.

He was diagnosed at around six months after, you know, standard testing, MRI, EEG, lots of laboratory studies. He seized uncontrollably with up to nine clusters of seizures a day for over three months.

We took him to pediatric neurologists after his second cluster. He was assessed at a one- or two-month level a month and a half after his diagnosis. He stopped rolling, he stopped using his arms and hands. He was lethargic, minimally interactive.

He ended up failing multiple medications. He failed depacote and he also failed vigabatrin, and he was given a poor prognosis due to the amount of regression and

his refractoriness to medication.

After changing neurologists, we went to a very experienced one. We went to Children's Hospital in Michigan and we now work with Dr. Chugani and Ruth Roeder, his nurse practitioner. They are amazing and ACTH was effective.

They gave us thorough patient and parent education, vigilant monitoring, as well as accessibility to support services, like a nutritionist, dietitian, monitor sodium intake, all that kind of stuff.

We were given a plan of care itinerary with the necessary appointments outlined in a dosing regimen very clearly delineated. As far as it goes, it is not an easy treatment, as most parents will attest, but it is safe and effective, I feel, with proper medical management.

So, today, he is six months seizure free. He is 14 months old now. He crawls. He is beginning to walk. He says mama and dada appropriately. He smiles, laughs, enjoys his toys, and plays with his three-year-old brother. He is totally appropriate, maybe just a couple months behind.

ACTH and ACTHAR Gel was truly a miracle for our son, his recovery has been miraculous. His only adverse side effect was moderate weight gain with some Cushingoid

features. ACTH has given my son the possibility of a happy, functional, and productive life from what I feel at this point although it is early. But we feel good about it.

So, why am I here today? Had Ben's first neurologist before Dr. Chugani felt comfortable prescribing ACTH, his road to recovery may not have been so long and his regression may not have been so profound.

It is my hope that ACTH will gain FDA approval so that children suffering from IS will have improved access to a treatment option with proven efficacy.

DR. ANDERSON: Thank you very much, Ms. Kather.

Our next speaker is Megan Daniel.

MS. DANIEL: Good morning. I brought a picture, too. This is my daughter. You can't really see her, but she has got a big smile in the swing here.

I, along with my husband, am here with you today to share the still unfolding story of our daughter Ella's journey with infantile spasms. Questcor has covered our travel and lodging expenses in being here for these proceedings.

In May of 2009, while not yet five months old, Ella began to have odd staring spells. Up to this point,

she was on track developmentally, but being a nurse, I immediately knew that something very serious was wrong with her.

Within the week, her spasms became more pronounced and began to cluster in short succession several times a day. By mid-June, after an EEG that was determined to be very abnormal and worrisome by our neurologist, Ella was admitted to Children's Hospital for treatment of what was presumed to be infantile spasms.

We had already researched the possible causes of what we were seeing and we knew what this term was, and it was devastating in its prognosis.

I will never forget one of the first things I read about this catastrophic disorder, that the incidence of mental retardation associated with it is estimated at 75 to 90 percent. There were also grim statistics about shortened life expectancy that I quickly banished from my mind.

After a few days of EEG monitoring and observation, Ella was diagnosed officially with infantile spasms. Quickly, the neurology team decided that ACTH would be the best course of action for our baby. We weighed the risks and agreed, and she started treatment the very next

morning.

The case manager immediately began communicating with our insurance company to cover the prohibitive costs of the medication knowing it would be a hardship on our family.

Because Acthar is not FDA approved for use in infantile spasms, our insurance company denied coverage, calling it experimental. An appeal was also denied for the same reason. But the National Organization of Rare Disorders, along with the Acthar support and access program had already come on-board to help us get this medication our daughter so desperately needed.

Through their combined efforts, even though our insurance company never approved our claim, we were given Ella's entire six weeks course of treatment free of charge and without delay. We will be forever grateful for their assistance.

On her eighth day of treatment with ACTH, and exactly a month after her staring spells began, Ella had her last spasm, which was well over ten months ago. Now, 15 months old, our daughter is a happy, beautiful, active, loving little girl who charms everyone she meets.

She attends a full-time early intervention program

that provides her with daily physical and speech therapies, and although she is delayed, we have great hope that she will continue to progress and will someday reach her optimal development.

We take nothing for granted, knowing that hers could have easily been a very different story. We believe that ACTH gave our daughter back to us. We hope that you would strongly consider approving Acthar for the use in the treatment of infantile spasms, so that more children like Ella would have access to this life-giving medication.

Thank you.

DR. ANDERSON: Thank you, Ms. Daniel.

Our next speaker is Diane Dorman from the National Organization for Rare Disorders.

MS. DORMAN: Good morning. My name is Diane Edquist Dorman and I am Vice President for Public Policy for the National Organization for Rare Disorders.

I have no personal financial relationship with Questcor. However, NORD has administered an allotment for free product for the uninsured through our ACTHAR Gel patient assistance program. Questcor also provides a donation to our infantile spasms co-payment assistance fund

for the Uninsured.

In 1996, the FDA received word from concerned pediatric neurologists that Acthar was no longer going to be manufactured. Shortly thereafter NORD received notification from the FDA that we were to serve as the official gatekeeper for the remaining supply until additional drugs became available.

As a result of the shortage, an emergency process was established where all requests for Acthar were routed through NORD. Doctors referred to NORD, to the NORD ACTHAR Gel Call Center, and had to submit documentation stating that he or she was prescribing the medication for infantile spasms or for severe exacerbations associated with MS.

All requests for prescribing Acthar for other conditions had to be turned away due to the limited supply. The remaining Acthar supply was housed at one specialty pharmacy in order to provide it to prescribing physicians within a 24-hour turnaround period.

There was no charge for the product during this period. As a result of this emergency plan that was in place for over a year, hundreds of infants received Acthar, thus saving them from brain damage or possible death.

We did receive today an e-mail from a parent. I would like to read it to you.

"Hi. This is Candice McGeshick. I am the mother of a child that has been diagnosed with West Syndrome. The treatments that we have tried have not worked. We needed to get ACTH and weren't sure how to get the money for it. This program helped answer our prayers by paying for the med and getting it to us faster than the staff believed possible.

My daughter's seizures have almost completely stopped and her EEG is reading close to normal. It has been only two days. Thank you so much. It is the most wonderful thing to see my five-month-old able to be able to sit still, lay still, and be alert. I don't know where she would be right now without your help."

As you continue to deliberate today, I ask only that you keep two things in mind. Patient affected by rare diseases are willing to take on a far greater degree of risk than patients who have the diseases affecting wider populations. Number two, because there are only 357 orphan products that treat few rare diseases, patients and their doctors have very limited treatment options available to them. ACTHAR Gel will give physicians, patients, and their

families a life-saving and critically important alternative.

Thank you.

DR. ANDERSON: Thank you, Ms. Dorman.

Is Speaker No. 6 here? If you are Speaker No. 6, I am sorry that we will have to skip you.

So, that brings us to Speaker No. 7, which is Leslie Herring.

MS. HERRING: Hi. My name is Leslie Herring, and I have two children. My son Mason is three and a half years old, and my daughter Debbie Ann is 19 months old. She was born at 33 weeks gestation by emergency C-section due to lack of fetal movement. We spent 33 days in the NICU at Lehigh Valley Hospital in Allentown.

Debbie Ann had all the normal associated problems, initially, low blood sugar, which was easily corrected. She was unable to regulate her temperature, Grade I IVH and poor feeder.

She was fed by NG-tube for 32 and a half days. We brought Debbie Ann home the first week of November. We were so happy, but soon realized that she was not like Mason. She cried all the time, was a poor feeder, and my motherly intuition just kept telling me something was wrong. Debbie

Ann always had some odd movements that Jerry, I, and the doctor attributed to her being a preemie and having an underdeveloped nervous system.

Finally, in May, I knew something was seriously wrong with her. She was not developing. She never smiled, had no head control, and was not even trying to move. I was not giving up. I was not going to stop until someone told me what was wrong.

I contacted her neurologist and explained to him that I thought she was having some type of seizure. He agreed to have an EEG done. The results showed myoclonic seizures and she was placed on Keppra.

A few days later she started having clusters of seizures. Again, I contacted her doctor, who advised me just to up her Keppra. I had had enough. I put her in the car and I took her to the Children's Hospital in Philadelphia. Within a few hours we had our diagnosis of infantile spasms.

We were immediately admitted to the floor. That night I didn't know if I should cry or vomit, and I did the worst thing a mother could do. I got on the Internet. Wrong thing to do. Out of every hundred articles on the

net, you find one success case. The odds did not look very good for Debbie Anne. Mental retardation. She might never walk, and the list went on.

Jerry and I were lost. We had no clue where to look or turn as this is so rare. The next day we tried vitamin B6, didn't work. Two days after that we started ACTH. Immediately, we saw less spasms and, finally, on the fourth day, we were seizure free, one of the best days of my life.

We have been seizure free since May 29th of 2009.

We were very lucky during our course of ACTH. We had very little side effects, and the side effects we did have were easily corrected and far outweigh the consequences on not trying ACTH.

Her brain was finally able to think clear. Jerry had the best Father's Day of his life in June 2009. She smiled at him for the first time. That was the start of better days to come. She can now roll over, smile, and laugh at her big brother, and is making small strides every day. ACTH was our lifesaver.

Every day that my daughter remains seizure free is one more day that she can grow and learn and have the chance

on her life where she can function in society.

Thank you.

DR. ANDERSON: Thank you very much for coming in.

The next speakers are the Farrells.

MS. FARRELL: Hello. My name is Lois Farrell and I speaking today with my husband Warren on the amazing effect that ACTH had on the health of our first child Ted almost 50 years ago.

Questcor has covered our travel and lodging.

Ted was born on April 19, 1961. He seemed to be a perfectly normal baby. However, when he was five and a half months old, he suddenly had massive myoclonic jerks. Our pediatrician said he had severe epilepsy and he was hospitalized at Boston Floating Hospital.

His brain-wave pattern showed that he had hypsarrhythmia. He was in the hospital from October 16, 1961, for 15 days. His prognosis was very poor. The doctors said the seizures would adversely affect his brain, and it was likely he would eventually need to be institutionalized. Needless to say, the news was devastating to us.

He was put on prednisone, which controlled the

multiple seizures, but he continued to have ten or more seizures a day. After several months, we asked our neurologist who had identified hypsarrhythmia. He told us that it was Dr. Frederick A. Gibbs, the founder of the Brain Research Foundation of the University of Chicago.

Several months later, I happened to be reading Time magazine and noticed Dr. Gibbs had written a letter to the editor in which he included his name and address.

We wrote to him, explaining Ted's condition and asked for any helpful information he might have. A short time later Dr. Gibbs telephoned us and asked us if Ted had been on ACTH. Our answer was no. He called our neurologist and Ted was hospitalized on July 9, 1962, and given ACTH.

After six days, he was sent home having injections of ACTH once a day. He continued to have a few seizures for the next four days and then the seizures stopped entirely on June 19, 1962, and never returned. He was exactly 15 months old. He continued to have ACTH injections twice a week for several weeks, and we had saved our records from that time.

MR. FARRELL: Ted is now 49 years old with two children. He has a Master's degree in Business and holds a management position in a high-tech computer software firm.

There has been no recurrence of any form.

Lois and I have two more sons, and we have a total of eight grandchildren, none of whom have had IS.

Needless to say, Acthar was a miracle drug to us and to our family. We will be grateful to Dr. Gibbs forever. It is our hope that Acthar will be approved by the panel today. It also seems to us that very possibly 50 years have been quite long enough.

Thank you.

DR. ANDERSON: Thank you both very much.

The next presenters are the McLaughlins.

MR. McLAUGHLIN: Good morning. Thank you for having us here today. Questcor has covered the cost of our travel and lodging to be here, and I wish that we had a good story to share, but we don't, and I think it's important that we tell you our story.

We have included picture of our son Grant that you may see. He was born a healthy, normal baby in January of 2000, a beautiful son, our only son, and had normal development as you have heard many times up until three months, and he would stop breathing from time to time starting at about three months. After many arguments with

pediatricians, they decided to hospitalize us and my wife's insistence, and was diagnosed with partial seizures.

In researching partial seizures ten years ago, unfortunately, we remember reading a very small section on infantile spasms and were thankful that that isn't what our son had. Unfortunately, in about three to four weeks, they progressed into infantile spasms, and the way we knew was from reading that small amount of information.

My wife saw it first and then via a physician and an EEG, video-EEG, we were able to diagnose the spasms. Unfortunately, our son failed everything. He failed vigabatrin, he failed ACTH, he failed every combination of drug you can think of. Within three or four weeks, he could no longer see, he could no longer move, he couldn't respond, he couldn't cry at blood draws.

He would spasm ten to 15 times a day. This went on for weeks and months, and the cost to our family was both emotional and to him was devastating. Eventually, after several years, he has progressed into clusters of tonics. The seizures were relentless. He seized basically when he was awake, he would fall asleep or pass out, wake up, and begin seizing again. Eventually, at age seven, he went into

status epilepticus and effectively seized to death,

But I think it is very important that you understand what the down side is, what the negative impact is, and what the path is when you fail, and we think it is very important that parents have every opportunity and every option to be able to hit this up front, hit it hard, and resolve it, because the impact downstream is so devastating.

MS. FARRELL: Imagine yourself with your child or your grandchild sitting in an ER, sitting in the PICU, and they are seizing in your arms, and there is nothing that can be done.

Thank you.

DR. ANDERSON: Thank you both very much for coming here and sharing that with us.

Our next speakers are the Charlans.

MR. CHARLAN: Thank you. Questcor paid our way here and paid our lodging.

Our story is with our first born son Zachary. He had a complicated birth in March of 2007, and he spent 30 days in the NICU and came home to us. At seven months old, he started having these spasms. We recorded them, so that we could take the video to our neurologist, because he

started having them over a weekend.

When we took him in to the neurologist, he diagnosed him right away with infantile spasms or West Syndrome. You can probably turn the volume down on that.

The neurologist told us of the dire consequences if it didn't stop, and they said that there is always an underlying cause to this, which resulted in us getting an MRI revealing severe brain damage, giving us another diagnosis of cerebral palsy.

So, that was a devastating blow to us right there. The neurologist told us that we have to stop the seizures, otherwise, it will continue causing more and more brain damage the effects being severe cognitive delays or mental retardation.

He recommended--it was Dr. Paul Levinson of the Children's Hospital in Denver--and he recommended us to take vigabatrin. We took it for three weeks, which basically did nothing, and at the third week, Dr. Levinson had enough of it, and he said we will do the ACTH.

We were notified of the negative side effects that could possibly happen, but we knew that the situation was already worse, I mean with him having cerebral palsy and the

brain damage getting worse and worse each time.

He would have these clusters of seizures about five to ten times a day, a video like this, lasted about five minutes. With the ACTH, we were admitted to the hospital. After the sixth injection he stopped having seizures completely.

We were sent home with the drug, we did the full dosage and the tapering off period. He is now three years old. He has never had a seizure since. He is bright. He still has the effects of cerebral palsy, which affects all four of his limbs, but he is a smart kid. He is healthy, and he is absolutely seizure-medication free.

The worst side effect that he had was significant weight gain, but being three years old now, and being completely seizure free, that wouldn't have happened without the ACTH that we had, and he would have been worse off now than he is today.

Thank you.

DR. ANDERSON: Thank you very much, Mr. Charlan.

Our next speaker is Dr. Barbara Olson.

DR. OLSON: The sponsor has covered my travel and lodging for me to get here today.

As a pediatric neurologist in private practice, approximately one-half of my patients have epilepsy coming as far away as a 200-mile radius to Nashville, Tennessee. I feel morally and ethically obliged to give them my best professional care and guidance.

In addition to being their doctor, I get to be a teacher, counselor, educational advocate, and sometimes even a minister on very difficult days.

When a young family presents with a lovely child having brief, but ominous spasms like we just saw, and a subsequent EEG reveals hypsarrhythmia, I suddenly feel like I am a soldier.

I have been very well trained with board certification in both pediatrics and neurology. I am well-credentialed as an assistant clinical professor of both pediatrics and neurology at Vanderbilt University, and I am very battle hardened and experienced with almost 30 years in the field.

Treating this form of catastrophic childhood epilepsy syndrome is not for the faint of heart. ACTHAR Gel has always been my initial drug of choice in treating patients with infantile spasms, in whom I begin medication

as quickly as possible.

Although the optimum dosage and duration of treatment has not always been clear, as an experienced physician, I am able to manipulate these parameters as indicated by individual patient situations.

The side effects of ACTH are well known, they are treatable, and they are reversible. Although the majority of patients I have seen have had infantile spasms secondary to an underlying etiology, I have also cared for several children with no obvious cause for their seizures.

In those patients with idiopathic IS, I have seen children stop having seizures, resume their development, and be released from the shackles of this disorder. I have watched with joy as normal development occurs, realizing that aggressive, immediate treatment with ACTH was essential.

In patients with underlying causes for their IS, I have seen the seizures stop completely, remit for a period of time, or then continue to another form of seizure type. Continued seizures and the secondary associated encephalopathy as disheartening, resulting in a potential lifetime burden to the family and caregivers.

Treatment with the most appropriate and effective medication without delay can ease that burden.

I am fighting against the potential devastation associated with infantile spasms, and I need weapons. ACTH in the form of ACTHAR Gel should be immediately available without delay and it is important for me and for my little friends and their families.

Thank you.

DR. ANDERSON: Thank you, Dr. Olson.

Next up, Joyce Cramer.

MS. CRAMER: Hello. I am Joyce Cramer. I am President of Epilepsy Therapy Project and Associate Research Scientist at Yale University School of Medicine.

The Company has provided a grant to our non-profit organization to support my travel here.

Epilepsy Therapy Project is a non-profit formed by parents of children who are living with uncontrolled seizures who have tried all the meds currently available. Our mission is to advance new therapies for people living with epilepsy, and my job is to support companies to bring new therapies to patients as soon as possible.

We educate patients and health care providers

through our website epilepsy.com that reaches 250,000 unique viewers every month to give them information written by epilepsy specialists to inform them.

The situation we are in today is to talk about risk-benefit ratio. Every treatment has adverse effects even aspirin, and particularly so for children.

We understand this, that adverse effects must be weighed against the drug's efficacy, its ability to stop seizures that can have devastating consequences for the mental and physical development of children.

We look at ACTHAR Gel treatment. We know the negatives, you have heard them all. Yet treatment with ACTHAR Gel can be given once or twice a day by parents at home, so that children don't have to be hospitalized. It is only for about six weeks. The side effects that you will hear about do go away once the treatment is stopped.

Now, I am quoting from our website. This is information written by Dr. Gregory Holmes, one of the few child epileptologists not present in the room today, but he recognizes the value of this drug.

We all know that infantile spasms, if uncontrolled, will lead to severe devastation. The parents

know this nowadays, as was mentioned earlier, with the Internet. Parents know this and doctors feel obliged to inform them.

Nonetheless, few studies have evaluated the efficacy of Acthar Gel, but it is generally agreed that early control may improve prognosis. This comes from an NINDS website. So, again, all based on information from experts, such as those in the room who have been treating this disorder for years.

Let's look at another venue. What about insurers? They are the ones paying a lot of money to treat this disorder. We know that insurers are the best gatekeepers in the world, and yet CIGNA and Aetna, among others, do pay for ACTHAR Gel based on the Academy of Neurology recommendation.

If you disapprove this drug today, they and others may stop paying for the drug. Then, where will we be? To date, they have grandfathered this drug in and paid. Please consider this possibility to a negative vote today.

I also want to leave you with the concept it is the parents' right to make an informed decision. I urge FDA to give parents a choice.

Thank you.

DR. ANDERSON: Thank you very much.

Next, is Dr. William Gaillard.

DR. GAILLARD: Good morning. I am William Davis Gaillard. I am here on behalf of the American Epilepsy Society in support of ACTH for therapy for infantile spasms. I do not have any financial disclosures.

The American Epilepsy Society promotes research and education for professionals dedicated to the prevention, treatment, and cure of epilepsy. Our annual meeting is the premier conference for the exchange of information about the diagnosis and treatment of epilepsy for all ages.

We are a multidisciplinary society. We include neurologists, neurosurgeons, nurses, neuropsychologists, psychiatrists, pharmacologists, and basic and translational neuroscientists as well as other health professionals.

We have close working relationships with other professional organizations including the American Academy of Neurology, the Child Neurology Society, and the International League Against Epilepsy.

Epilepsy clinicians choose antiepileptic drugs based on their individualized assessment of risks and benefits, as we have heard.

This assessment is based on available information, clinical experience and training, detailed knowledge of the individual patient's circumstance.

Pediatric neurologists make these decisions in the setting of few, if any, FDA approved medications for the treatment of the infantile epilepsies.

Infantile spasms is an uncommon but important syndrome with many causes, and is characterized by devastating epilepsy, a unique EEG pattern, as we have discussed, and is almost invariably associated with developmental delay, often debilitating.

There is traditionally poor or no response to traditional anticonvulsant medications, and there is a specific need for FDA approval of therapies for infantile spasms.

ACTH is an important and time-honored standard treatment option currently only available as an orphan drug without FDA approval.

Published clinical trial data support its use in infants with infantile spasms, supported by the American Academy of Neurology Practice Parameter, which is endorsed by the American Epilepsy Society.

Its potential side effects are well described and known.

Vigabatrin is considered by the FDA to be effective for infantile spasms, but this is effective only for a subset of patients and emphasizes the need for treatment options.

I have cared for thousands of patients with epilepsy over the last 25 years. I have personally seen and treated, and seen the devastating effects of infantile spasms on scores of infants and on their families.

I have personally witnessed the efficacy of ACTH on infants, not only in cessation of spasms, but also of normalization of the EEG, and the reversal of developmental decline. This experience is shared by my professional colleagues.

Infantile spasms is an uncommon but devastating epilepsy for which few medications are effective and may optimize developmental potential. The best clinical evidence and personal experience supports ACTH as an effective treatment option for infantile spasms.

We thank you very much for your careful consideration.

DR. ANDERSON: Thank you, Dr. Gaillard.

Our next speaker is Dr. Michael Katz.

DR. KATZ: I would like to disclose the sponsor paid my expenses today. My name is Dr. Michael Katz. I am a practicing pediatric neurologist since completing my pediatric neurology training in 1991.

I am here today to discuss why I believe ACTH should be approved and made available to the next generation of neurologists and their patients. In my greater than 20-year medical career, my professional life has shadowed the trials and tribulations of ACTH.

The most important thing that I have seen is the profound effect that this drug has had on the most vulnerable. These individuals have no voice. We are their advocates. We wrestle with what constitutes effective treatment.

With infantile spasms this has been a problem. We have very few therapies that are proven and available. I believe every option needs to be on the table. Child neurologists would agree that ACTH as a therapeutic option needs to be approved and available as part of their treatment armamentarium.

In the course of seeing thousands of children, pediatric epilepsy continues to be a challenge with infantile spasms presenting a particularly difficult problem.

These challenging individuals are memorable. One of my most memorable patients came to my doorstep in the form of a six-month-old girl from out of town. She was turned away from another institution because of their inability to obtain ACTH to treat her infantile spasms.

Thankfully, we were able to obtain ACTH for her with a dramatic response. Time moved on and I had forgotten that girl and her family. I was in my hospital meeting place, the cafeteria, when I heard a familiar voice call my name. It was that family. They spoke little about her infantile spasms and ACTH, but mainly about the chance they had been given. That chance was a gift to my family.

I would like to ensure that families in the future will have that same opportunity. In order for this chance to be given, to other families, ACTH needs to be approved and available to prescribing clinicians. The approval will enable my colleagues to recommend ACTH with confidence.

This medication is an effective proven therapy for

rare and disabling disease. There are not a lot of options, but approval will keep this option readily available to families.

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

Our next speaker is Dr. Andriola.

DR. ANDRIOLA: I am Dr. Mary Andriola. The sponsor provided my lodging and travel.

I am a Professor of Neurology and Pediatrics, and Director of Child Neurology and Epilepsy at SUNY Stonybrook in New York.

I began using ACTH in medical school in 1963. My training was completed in 1970 and, since then, in 40 years of practice and teaching, I have been using ACTH. I almost could have, sort of treated Ted. The medication has been out in this country since '58. I was taught initially, as we used to call it, the recipe of using 40 units per day for a month.

In the '90s, when I heard Talley's new recipe for high dose twice a day, two-week treatment, it sounded great; shorter treatment period, shorter period of time for side effects, and a higher response rate.

In my personal experience I have seen

approximately five to ten patients per year, and at least treated over 200 patients over the years. I have taught residents and fellows to use ACTH. So hopefully, in spite of all the difficulties that we have encountered over the years, at times obtaining the medication, they have learned to use this as the first-treatment choice.

It is true we have a new drug that is available and FDA approved, and particularly for TS, but nevertheless, ACTH has been, and is, the gold standard in spite of us using it for 50 years off label. It does have predictable side effects which can be monitored and managed, and I definitely feel that the incidence of response rate has improved with this higher dose protocol.

I have followed developments over the years. We have certainly seen the symptomatic versus cryptogenic or normal patient rate appear to change as we have developed MRIs. We have learned much more with video monitoring. Before, we just looked at an EEG after a month.

Certainly with the development of this new protocol, also in the '90s, we had the video-EEG monitoring.

I have actually seen patients who have had the wonderful history given of the children here today, and of

Ted. I have had a patient who responded and went off to college. I think it's urgent that this medication be approved, so it's available and we don't have a shortage.

DR. ANDERSON: Thank you very much.

Our next speaker is Lynn Gay.

MS. GAY: Hello. My name is Lynn Gay. This is my husband Kevin and my son John. We are from Boston.

Questcor paid for our travel expenses today, but we are here on our own free time.

My son John was diagnosed with infantile spasms at seven months, initially diagnosed as acid reflux. It was later determined that he was having 50 to 100 spasms daily.

John had stopped developing and appeared to be losing touch with his surroundings. For example, he was no longer making eye contact.

After extensive testing, no underlying cause of his infantile spasms was ever found. John was immediately given a pulse of ACTH. This pulse significantly ameliorated his EEG. The hypsarrhythmia was no longer present and John had more normal awake and sleep patterns, brain wave patterns.

We were cautiously optimistic of his outcome. As

we were coming to grips with John's diagnosis, we then started to worry about John's two brothers who were both close in age, one a fraternal twin and the other a year older. We lost many a night's sleep waiting for the other shoe to drop. We could not fathom the prospect of having another child face such a terrifying diagnosis.

My husband and I came up with a plan to take care of our young family in the short term. I would set aside my career to stay at home, and he would take on a higher paying job closer to home at another institution.

Unfortunately, this entailed switching to a new employer's health care plan. After four months, John had relapsed and his neurologist ordered another pulse of ACTH. We were admitted to the hospital to commence the medication.

However, much to our surprise, the new insurance company denied us access to ACTH.

This was especially surprising since we had confirmed in advance, before my husband accepted the new position, that the new employer's health care plan would, in fact, cover the medication if the need arose.

Regardless, after two days of negotiations with the new insurance company, ACTH was eventually approved.

This was a very dark moment for us in our lives. We were overwhelmed by the fear that we had failed to provide for our child.

Today, although John never recovered from infantile spasms, each pulse of ACTH did seem to help. He is able to walk and participate in his surroundings, and most importantly, I believe that John understands he is well loved.

Having felt what it was like to be denied access to a medication that could help save your child from such a devastating disorder, I urge you to approve ACTH for use in infantile spasms.

Thank you for your time.

DR. ANDERSON: Thank you for coming.

The next set of speakers are the Horns.

MS. ALEXIS HORN: Hi. I am Alexis. Questcor did pay for my travel down here, and these are my parents.

MS. LORRAINE HORN: Good morning. I am Lorraine Horn. My husband and I have no financial compensation or interest in Questcor. I am also an R.N.

Our family would like to tell our story of infantile spasms. Twenty-six years ago, ACTH saved our

daughter from a lifetime of seizures and mental retardation, resulting in normal growth and development.

Alexis is now 26 years old, and enrolled in an MBA program, and getting married in August. Alexis was born November 26, 1983, after a normal vaginal delivery, had normal growth and development, met target developmental stages at well visits.

At four to five months old, my aunt noticed unusual arm movements and staring. Looking back, I believe a fall off a changing table at five and a half months may have been from spasms. Subsequently, I saw arms jerking forward with staring. Alexis was seen by her pediatrician who also saw these jerky arm movements.

On May 16, 1984, Alexis was admitted to Mass General Hospital in Boston. She was discharged after a two-day stay with a diagnosis of seizures, unknown etiology. Her medication included phenobarbital. Her EEG impression at the time was parietal and occipital activity.

Alexis continued to have these jerky, tonic-like seizures with a phenobarb level of 36. Visible spasms were three to ten a day. On repeat EEG, on June 3rd of 1984, impression was continuous bursts and spikes. Alexis had

stopped babbling and seemed to withdraw from outside interaction.

Being an R.N., I was determined to get a second opinion. On June 12, 1984, after the 27th day after her hospitalization at Mass General, Alexis was seen at Children's Hospital in Boston, Mass, in a research unit for seizures. It was during physical examination by a pediatric neurologist, Dr. Giuseppe Urba, the diagnosis of infantile spasms was made, and the treatment plan of ACTH was initiated immediately.

Within 24 hours Alexis had a dramatic response to ACTH, having no further visible spasms. During her eighth day of hospitalization at Children's, her EEG pattern improved with the reversing of hypsarrhythmia. Alexis began babbling again, interacting with us, and sitting up again.

Alexis was discharged on June 20th, 1984, to home on daily ACTH injections. I monitored her daily weight, blood pressure, urine for glucose, stool for blood. She had manageable side effects.

After five and a half months of ACTH, on November 24th, 1984, two days before her first birthday, she was switched to a tapering oral prednisone. By December 22nd,

1984, Alexis was off prednisone and continued care under a pediatric neurologist until discharge at three years old.

In conclusion, early detection, early treatment on ACTH resulted in a great outcome.

Thank you.

DR. ANDERSON: Thank you very much for coming in.

Our next speaker is Ryan Allen.

MR. ALLEN: Good morning and thank you for giving me an opportunity to speak with you today. Questcor provided my transportation and hotel for this stay.

My son Logan was diagnosed with infantile spasms at six months of age. From all the research I have done over the last five years, Logan was similar to most idiopathic kids, diagnosed with IS. He started having seizures at six months of age, had hypsarrhythmia, and was given the grim diagnosis of IS.

Logan was diagnosed by a neurologist and started on a different antiseizure medication which had some positive effects, but nothing permanent. We were told that ACTH was unsafe, unproven, and they would not recommend it.

We weren't confident in this physician's understanding of the disease and after doing a lot of

research on line, went looking for a new one. We were fortunate to find a great neurologist in Dr. John Roe who provided us several options as a gold standard first-line treatment for IS. One of those was Acthar.

After much discussion, we decided to try it. Logan experienced similar side effects being discussed today. They included elevated blood pressure, weight gain, intense irritability. Logan was on ACTH for eight weeks total.

Five days after his first injection, Logan became seizure free and has continued to be seizure free since. His hypsarrhythmia and spasms were eliminated, and currently, at five and a half years old, is developmentally normal.

As a parent having gone through this experience, there is nothing more humbling than a sick child. We are forever grateful to everyone and everything involved with Logan's success.

As a parent advocate, I have spent a great deal of time sharing Logan's story with other families and organizations to create additional awareness of this terrible disease.

Throughout the last five years, I have spoken with hundreds of parents whose children started down this path just like Logan. These families have had similarities specific to early diagnosis, taking Acthar in similar dosages, and great medical oversight.

Unfortunately, most children have not had similar result to ours, specifically, having children who are developmentally normal after seizure and hypsarrhythmia cessation. Logan is in a small percentage of positive outcomes.

The majority of children diagnosed with infantile spasms have permanent changes in their ability to function. These range from minimal developmental delays to severe outcomes, such as unable to function other than that of an infant for the rest of their lives or death.

When I was asked to participate in this hearing, I spoke with many individuals on what it would mean for FDA approval. The answers ranged from more awareness of the drug to better educate medical providers on its usage, which would in turn help more kids in receiving it faster, to Questcor cornering the market and increasing the price, again making it more difficult for children to receive and

everything in between.

I am here today because I would like every child who can potentially receive this drug be given an opportunity to take it, and if FDA approval can provide additional awareness and education of this disease and help other families receive the drug faster with no delay, then, I support it. I am putting my trust in Questcor that they will continue their commitment with the ESAP Program, that no child will go without an opportunity to take Acthar regardless of that child's circumstances.

This drug helped my son and I hope as many children as possible are given an opportunity to take it.

Thank you.

DR. ANDERSON: Thank you very much, Mr. Allen.

Our next speaker is Dr. Laurence Brown from the Child Neurology Foundation.

DR. BROWN: My name is Dr. Larry Brown. I am here as a pediatric neurologist and as the President of the Child Neurology Foundation, which is the national organization that supports research, education, and advocacy for children with neurologic diseases.

My way here was paid for by the sponsor. Questcor

is part of our corporate advisory board of the foundation, and has supported various projects of education and advocacy for children with epilepsy.

As a practicing academic child neurologist and epileptologist in large tertiary care pediatric hospitals for almost 32 years, I have seen several hundred children with infantile spasms. In my experience, ACTH has always been the first line approach for this devastating form of age-related epileptic encephalopathy.

While there have been other treatments available, we have always returned to ACTH since it is the most consistently successful in controlling hypsarrhythmia and clinical seizures, which we have heard are so critical to the preservation of neurologic and developmental function.

Other approaches are there, but they have lesser rates of success, and we must remember the other side effect profiles. It is my strong opinion that oral corticosteroids, topiramate, valproate, the ketogenic diet, and others all have their place, but none are the first treatment of choice for most children.

Certainly, it would be better if we had more data on mechanism, early predictors of success, and an algorithm

that would allow us to choose the best initial drug for a particular infant. Unfortunately, we do not have those answers except possibly for tuberous sclerosis with vigabatrin is an equally valid primary alternative to ACTH.

As the current President of the Child Neurology Foundation, I organized Infantile Spasms Awareness Week last year in 2009. Our goal was to help primary care providers, pediatricians, and parents to understand the importance of early diagnosis and treatment.

We developed a website, we had a DVD, we had brochures to be distributed in doctors' offices. As part of that effort, we also raised money to fund research that will hopefully answer some of the fundamental questions about pathophysiology and clinical management of this severe epilepsy.

At this point, however, we have a limited repertoire of safe and effective options, and we absolutely need Acthar in order to be able to manage our patients with infantile spasms.

Thank you.

DR. ANDERSON: Thank you very much, Dr. Brown.

Our next speaker is Robert Moss from the Tuberous

Sclerosis Alliance.

MR. MOSS: Hello. Thank you for allowing me to speak today. I am the father of a six-year-old boy with tuberous sclerosis or TSC. Evan was diagnosed with epilepsy at six months, and has been on over 11 different medications to control his seizures.

A brain MRI when Evan was two years old revealed multiple tubers in his right hemisphere and it was suggested that we rule out tuberous sclerosis complex. Evan was subjected to a barrage of tests and subsequently diagnosed with a rare genetic disorder.

My wife and I turned to the Tuberous Sclerosis Alliance for support, guidance, and fellowship. We currently chair the Metro D.C. Community Alliance and are active on a national level, as well.

We have met many families struggling with the surprise similar diagnosis along with families dealing with the day-to-day trials and treatments associated with issues related to tuberous sclerosis.

All too often we meet families who have just been given the news that their child has infantile spasms and needs treatment right away. Most of us can barely pronounce

hypsarhythmia, and when researching the simple reference of infantile spasms, we quickly realize its seriousness.

We are told the decision to medicate for infantile spasms needs to be made immediately, and the situation is dire. While our son Evan never experienced infantile spasms, we made the difficult decision to give him Sabril to treat his uncontrolled seizures.

It was not approved for any use in the U.S. at the time, and the decision was not easy. We had weeks to work through the process of getting the medication and have never experienced making that decision under the looming epilepsy emergency of infantile spasms.

My wife and I have met many--or have met families who have gotten the diagnosis of infantile spasms by choice after mentioning the tell-tale concerns to their pediatricians. They are often told that what they are seeing is normal infant behavior.

We have met tuberous sclerosis families with children who have been prescribed classic antimedication drugs to treat infantile spasms, and their spasms keep getting worse.

The time for improved education and proper

diagnosis of infantile spasms is now. Many children with tuberous sclerosis have had infantile spasms and respond rapidly to Sabril while others do not.

These children need to have FDA-approved treatment options including ACTHAR Gel. The time for improved education for physicians and the proper use of ACTHAR Gel is now.

The TSC advocates for improved access to drug options for our community including ACTHAR Gel, Sabril, and other future treatments. Your decision to approve the use of ACTHAR Gel for the treatment of infantile spasms will greatly aid us in this endeavor.

Thank you.

DR. ANDERSON: Thank you, Mr. Moss.

Our next speaker is Dr. Gridharan.

DR. GRIDHARAN: Good morning. I am Dr. Radha Gridharan. I am from Brooklyn, New York, the famous place, and since I think I am going to be one of the last speakers, I think I should lighten up because we are getting teary eyed.

As mentioned, West Syndrome is unique, age-specific epilepsy of early infancy, infantile spasms with

the associated EEG pattern, hypsarrhythmia, and neurodevelopmental regression.

It is fairly common, it is 2 to 3 percent of childhood seizures, with devastating impact on the development. That's what is the crux of the situation.

It is a relatively neglected area of epilepsy and in need of better treatment. As mentioned time and time again, it is resistant to conventional anticonvulsants.

Searle in '58 reported the efficacy and 50 years later we are still discussing it. Any number of studies have shown that between ACTH, prednisone, and others, that ACTH is the gold standard.

I, over the years of 30 years of practice, I am very convinced that I don't have anything better. Vigabatrin was recently approved, but when trying to tell families where the outcome is going to be so bad, that I am going to add another layer of the possibility of visual impairment. It's awfully hard, and if it's not tuberous sclerosis, I don't go that route.

Again, I go through a specialty pharmacy to get it, and have visual fields done, and so on, and so forth, whereas, with ACTH ACTHAR Gel is also specialty pharmacy,

but they have made my life enormously easier in getting it for my patients and the families.

We know the significant side effects, but they are manageable. I know how to handle them and maximize the benefits. Spasms are the clinical manifestation and hypsarrhythmia is the EEG manifestation of the underlying encephalopathy.

I explain to the parents that the chaotic high-voltage cerebral activity is an electrical storm that prevents the children from connecting and developing normally. So early treatment is paramount, and that is the only thing I can make a difference in, so I need to get them the medication.

With my years of experience, I can again explain to them and help them make that decision. But again, when my junior colleagues, my residents approach it, they may not have the confidence, and that is why FDA's approval is very important because then they will be able to again present it in a better light to the families who are struggling with so many decisions.

Even if one child began to reverse their developmental regression, what more could we ask? For

everything else there is Master's Card.

Thank you for giving me the opportunity.

DR. ANDERSON: Thank you, Doctor.

This concludes the Open Public Hearing session.

The Open Public Hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee, as well as the public comments, which we will resume after our lunch break.

We reconvene again in this room about one hour from when I finish speaking, so that will be about 1:05, about five minutes behind schedule.

For members of the Committee, I urge you again to remember to not discuss the deliberations that are before us outside of the public meeting or at lunch, so that we can all benefit from your perspectives.

If you have any belongings that you want access to during the lunch break, you should take them with you because the FDA will secure this room during the lunch break, and you will not be allowed back in until we can

reconvene.

We now stand adjourned for one hour.

[Luncheon recess taken at 12:05 p.m. to 1:05 p.m.]

AFTERNOON PROCEEDINGS

[1:05 p.m.]

Clarifying Questions (Continued)

DR. ANDERSON: Our purpose for this part is to have some discussions and address the FDA's questions, but before we do that, we have a couple of issues left over from the morning. So there were sort of two open questions, and then a few people that I didn't have a chance to get to that I will give another opportunity.

We had a question about the manufacturing safeguards that relate to sort of production issues and the we had another question about what we know concretely about relapse rates from the analyses of the data that is available.

Dr. Young was going to facilitate some responses to those two questions.

DR. YOUNG: Thank you. I hope lunch went well for everybody. I am not the CMC expert, so I have some information. If you don't mind, I will probably read some of this from here.

In terms of our manufacturing, as you know, we have been manufacturing Acthar, or Acthar has been

manufactured for 50 years. We took it over in 2001 and started manufacturing. At that time in manufacturing, there were discussions with everything going on with the FDA.

Right now we have processing steps and specific processing conditions to eliminate and reduce the virus load in the product. Some of that is confidential. I can't share some of it, but I can tell you that there are control systems to monitor virus load and we are continually trying to update that and make it more modern as we go.

So, that is the status right now, and the FDA knows about everything happening on this.

DR. ANDERSON: Okay.

DR. YOUNG: The second is the relapse and I would like to ask Dr. Shinnar to address that.

DR. SHINNAR: The relapse data comes from several sources. You have heard Dr. Trapnell present the data, the preliminary analysis of what they could get from Hrachovy 04 study, the high dose versus low dose, which was 21 and 15 percent. The Baram paper published 15 percent with the median follow-up of over a year, a length of follow-up up to 48 months with no relapse, and these are the other data.

Now, for practical and logistical reasons, to

admit children again who are doing well for 24-hour EEG is impractical, but the clinical experience, as Dr. Duchowny has indicated, is that if hypsarrhythmia does recur, then, spasms will almost certainly recur, and these parents are trained, even though they may have been delayed to initial diagnosis, to recognize it.

We do have data from non-RCTs. I mentioned in the Finnish cohort that we have some other data. So Lombroso, for example, published his cohort, and he looked at the cryptogenic children with six years of follow-up, 100 children, and basically found no seizures at all, that six years later they were completely seizure free in over 60 percent of the cases treated with Acthar.

Those treated within one month of onset did better, 67 percent seizure free versus 33 percent. So, both we have some evidence from this intracohort analysis that they do remain seizure free for a long time, and they were followed by him for that period, as well as that early treatment seems to matter.

In addition, we have data from another cohort study by Sher, et al. published in which these are now symptomatic cases where you would expect to have a somewhat

worse outcome, but in those that had complete cessation of spasms, 50 percent remained seizure free clinical long term, whereas, essentially, 100 percent of the non-responders continue to have seizures of various types.

So, we do have data that when you do induce remission--now, is it specific for that two-week regimen? Well, the data from the Baram with follow-up of over a year suggests it is no different.

As far as we can tell, these relapse rates, which on the clinical literature, are sustained and are really dependent on attaining a no spasms, a no hyps, picture rather than duration of treatment and how long it takes you or taper regimens, or the actual dosage given.

It is an all-or-none response and when you achieve that all response, your relapse rate seems to be not very different, and our data in all these studies that have gone on for many years is that remission is maintained.

DR. ANDERSON: Did you want to pursue that at all, Dr. Katz, or does that address your question?

DR. KATZ: Mostly, but I gather you suggest that it is not the treatment regimen so much, but the initial response. If you have responded as we have defined it, you

have a better prognosis.

But I am interested in the first study where there was six years of follow-up. What was the treatment regimen, was it standard for those patients, or was it variable?

DR. SHINNAR: The Acthar dosage was a high dose regimen which did change somewhat over the years, because that cohort was assembled over more than a ten-year period.

DR. KATZ: Right, but you said it was high dose. Was it two weeks or three?

DR. SHINNAR: It was longer duration, but the results are not very different than what with one to two years of follow-up is reported in the Baram study, or that is reported in the Hrachovy study with a low-dose regimen was short duration. If they achieved remission, they again had the same relapse rates.

So, it appears if you look even at the RCTs to be independent of either dose duration or dose magnitude, because the high dose for a long time in longer period of time in the Hrachovy study, again had the same relapse rate in those who achieved remission.

DR. ANDERSON: Dr. Lu, you had some questions left over from before. Did you want to take another opportunity

here?

DR. LU: Thanks. I have a question about safety data because I think earlier one of the panel members already raised the completeness issue.

So, in your review, chart review, was there evidence that physician actually--my understanding, retrospective chart reviews was within the medical center, so the patient may seek the service outside their particular medical hospital also.

So, was there a chart that indicated the completeness of their follow-up beyond their single institution?

DR. YOUNG: Well, there was in terms of the parent also had--we also had a parent-reported AEs. So if the child went to a pediatrician, that parent would have reported what was going on in terms of happening at the time. But are you asking about beyond in terms of time after the fact, is that the question, or during--

DR. LU: I think more during the time.

DR. YOUNG: So, during the time we had the parent-reported AEs, so they reported everything going on with the child. Even if they went to a pediatrician or they went to

somebody else, they reported everything there, yes.

DR. ANDERSON: Dr. van Belle, did you have another issue?

DR. van BELLE: Thank you. One context question again. I guess I have been surprised there has been no reference to any kind of international experience with the drug. What is going on internationally? Is it used at all, and what is the experience?

This is unusual that we have reference only to United States experience in this particular application.

DR. YOUNG: Acthar is not approved in any other country. So like typically, you know, people get their drug approved in the U.S., but then also submit an application in the rest of the world. It is not approved in any other part of the country--or the world, I should say, it is only approved in the U.S.

DR. ANDERSON: So, then, what are the Finnish people using?

DR. YOUNG: I will let Dr. Shinnar answer that one. They are using some--they have some Acthar information.

DR. SHINNAR: I can't tell you what they are using

now, but in the '70s, they were using the same formulation of Acthar that--the Sovelle original description is, as far as we know, from the same Acthar, and the description is Lycona. But those were not synthetic.

The British experience and the Italian experience and the Canadian one, that is synthetics.

DR. YOUNG: Now, they could have got in there from Ireland, because at one time Acthar was approved only in Ireland. why only in Ireland I don't know, but it was only in Ireland, and so Acthar was actually sold in Ireland early on, and then sometime in 2000, it was stopped being sold in Ireland. but that could have been where they got it from. I don't know.

DR. ANDERSON: I will let Dr. van Belle finish his thread here.

DR. van BELLE: One more question. I am still trying to get my arms around the endpoint in terms of what was agreed to and how was the endpoint indeed determined.

So, the endpoint was complete cessation of seizures and clean EEG. That's basically the endpoint. Was that the endpoint agreed to by the FDA, and also how was the endpoint determined by the company in terms of quality

control, reliability, what made you certain that you had categorized the response correctly?

DR. YOUNG: I can answer that from my understanding and Dr. Katz can say if I misunderstood. But with the agreement that we had with the FDA is that the endpoint would be both the complete cessation of spasms, clinical spasms, and the resolution of hypsarrhythmia, and that was determined through the prolonged video-EEG.

Now, in terms of the prolonged video EEG and the actual measurements, I will pass that on to Dr. Trapnell.

DR. ANDERSON: Do you want to hear the details of the video-EEG, or did that address your question? Did you want him to talk about the details of the video-EEG monitoring or did that address your question? Okay.

DR. van BELLE: I would like to hear something about the quality-control issues.

DR. ANDERSON: I guess I want to make sure I understand the question. So the quality control, the date of re-review or the quality control of the original studies in terms of how they selected their outcomes and what they utilized?

DR. van BELLE: No, I am interested in what they

did with the data once they got it from the original investigators. Thank you.

DR. TRAPNELL: For Study 01, we received the data from Drs. Baram and Mitchell in database form, and in that database it actually had an interpretation of the video-EEG results. So, in the data it said spasms resolution yes/no, and hypsarrhythmia resolution yes/no, and from those data we were able to determine the overall response endpoint and do our analyses.

Similarly, in 05 and 04 studies, we also had the EEG interpretations from the investigators, which included the statement about the clinical spasms. The only way you can really be sure about the spasms being gone is the prolonged video-EEG. So. even if the parents had said the spasms were gone, or they didn't see any, the bottom line is we took the results from the prolonged video-EEG to assess spasm cessation, as well as the hypsarrhythmia resolution, and that was then used in the data analysis for the endpoint.

DR. ANDERSON: I have three more names on the list. I have got Dr. Khanna, Ms. Vega, and Dr. Pearl, and then what I would ask is I guess for everybody to sort of

reflect on whether they have actual clarifying questions or just issues sort of for our general discussion.

We should go through more clarifying if they really exist. But on the other hand, if it's more of a sort of working out what the decision should be, maybe we could then move on to the questions in general.

Let's go to Dr. Khanna.

DR. KHANNA: Thank you very much. I am not a pediatrician or neurologist, but I am a specialist in public health, and so I have some questions relating to kind of the distribution of infantile spasms.

We earlier saw that there was a gender disparity in treatment outcomes, which I think was statistically significant.

What is the demographic distribution of infantile spasm in terms of gender, socioeconomic correlation, and/or racial or ethnic association?

Secondly, in the cases that we saw where the patients did not relapse, is it safe to say that they were cured of infantile spasms? Is that a safe word to say? Is there an age range after which--since we are calling it infantile spasms--after the age of one or more, that if they

no longer show symptoms or EEG abnormalities, that we can say that they are cured?

DR. YOUNG: I will ask Dr. Shinnar to address some of those issues, but let me first address the issue of the cure issue. Through our studies, as we said, what we have seen, and as you saw from some of the patients or advocacy people who came up and talked, that, in fact, if they seemed to respond, they seemed to stay responsive, and they seem to move on positively. So that appears to be the case.

DR. KHANNA: You are being very careful. Are we able to say that they are cured?

DR. YOUNG: That is why I am going to let Dr. Shinnar actually give the specifics.

DR. SHINNAR: Let me address the cure part first. Cure is a very broad word, and one can talk to it about cognition, about any seizure types, about spasms.

So, if you are talking about relapse of spasms, relapses occur early, within weeks to a month. It would be extraordinarily rare to have a relapse more than a year, and actually quite an out--and quite unusual to have a relapse of spasms more than six months out.

So, in terms of being over, cured in the sense

that you would not have spasms come back, we reassure our patients after six months to a year of seizure freedom. That is very different than telling them you will never develop partial seizures, you will never develop any other seizures or that we know you will be normal when you grow up.

But in the strictest definition, if you are going to relapse, the epidemiologic data, regardless of what treatment we are talking about, this is not Acthar specific, says if you go a year without any recurrence of your spasms, spasms are not going to come back. So, in that sense, you don't have to hold your breath for 10 years. You do know if your kid will be normal-normal, but not in terms of spasms.

In terms of the other questions, there is a slight female preponderance in some studies. This is not one of those disorders with a striking gender preponderance, and there is no data that gender plays a role in either drug response or outcome in this disorder.

Unlike many other neurologic disorders, there does not appear to be any striking ethnic or socioeconomic predisposition, and these are occurring in very young babies where many environmental factors have not yet come into

play. So, there does not appear to be much difference. There are no good data on whether there is a difference in time to recognition, which you might suspect there might be, but there is simply no good data on that. But all the other, they are not major issues of disparity.

DR. ANDERSON: We have a lot of pediatric epilepsy people on our committee. Does anyone who is not affiliated with the sponsor want to address the issue whether they consider sort of failure to relapse within a year is sort of indicating the cure of spasms, or whether that is a safe deduction or conclusion?

So, none of you feel like you would want to say that? Dr. Pearl.

DR. PEARL: I would be willing to say that's a real success is no relapse of spasms within a year. I wanted to follow up on a prior comment, but I will wait for you to call on me.

DR. ANDERSON: Ms. Vega, you are next.

MS. VEGA: This is a question. It is surprising for me to see that, since this medication has been used in America for more than 50-plus years, that none of the previous pharmaceutical companies that acquired the

medication did any studies of their own to assess the efficacy and the safety of the medication.

So, my question is since Questcor obtained the medication in 2001, why you didn't decide to do a study of your own to assess the safety and efficacy of the medication.

DR. YOUNG: When we acquired it in 2001, the biggest hurdle we had to deal with or the biggest issue we had to deal with was manufacturing, making sure the manufacturing was appropriate, making sure we could distribute it, making sure that we could make it under the standards necessary for the FDA, and that is where all our efforts went in the beginning.

Over time, we realized--even then we realized we needed to do other things, but we just didn't have the resources to do other things than making sure we could actually produce this and get it on the market for the IS patients.

Again, over time, we know we have to get a submission, we knew we had to get approval, and so that is what we have been doing over time.

In terms of why didn't we do our own study, as you

heard before, logistically, for us to do a study, when we went to the leaders and individuals in pediatric neurology, and we talked about doing studies, they told us it would be very, very difficult to do it, almost impossible. So, that is why we were not able to really do that type of study either.

DR. ANDERSON: Dr. Pearl's comment/question.

DR. PEARL: Thank you. I actually have two areas I would like to clarify. The first is to expound on Dr. van Belle's question about international experience.

The United Kingdom Infantile Spasms Study Group published--Dr. Shinnar probably will respond since he was up earlier--I mean Lux, et al. published-- they randomized over 100 patients to a synthetic analog of ACTH versus prednisolone at a pretty high dose--I think up to 4 per kilo--versus vigabatrin and they published that the initial spasm response was better on the steroids versus vigabatrin.

But then they did follow-up. They published in Lancet a year later, in 2005, showing the developmental outcomes and the seizure frequency at 12 months to 14 months follow-up was no different between steroids and vigabatrin.

So, I am a little surprised Dr. Shinnar didn't

refer to that data, and I think there is some rich international data that has not been covered. So, I thought you might want to respond to that before I enter my next foray.

DR. YOUNG: Let me respond to that. Those are actually different molecules. That is a different molecule than we have.

DR. PEARL: It is still steroids versus vigabatrin, so I think it is still worth commenting. But go ahead.

DR. YOUNG: Well, in our initial submission, we actually included all of that, the synthetic, which is 1 to 24 amino acids versus the natural, which is the 1 to 39 amino acids. We submitted that all together in our submission in the NDA in 2006. We were told at that time that is not appropriate, we needed to take away all of the synthetic out of our submission and just deal with Acthar, which is the 1 to 39, because that is the real molecule we have in Acthar. We don't have 1 to 24 that we know of in Acthar.

So, we have the 1 to 39, that is the active ingredient. That is why the only thing we have presented is

the 1 to 39, because that is Acthar and that is the reason.

If you are talking about overall what is happening with steroids, prednisone, et cetera, et cetera, yes, we could talk about that. But, again, we were following the charge that we had with regards to the FDA and our submission, which was 1 to 39.

DR. PEARL: I understand. It is just that we are supposed to deliberate on how this affects long-term outcomes, so I think long-term account data would be helpful. But that is all I have on that.

DR. ANDERSON: I would agree, but it seems like that is part of more of our deliberation than the sponsor's, you know, sort of clarification. You know that data and you can bring it to our attention rather than their interpretation.

DR. PEARL: Can I bring up the second and final point? This is really to get it on the public record. This is the elephant in the room, and that is that the price of Acthar escalated by something like 30 times when the sponsor took it over, for whatever reason, whether it is production costs or that's the market value for orphan drugs, I don't know.

But it changed a lot of things. It made it very difficult for families. NORD had to take over. A lot of us had to ride this roller coaster of whether to use it, whether to use oral steroids first. It has affected practice across the country, and I thought it may be helpful, while the company is still able to give us input, if they could comment on this issue, because it is a major issue in practice even if is outside the scope of this hearing.

DR. ANDERSON: Would you like to clarify on the pricing scheme?

DR. YOUNG: Sure. Actually, what happened is that, when we took over the product in 2001, there really wasn't any large price increase. It was the normal increases that occurred.

What happened is in 2007 is when we increased the price. And at that time in 2007, we increased the price, but we had a very low volume of the drug being sold, very, very low. As somebody mentioned in the audience it was a very complex manufacturing.

The former price actually it was just not economically viable for the company. We were not in very

good standings in terms of our economics for the viability of the company as well as the product itself.

As you know, Aventis, in 1996 to 2000, had problems making this. We had a shortage. It was a serious public health issue, and we wanted to make sure that we were still able to make it available to everybody.

The only viable way that we thought we could make it available was to increase the price. And that increase made the company viable, but also made the product viable, which was more important. It made the product viable for every patient who needed it.

With that price increase, what we have been able to do is to assure availability. Just like with the submission, we are hoping to be able to ensure availability. That price increase allowed us to make things available to NORD, so that every patient who needs it can get it.

We have heard examples in the audience about people who needed the drug, they can go get it, they can go to NORD. That's drug that is given by Questcor through NORD free. We support--you know, if they can't pay the co-pay, we support the co-pay. We pay for that for them.

So, any patient who needs it, we want to make sure

they get it. So, there really is no question about our desire for that.

The other thing that we are doing is that we also have an existing sample program, sample vial program, where if a hospital wants to have a sample vial, they can have a sample vial, and we give them the sample vial because if, you know, they say they want it, that's fine. If they then feel the need to--a patient comes in, and it's an emergency, then, they can deal with that as they feel necessary.

So, we are trying to be good citizens to make sure that every patient who needs it gets it.

DR. ANDERSON: All right. So, continue to search your conscience to make sure your questions are clarifying. We can actually bring back anybody we want during our deliberations if we feel there is a point that is sort of critical to our assessment of a question.

We can ask for additional clarification.

Dr. Gorman.

DR. GORMAN: I would like to follow up on Dr. Katz's question with a slightly different point of view.

You have talked about the relapse rate. Do you have any information in your database--this is a two-part

question--do you have any information in your database about retreatment of relapses and the success rate of that, and is that different between the cryptogenic group and the non-cryptogenic group?

DR. SHINNAR: So, the Questcor database does not, but I will give you data, the literature. Now, you get to the level from cohort studies to anecdotes, but long-standing clinical practice, certainly retreatment does occur.

I don't know that there are much data that is different between cryptogenic and symptomatic. I can tell you that you are more likely to give another round of this drug to a cryptogenic case hoping to still achieve normal outcome, then moving on to the next drug with a symptomatic case. But in terms of short-term success rates, there really doesn't appear to be much difference.

Since the goal was for long-term outcomes, I think there are differences in clinical practice, how likely you are to give another course. But the published data about retreatment include basically off-the-cuff remarks in the literature, a proportion relapse, and the respondent.

So, based as all the pediatric neurologists here

are on the baby with only 27 years of experience, I have treated over 100 patients. We have all retreated, and have had some successes, but you really are asking something on which there isn't anything that arises even at the level of a non-randomized trial.

DR. ANDERSON: Dr. Crawford.

DR. CRAWFORD: Thank you. For the sponsor, earlier this morning Dr. Gardner had asked you about aspects of a potential REMS program, and we saw two slides which are not in our material. So, if I could summarize, they appear to be primarily provider or patient representative education and other information dissemination as proposed by the sponsor.

I wanted to ask what thoughts you had to any other aspects of a potential REMS program, and also during the end of the public hearing, one of the speakers was talking about the availability of ACTH through specialty pharmacies for those who may or may not be familiar with that, that tends to be a distribution channel for drugs at a higher cost, often infusion of other injectables, relatively high cost.

I wanted to ask if the sponsor has given any thought to whether there be any changes at all, or would it

still go through traditional pharmacy dispensing channels, probably more so in specialty pharmacies.

DR. YOUNG: I don't remember all the questions, but let me try to answer the last one first.

Right now we go through a specialty-pharmacy company right now, as you said. At this time, we have not thought about changing that, that we would probably continue doing that. We do that because we have a lot of control over what is going on. We do that because if a prescription comes in, and we needed to get to the patient immediately within two days, we can do that, we control it.

If It goes, and it goes to every pharmacy, the prescription comes in, there is no assurance we can get that drug to the patient as fast as we need to.

By going to the specialty pharmacy, we are able to interact on the ground with them to make sure we can get the drug out as fast as possible, and that is the reason we switched over to that. Previously, we did not have one. We switched over because we wanted to make sure we got the drug out as fast as possible to the patient, and that is the reasoning for that.

DR. CRAWFORD: Mr. Chairman, may I modify that?

The first part of the question was in terms of potential other aspects, if any, for the REMS, but since you are contracting right now at least with one specialty pharmacy, do you look at studies as part of that, safety studies through a lot of data that might be available through that one distribution channel and, if so, might that be used as part of postmarketing surveillance?

DR. YOUNG: Right now we don't collect any data from them in terms of safety or anything like that. That is now how it works with them right now. All we do is again distribution for fast distribution.

In terms of the first part where there was something a REMS--

DR. ANDERSON: I think she just--what are your plans, if any at this point, for a REMS program.

DR. YOUNG: At this time, we have not discussed a REMS program with the FDA. We believe that the safety of, and the adverse events associated with, Acthar, again, as the physicians and other people have said, it is known as a steroid class effect. It is clinically recognizable. We will have educational programs that will teach people, both physicians, nurses, health-care givers, as well as parents,

how to recognize things. But at this time we have not discussed the REMS program with the FDA, nor have we put together a REMS program. We haven't done that

DR. ANDERSON: Dr. Dure.

DR. DURE: Actually, I think my clarifying question is directed at the FDA. Should that wait for deliberations? It's okay with me.

DR. ANDERSON: Then, let's let it wait.

DR. DURE: Okay. Keep me on the list.

DR. ANDERSON: Dr. Katz has waved a few times.

DR. KATZ: You can tell me if you think this is a clarifying question or not, but I want to ask a question analogous to the one I asked about relapse rate and what the sort of the specific data were on relapse.

With regard to the question of long-term sequelae, we have talked about those, you know, sort of a fair amount, but somewhat superficially, so again I am interested in what the data actually are with regard to the rates of neurodevelopmental delays and/or the onset of other seizure types with a regimen approximately like what the sponsor is proposing now, some more detail to flush that issue out.

DR. ANDERSON: Are we interested in what the

community of pediatric epileptologists think or specifically in terms of what their review of the earlier studies provided as hard data?

DR. KATZ: Yes, the data. I think I know what the community thinks, but the data--and again I know that none of that data comes from the controlled trials that we have had presented to us, but I would be interested in what the data are.

DR. SHINNAR: So, again, I will refer you to the Lombroso trial and the cryptogenic cases. You had 62 percent with six years of follow-up, which would correspond to age six to seven, since these are mostly in the first year of life. 62 percent had no neurological deficit, which would be an IQ of greater than 70, and no cerebral palsy, autism, and half of them had an IQ of greater than 80.

In other studies, using Acthar, the ones who responded to treatment, even in the symptomatic cases, in the Sher study, had no loss of development, and the majority improved developmentally although they were not normal--these are symptomatic cases--compared to those who did not respond.

Data again from the Finnish cohorts suggest that a

high proportion of cryptogenic cases successfully treated early in life will have outcomes similar to what you heard some of the audience presented, employed, normal functioning adults. That is published by Liukkonen from those series.

There are no data from RCTs. There is supportive data from other drugs that again abolishing hypsarrhythmia early will improve result in good outcomes especially in cryptogenic cases, that are also published case series similar to the Lombroso one with valuable length of follow-up.

Again as with the relapse, it does not appear to be a specific dosing regimen, but whether or not you achieve the all-or-none response, and in this case, etiology, as well.

The difference in regimens have to do with the proportion that achieved the all-or-none response. But, in the group that achieves it, there does not seem to be much of a difference that we can tell among different regimens or different drugs.

DR. KATZ: Do you think there is a number that you could sort of reliably quote about what proportion of patients who respond completely go on to be normal?

DR. SHINNAR: The data from that come not so much from Acthar, but from other data, but it is also suggested in Lombroso, Sher, and Singer in an Acthar study.

If you look at cryptogenic cases who were treated either within one month or before they had regression of milestones, then, a majority, more than 70, 80 percent in Finnish, Icelandic, and other studies, are normal.

As with many other cases in neurology, it is easier to maintain function than to restore lost function. Once you look at the group that has already regressed, while a proportion of them will do normal, may be as high as 50 percent in the cryptogenic cases, the proportions are much less.

But the best data comes cryptogenic cases treated before there is regression, and there, the data is that more than three-quarters of them appear to be normal, defined as finishing normal, being in the normal classroom, learning disabilities are not yet counted, not retarded, not autistic, not having seizures of any kind, on no medications.

DR. ANDERSON: Go ahead, Dr. Lu.

DR. LU: I am sorry, I just keep on getting back

to these issues. There are two questions I need to maybe clarify a little bit. One is I hear the explanation why another trial is not possible. The main reason, one is double blindness, and the second one is recruitment.

When I look back for the pivotal studies that you choose, it is single blind and not double blind, and also it was carried out at one single hospital from 1990 to 1994, and, in fact, size almost the same, because the control group had 26 percent, roughly the same.

I am still not convinced why it is not possible in a multicenter setting, you know, even single blind can get the study being done.

And the other question that I think the sponsor present the limitations in, but did not address one issue raised by FDA review, and I would like to see if you can comment on that.

The data that they select is pivotal study, of course, has the strongest evidence, but that was based on known results, and then the conforming study was kind of weak and depending on which population that you specified.

Again, you already know the results. So the last study which was non-significant result, and so all the order

reflects, but with pre-known knowledge of the results. So, how do you carry that weight, and was that select pre-determined?

How can we weigh the evidence relatively to a prospective study? Thanks.

DR. ANDERSON: So, I understood two questions. One is if you would clarify again the challenges that preclude you from conducting another direct trial of efficacy and, secondly, if you could address how it came to be that you chose to order the pivotal and confirmatory evidence in the way that you did.

DR. YOUNG: Let me deal with the first point, can we do another study. I know that is really what you are asking, can we do another RCT. Regardless of the design and regardless of the drug, I think you are asking, too, is that correct? Of course, there is Acthar.

DR. LU: Yes.

DR. YOUNG: First of all, with the response rate of 87 percent that we already have with our drug from our pivotal 01 study, that means I would have to enroll patients and randomize them to a drug that is either 87 percent responsive, or a drug or a dose that is less than 87

percent.

I am not a clinician, but if it was my child, and you told me I am going to randomize them to a drug that has 87 percent probability of success versus a drug that has 60 percent probability of success, I am going to say I am not going to do that. I am going to go just to the 87 percent probability and just use that drug.

So, I think doing that, you know, that is one issue, just the logistics of getting the patients enrolled in that study when they have to take maybe possibly an inferior dose, a little lower, you know, a different drug, maybe they are a patient that should be getting vigabatrin, and you are not giving them vigabatrin. So that becomes a problem just from the clinical management. As a parent, I would have a lot of problems with that.

So, I think enrollment would be difficult to that.

DR. LU: But you base on the assumption that is the real response rate; right? So isn't that--

DR. YOUNG: That is partially correct, I am basing it on the assumption that the 01 study, which was a well-controlled study, was true at 87 percent, and has the supportive evidence of the Snead studies, which were not

randomized, controlled trials--I agree with that--but again they supported with the 90 percent.

DR. LU: Excuse me. I just want to bring attention that the sample size is very small, so the precision is not there to say that is the point estimate.

That is why the question raised whether, you know, how sure you are in terms of the response rate.

DR. YOUNG: And I think Dr. Duchowny talked about the robustness. So we are not only talking about the 87 percent of those patients who are naive. We are also talking about those patients who failed prednisone, received Acthar again, and that also was 87 percent.

So, if you look within the study, you don't only have the one group of 87 percent. But there is robustness in the study because of again the failed prednisone patients received Acthar. 87 percent of those patients responded when they didn't respond on prednisone, so further adding robustness to it.

The p-values were 0.0015 or 0.003, so they are very small, a very large difference. So if you look at just the study itself, Dr. Katz brought this up in his first talk when he first talked about there is confirmatory evidence is

within a study as well as outside of the study.

We believe that we have confirmatory evidence within the study because of again the prednisone patients, the large difference, the p-value. But we also have confirmatory evidence outside the study looking at other studies, Snead, which had the same percentages, 97, 93 percent, the same kind of percentages. And also Dr. Trapnell talked about the 05 study, which is confirmatory, which really showed that there was the tendency for the higher dose to have a higher effect rate, which was also confirmatory.

DR. ANDERSON: The second question had to do with why you chose to order one trial as pivotal, and others as confirmatory, which I will let you answer if you want, but I think some of these questions about whether another trial could be done or not are as much our prerogative as the sponsor's.

Also, the issue of whether we accept as statistically justified or clinically persuasive, how the evidence was ordered is, you know, what we are going to be deciding.

So, if your question is of that sort, to the

panel, then, I think we can deliberate and debate those points. But, since it was raised, if you would like to address why you chose to order them in the way that they were, then, you should please do so.

DR. YOUNG: Yes, at the 2007 meeting with the Food and Drug Administration, we presented all the possible studies that could be looked at in terms of RCTs and, in looking at all the studies, there was an agreement that we had to obtain all the studies and evaluate all the studies that we could obtain the source data.

Those three studies that we talked about before were the three studies that we were able to obtain the data and then move forward. But also at that meeting, in the discussions, we also agreed that the probability was that the Baram study would be our pivotal study, and that was chosen specifically because we thought it was the best designed study.

As we said before, it was a straightforward, clean study. There really were no dose escalations, changing of things, and so we thought from a design point of view, that was the best designed study.

Again, that was in agreement with the FDA for us

to look at that one.

DR. ANDERSON: So, in order, I am going to give Dr. Felner and Dr. Chapman the last chances, and then unless there is a mutiny, I will move on to the consideration of the questions.

Dr. Felner.

DR. FELNER: I am sorry. I probably would have asked this earlier if--I didn't realize that some of the questions that were coming up, came up, but the vigabatrin I guess what was that actually compared to when it was approved by the FDA. Was it compared to placebo? Was it compared to prednisone? Does anybody know?

DR. SHIELDS: High dose, low dose, and versus placebo.

DR. ANDERSON: Could you repeat it into the microphone, please?

DR. SHIELDS: Sorry. The vigabatrin study was a high dose/low dose comparison study, randomized study.

DR. ANDERSON: Will you also identify yourself, please.

DR. SHIELDS: Don Shields from UCLA.

DR. ANDERSON: Did you want to proceed with

something from there, Dr. Felner?

DR. FELNER: I will bring it up in the discussion.

DR. ANDERSON: Okay. Dr. Chapman.

DR. CHAPMAN: I am done.

Panel Discussion/Questions

DR. ANDERSON: Seeing there are no further questions, we will now move to a panel discussion and questions.

At this point, I would like to remind the public observers at the meeting that while this meeting is open for public observation, public attendees are no longer able to participate except at the specific request of the panel.

The plan is to discuss questions up until 3 o'clock, and then I will have a small break, and then we will resume and finish any remaining questions that we have at that time, so people can plan.

There are both voting questions and discussion questions. I will read the questions and then we will have a period for discussion. Those that require a vote, we will vote on, and then those that are only discussion, we will just sort of acknowledge that we have sort of exhausted that topic, and then we will move on to the next one by sort of

mutual consent.

The first question reads as follows:

Substantial evidence of effectiveness can consist of data from adequate and well-controlled clinical investigations (replication) or a single adequate and well-controlled clinical investigation and confirmatory evidence.

Part (a) of the question reads: Has the sponsor provided substantial evidence of effectiveness for Acthar Gel as a treatment for patients with infantile spasms?

At this point, I would like to open it up for anybody who would like to start the discussion about questions or voice an opinion as to whether they feel that this has been established and, in passing, if you feel one way or the other, if you feel that it is the case, if you would sort of just discuss out loud which of the standards you feel has been met in reaching that conclusion.

All right. Well, for the purpose of giving a target, I will give my opinion first. When I was reading the briefing materials, I had a lot of personal difficulty in that I felt that ACTH was what I would want to give my child, but I wasn't sure that I felt that the evidence was such that I sort of really felt that I would want to base

sort of a regulatory decision on essentially one--you know, 15 patients treated with the recommended dose.

So, in my own deliberations, I sort of flipped it the other way around, and I thought, instead of thinking dose first, I just sort of felt had the efficacy of ACTH been established, and I think from my own deliberations I think that there was one adequate, well-controlled trial that to me was convincing that against a reasonable control treatment, ACTH was a superior effect, and that that was sort of the one trial.

The remainder of the data, both controlled and uncontrolled, served for me as sort of a confirmatory evidence that ACTH was effective against what we understood to be other potentially effective therapies and against an understanding of the disease itself.

So, then, it is only secondarily that sort of in my own mind, I tried to consider whether this dose was a justifiable dose or not a justifiable dose. But I sort of felt that the--so personally at this point, barring you persuading me otherwise, I sort of had the sense that considering ACTH as a treatment sort of separate for a moment from the dose that should be used, there was one

well-controlled trial with a variety of confirmatory evidence, and so I would like people to perhaps comment or challenge me, or sort of give their alternative.

Dr. Snodgrass.

DR. SNODGRASS: I have the same opinion. For comparison, I would like to just point out that this is sort of a hard endpoint; in other words, it's physician observer or parent observer they are having spasms, and you can have video-EEG data. So that is one piece of data. This is not as subjective as, say, rating scales for depression in adults for all sites and data. That is one piece of information.

The other is the effect size, even if you don't believe 87 percent is correct, that it is somewhat lower, is still a very clear effect size, and it is probably at least more than 50 percent perhaps in most of these data.

By comparison, the SSRIs or most antidepressants have effect sizes as low as 15 percent, maybe an average of 30 percent, and those get approved. I feel it's the single, adequate, and well-controlled with confirmatory evidence and that we have that.

DR. ANDERSON: Dr. Clancy.

DR. CLANCY: I would just like to comment on the effect size because I get the impression that you don't quite believe the 86 or 87 percent, nor do I. In my personal experience, if I had to pull a number out of the air, I would have said 50 or 60 percent.

It is still much more powerful than placebo and, from that point of view, it would support approval. But it would take against part of the argument about not conducting another trial because, if it really was 87 percent, done deal. But, if it's more like a 50 percent, there would be at least more room to discuss additional trials.

DR. ANDERSON: Ms. Kandell.

MS. KANDELL: I come here as a--I am probably the only non-scientist in the room, so I come here as a patient representative. I had intractable epilepsy for about 15 years. I was on vigabatrin. You know, it was not approved.

I had to get it from Bermuda and Canada and London. It was a pain in the--well, pain in the neck to get it.

So, I had a time getting my medicine the right way in order to get it in time in case Customs seized it and inspected it and delayed it, and all that. I was fortunate that the engineering firm my husband works for is self-

insured, so even though vigabatrin wasn't approved, I was told when I started it--Dr. Stanley Rieser from Columbia put me on vigabatrin after my second son, who is now 17, was born, that it was going to be approved, and apparently never was, at least for adult epilepsy.

So, I was fortunate that my husband's firm was self-insured. So he spoke to somebody, and that's how we got it paid for. So, I bring kind of the patient perspective of the people that are sitting in the audience here, and I see no reason on earth not to approve this.

There is no compelling evidence of efficacy or safety risks here that would bar the FDA from approving it, and if it works for the people in the audience and other people, I see no reason for the FDA not to approve it.

As far as the standard, I am convinced that it establishes the single adequate and well-controlled clinical investigation with confirmatory evidence.

I would also add that I think there were a host of ethical issues in addition to all the scientific issues with doing another study, and I wouldn't want people that need this medicine to not have it in the interests of doing , another study.

Thank you.

DR. ANDERSON: I wanted Dr. Clancy to clarify because it's related to your thing. Concerning the effect size and maybe the need to do another study, what would that other study consist of? It has got to be placebo controlled or you are looking at different doses, or what sort of--did you envision might be--would it be necessary to conduct a second study, or it just would be desirable to do so?

DR. CLANCY: No, I don't think it's necessary to do another study, but I wouldn't accept at face value the concept that it's impossible to do. After all, we have just talked about three of them.

My point is that, in the pivotal study, I think there is enough data to show that it has efficacy compared to historic placebos in other trials. So that part I am very comfortable with.

I don't think I would accept at face value the response rate of 86 percent as being typical for all places, and anyone else wants to comment, please do. But if the argument against considering a study is that the response rate is 86 percent, and it's really impractical, like much lower, that would at least open the door to discussion of a

possible study.

DR. ANDERSON: Dr. Dure, I think you are next.

DR. DURE: To get the first part over with, I tend to agree with you pretty much wholeheartedly, I mean in terms of the standard, et cetera, with respect to treating infantile spasms,

But I mean maybe some guidance from the FDA--and Dr. Katz can probably put it together for me--because the way my understanding is, is that the FDA is--they are tasked to provide safe drugs for conditions, and you said at the very beginning that this is sort of taken on its head here.

As is usual for FDA meetings, we are arguing about drugs with like 10 percent better than something else, and this one I think most everybody around the table would say yes, ACTH really does work.

But we are doing that on the basis of some fairly flawed studies compared to the way the FDA usually works, and so I am not satisfied that there is equipoise with respect to dosing, and I am not at all satisfied with the analysis of the safety data even though--I use this drug. Don't get me wrong, but I also don't believe that there is only 1 percent reporting of weight gain, which is what the

data seem to suggest.

I mean there is obviously some under-reporting here. So, the reason I brought you up, Dr. Katz, was because I have heard a good deal from the sponsor about assuring availability. How does that fit into the FDA's paradigm? I am talking about safety, efficacy; how does availability fit into the FDA?

DR. KATZ: It's true. A number of people have said that we think the drug should be available. There are mechanisms to make investigational drugs available before they are approved, and, in fact, of course, ACTH is available. It is legally marketed, not for infantile spasms obviously; it is the treatment of choice people are using it. But in a generic sense the desire to have a treatment available isn't really the standard in law that we rely on to decide whether or not we should approve it.

We have to follow the dictates of the law, which of course allow for a considerable interpretation, but there has to be something that we conclude constitutes substantial evidence of effectiveness, and those are the definitions of substantial evidence of effectiveness. We have to decide that there is at least one adequate and well controlled

trial, and, of course, that is the question we are bringing to you today and if that is the standard we are going to apply, and something called confirmatory evidence.

Now, there is no guidance in the law as to when we apply this standard, the one study standard, or what constitutes confirmatory evidence. That is something that we deal with on a case-by-case basis, and, of course, it is one of the main questions we are asking you to decide, whether or not you think that standard or the other standard has been met.

So, the desire to have something available in and of itself doesn't really enter into a decision about whether or not a drug out to be approved. There has to be at least substantial evidence of effectiveness. And, of course, there has to be adequate safety data.

DR. TEMPLE: A couple of other points have come up. We do feel we need to find some dose that we can say is effective, but drugs have been approved, most of the drugs you know about, without our knowing that the drug that is approved is the very best dose. Dose-response is something that still needs a lot of work. It isn't always done optimally.

So, if the dose that seems to people to work seems unacceptably toxic, that would be a problem. But the fact that it isn't the optimal dose is not usually our reason for turning something down. We might as for further studies afterward to explore what the best dose might be.

As Rusty said, we have never--the people who wrote the law and the people who sort of advised the legislators on what to write never said what they meant by confirmatory evidence, but we have a lengthy guidance called the Evidence Document that suggests what some kinds of confirmatory evidence might be.

So, two completely different endpoints within a trial or substantially different endpoints both going the same way, that might make you feel stronger about something than the absence of that, and maybe that exists here. Other studies that are leaning, but don't quite make it could be convincing.

There is a wide variety of things, and you are looking at all those things. But it is not very precisely defined. It also says very clearly that a very strong p-value is often persuasive especially if you beat something that might have some activity of its own.

DR. ANDERSON: Dr. Chapman.

DR. CHAPMAN: I did want to bring up one issue, is that if you look at what the sponsor is recommending, that they are recommending a two-week trial, and then you basically figure out if you have responded or not.

So, I would make the argument that you could create a trial as a crossover where you do a two-week trial of either high dose or low dose and then, if they fail, you could cross them over to the other given the idea that we know that patients who respond to medications early do better,

But that early time limit is maybe arbitrarily set at one month, in other words, if you feel like--I think there is a way to do a trial. I mean if you do a two-week trial of a medication and then cross them over to the other arm of it--because at least the supportive study doesn't show that high dose and low dose really make a difference, I mean in the Hrachovy study.

So, I think you could make an argument of doing another trial if part of the issue for this committee was there is not evidence. I mean I do think it may be possible.

I personally think we need the medication and whether the evidence is a little bit, you know, up to the group, I think the statisticians know it better than I do.

DR. ANDERSON: Well, we get to debate sort of whether we feel the sponsor is established efficacy of the two-week, you know, recommended course, so we can come back to this issue on sort of how much in for how long.

But I wasn't sure that I got your sense of do you feel that there is data here sort of sufficient to address the regulators' concern about a single, well-controlled trial and confirmatory evidence or not?

DR. CHAPMAN: I think there is enough data to show that it's effective, but then I guess the other issue about dosing and such, I have more reservations about. But I just want to kind of point out that I think you could make a argument that there is a way to do a trial even though the sponsor may say otherwise because, once again, if you say that if they are treated within a month, those seem to do better than those who have a delay in treatment, and if you are only saying it's a two-week trial, it seems to me you have got a couple weeks to play with.

DR. ANDERSON: Dr. Green.

DR. GREEN: What I wanted to say has really been echoed by others.

DR. TEMPLE: There have been a number of expressions of reservation about the ability to do a trial, and this needs to be clarified. Does anybody think you couldn't compare, do a trial comparing two doses, or comparing this drug with vigabatrin, another approved agent for the same thing? Would those be difficult?

DR. ANDERSON: I think all those statements have come from the sponsor so far. So, does the Committee here, especially those who deal with the pediatric epilepsy population, want to sort of jump in as to whether they feel that it would be technically impossible or ethically wrong to conduct some form of additional studies on this medicine's dose and efficacy? Dr. Clancy.

DR. CLANCY: Of the two pivotal trials, the one by Dr. Baram was 150 U/m² per day, divided twice, and the hypothetical concept was that there is more of an effect on the adrenal axis, and so forth, and they had a superior result, 86 percent.

The Hrachovy study also used 150 U/m² per day given as a single dose, and they had significantly lower

response rate with the same, at least on paper, the same endpoints of cessation of spasms and resolution of the hypsarrhythmic EEG.

So, if we accept that ACTH is effective, then, the question could be, well, are these different numbers because they are reading the EEGs differently, or they have different criteria for success, or was there truly a biological difference between 150 units given once a day or twice a day.

I think that could be a study where the patients are randomized. They get the same drug, same total daily dosage, but one as a once a day, one as a twice a day, because to compare it to vigabatrin when we don't think that has a very high success rate compared to ACTH might be very difficult. There might not be equipoise on that, but there could be with two different doses of the same total amount per day.

DR. ANDERSON: Dr. Pearl.

DR. PEARL: So, despite the ethical concerns that have been raised, there are neurologists who are starting with oral prednisone at the United Kingdom study protocol dose. There are neurologists who start with ACTH. But a

practical limitation is you can't get ACTH right away because one often has to go through funding, NORD, to get the drug.

There are neurologists who start with a ketogenic diet, and there are probably some who start with vigabatrin.

Fin non-tuberous patients, and tuberous patients, I think most people start with vigabatrin.

So, one could ethically devise studies and get them done. Having said that, we badly need more studies in infantile spasms, but we really need them in dose-response, how to handle relapses and long-term outcome. I think those are the questions that are going to come in the ensuing minutes.

But my opinion from the preponderance of the evidence is really, if confirmatory data is as broadly defined as was described, I do think there is substantial evidence of effectiveness from the one Baram study and confirmatory data.

I mean I can accept that there is substantial evidence of effectiveness to approve this drug.

DR. ANDERSON: Before I go back to the list, anyone else want to comment on the trials, the ability to do

trials or the questions for trials, and then I will get the FDA's rebuttal to that? Dr. Snodgrass.

DR. SNODGRASS: I just have sort of comment to Dr. Clancy's--the specific here. You could do like a total daily dose as you are suggesting, but if the plasma half-time of IM ACTH is only six hours, then, by definition, you probably are giving a lower total area under the curve exposure even though--or to some extent perhaps, at least there is an interim period in a 24-hour period, so that you might want to think of other designs.

Even though the total daily dose might be a little bit lower, it might be twice a day at a slightly lower dose would give you some additional information.

DR. ANDERSON: You are on the trial question, right?

DR. KHATRI: Yes. Actually, a related question which Dr. Clancy brought up using 150 BID versus 150 Q day. I wondered, you know, as an adult neurologist, this is a question of the pediatric neurologists, is there a role potentially for a lower dose BID potentially for a more continuous effect and maybe a better safety profile?

DR. ANDERSON: Dr. Gorman, you had something on

this?

DR. GORMAN: This comes as a former IRB Chair for the ethics of the study. Besides the dosing, once a day versus twice a day, I would also consider the duration of therapy. The patient stories today told remarkable results in very short periods of time. Is two weeks too long would be another question that I think could ethically be answered study.

DR. ANDERSON: So far there seems to be a consensus that further studies could be done, and should be done, and several ideas for what should be done.

Dr. Mizrahi.

DR. MIZRAHI: I would say that I think we have enough data to be able to say yes to this answer. I think that we would like to have more information about dosing duration and have a better idea about the drug in general.

But I think any of that information is going to be very difficult to obtain and we may be sitting here in two years having the same discussion about whether or not that new study answered all the questions that we needed answered.

I think we would have problems in designing a

study in terms of blinding, how to power it, recruitment, and I think there is also an issue about treatment lag, and not everybody agrees with whether immediate therapy versus a few weeks is really an issue or not.

So, I agree that more studies would be nice, but I think in this particular issue, for this particular question, not essential in terms of our overall deliberation about the question at hand.

DR. ANDERSON: You wanted to come in on the trial question, Dr. Khanna?

DR. KHANNA: Yes, I did. I concur with the previous speaker, but also wanted to add two things. The first is that I do think the question has been answered, I do think the answer is yes. I mean even our own panelists are using the medication.

If we ask for more studies to be done, that will delay obviously a potential approval. That is one consideration.

The second thing is there is no reason that further studies can't be done concurrently with an FDA approval or recommendation for approval.

DR. KATZ: I just want to clarify some things. I

think the question of additional study or studies is a very important one, but I think it is potentially distracting from the question we are trying to get at.

If people think that another study needs to be done in order for us to determine that there is substantial evidence--in other words, that there isn't yet substantial evidence without another study--I think it is useful then that ought to be discussed at this point.

I think there are a lot of studies that are interesting. Some studies I think could absolutely be done and probably should be done. But we have a mechanism to get those studies done postmarketing, after a drug is approved, so it doesn't have to hold up approval.

Right now at this point in the conversation, if folks think that there is not yet substantial evidence, so we need another study, I think we should be talking about studies and study design.

But if that is not what people think, I would suggest that we table the discussion on additional studies until the end, because I do think it is important and I do think there is information we would like to have. But, if it's not critical to answering this question, my humble

recommendation would be to table the additional studies question until we are at that point, until we get to this question.

DR. ANDERSON: So far, everybody has come in, has sort of come in as sort of the yes, and then we have all had additional questions to make. So, maybe we could consider voting on this one.

So, I guess I would really like to give a chance for somebody who feels like they want to be a dissenter. You know, I don't want to sort of just proceed along. If there is somebody who has sort of serious objections that we not proceed to a vote on this question, let's take their comment at this point. If not, then, maybe I will just move on, and we can move on to the voting.

Dr. Lu.

DR. LU: I just want to clarify, because I think it's unusual at this time in the meeting that FDA didn't present anything. So, I want to understand the term that we are using here in this, substantial as well as well-controlled clinical trial here.

Usually, the pivotal trial are prospectively selected, not retrospectively selected, and usually the data

has been very closely monitored with all trials, and the quality controls, and so on.

So, I am just trying to understand in terms of world standards, and while a retrospectively selected study without, you know, the full recoverable data, and was not designed as indication data, will qualify as a well-controlled clinical investigation for the indication basically. I need the guidance from FDA.

DR. KATZ: First of all, there is a precedent for our accepting studies that were not performed under the auspices of a company, not performed with the intention of using those data as the basis for approval of an NDA, basically literature that we have then asked, as we did in this case, the sponsor to go and try to get the primary data.

So, I think the Baram study has the primary elements that we would consider to constitute adequate and well controlled. It was not double-blind, but we don't think that that was a particular problem here because the primary outcome measure was read by a blinded reader, and there is no particularly obvious reason to think that any sort of bias crept in.

It's randomized, which is of course a critical element from our point of view. The outcome measure was objectively measured. We have not reason to believe that the primary data that were available were obtained and re-presented and re-analyzed. We analyzed the data independently and came to the same conclusion.

So, I would say that even though the primary outcome was sort of retrospectively designated, it was the obvious outcome to look at. I think we think it has the elements of an adequate and well-controlled study. We have no evidence that it was poorly conducted or anything like that.

I think we think it qualifies.

DR. TEMPLE: Actually, the rules about what an adequate and well-controlled study is were written and revised in 1985 and, believe it or not, it actually doesn't say that you have to have specified all this in a protocol before the study.

It says if you didn't, you have to explain how you happened to choose them. So, that is probably more flexible than we would ordinarily be today. But I guess what struck me is these are the only endpoints anybody even thinks about

in that case, and they all go the same way. So I think that is partly why we are not worried about that. Everybody noticed the small sample size, but if drugs really work very well, then, you don't need a lot of patients.

But the rules are not absolute on these things. lot of judgment about how much was done later, how much was done earlier, and we usually get very nervous. It helps a lot, as Rusty said, that the EEGs were read blindly.

DR. ANDERSON: Dr. Gorman.

DR. GORMAN: I wanted to augment what the FDA had to say. I do not work for the FDA, I am about to reveal my age. In 1994, noticing that there was the absence of pediatric labeling on a large number of drugs that were commonly used, but not approved, for pediatrics, the FDA gave out a written guidance that said companies could submit data from the literature for potential inclusion to the label.

While it has been a long time since I have looked at the data, I think approximately 400 companies with agents took advantage of that, and approximately 80 drugs got labeling based on the literature, not necessarily randomized, controlled clinical trials, but patterns of use,

and data that was widely available but not submitted under an IND process.

So, this was used once in 1994 through 1996 with what I would consider great success, and then since that time, kind of fell off the radar again with the strengthening of the IND process.

DR. TEMPLE: One more thing. The same guidance, Rusty, that we mentioned before on evidence has an explicit section on reliance on data from the literature, and it says certain things may get more credible like being able to get through our data, being able to find out what the protocol is, having details, being able to do your own analysis.

So, it contemplates that. It is certainly true that the primary data usually from a planned study intended to do this, but that doesn't mean other sources of data can't be used.

DR. ANDERSON: Dr. Todd.

DR. TODD: I am personally a little bit underwhelmed by the data. The single adequate well-controlled trial certainly has an impressive effect size and p-value.

My biggest issue there is that we are basing the

crux of the decision on data done as a single center and administered by a single investigator, and the two confirmatory trials, Trial 04 and Trial 05, in my mind don't really confirm much of anything. They are basically negative trials, high dose, not substantially better than low dose, and low dose not substantially better than prednisone. So, I am not really sure what the compelling confirmatory evidence is.

I don't see it in those two trials.

DR. ANDERSON: At this point we will move on to a vote of the question. So I will read it one more time and then when I am done the process is that we will each privately push one of these buttons Yes, No, and Abstain, and after they have all been tallied in private, then, the result of the vote is displayed and then we each go around and state our name and acknowledge our vote, and make any additional comment we would like to make, if any, as to the reasons behind our vote. And then we will move on to our next question.

Substantial evidence of effectiveness can consist of data from adequate and well-controlled clinical investigations (replication) or a single adequate and well-

controlled clinical investigation and confirmatory evidence.

Has the sponsor provided substantial evidence of effectiveness for Acthar Gel as a treatment for patients with infantile spasms?

If everyone would please enter.

[Electronic voting.]

DR. NGO: We are still missing four more votes, so everyone press your vote again just to make sure we have your vote.

DR. ANDERSON: We are still missing one. If you don't want to vote, you should still push Abstain, so they have a full tally.

DR. NGO: We are still missing a vote. We should have a total of 23 votes. We are still missing one vote. Everyone press again, please.

DR. ANDERSON: Okay. There are 22 voting in favor, 1 No, and no abstentions. We will just go around and state your name and state your vote, and any other comment you feel that you wish to make, if any.

We will start on the end with Dr. Todd.

DR. TODD: Jason Todd. No.

DR. COHEN: Jeffrey Cohen. Yes. For the reasons

that were stated, it is always hard to get your mind out of being a clinician that takes care of patients, but I feel that the single study was adequate with the supporting studies.

DR. LU: Ying Lu. Yes, because I think it clears my consumer publication bias, because a small circle seems to know what is going on there and, as FDA explained, the standard is varied. Not necessarily all have to be prospectively selected. The study itself, even though the precision may be not high enough with confidence interval is not that wide in case of excluding, you know, as people mentioned, was 50 percent, 60 percent of efficacy. So I vote Yes.

DR. van BELLO: I voted Yes. It was kind of a hard vote because I think that the single trial is a small trial and you would really worry about variability from site to site. On the other hand, I think that, if you look at the total evidence, both the trials that have been supplied as well as the historical practice, there is enough evidence to support the claim that it works.

DR. AOKI: I voted Yes. I felt that Study 1 was compelling, and I thought that the argument that if you had

treated them with placebo, that it was at least 10 percent, and this is in all the studies that were done, Acthar was clearly superior to placebo if you use 10 percent. So, I thought that the data was there.

DR. ANDERSON: As you register your vote, can you go ahead and read your name in and state your name.

DR. AOKI: Tom Aoki.

DR. FELNER: Eric Felner. I voted Yes. I think the Baram study served the purpose and actually appreciated hearing the experts, the pediatric neurologists, who didn't really believe the 87 percent, because I don't think I would have believed it being that high. But cut it in half if you want. It is still better than just about anything out there, and the medicine has been around for 50 years. So I think that made the case there.

DR. CLANCY: Bob Clancy from CHOP. So I voted yes. I did think that the concept of the drug was effective as opposed necessarily to the particular regimen of administering it. I also felt that to vote No would be to negate what I have done in my practice for the past 30 years, so I would be in big trouble I think if I morally couldn't vote Yes to this.

DR. CHAPMAN: Kevin Chapman. I voted Yes, and I believe the Baram study was quite compelling and it sort of fits my own practice, that I do find it's effective, though maybe not as effective. But I do think it's an effective drug.

DR. CRAWFORD: Stephanie Crawford. I voted Yes. I do believe one of the studies in particular was adequate. Certainly for scientific evidence there was far more anecdotal evidence of effectiveness. But again, based on these studies that we were given and, fortunately, because it's not a double-barreled question that included safety as well, I voted Yes.

DR. GARDNER: Gardner. Yes.

DR. LESAR: Tim Lesar. I voted Yes primarily because of the hard endpoint that was mentioned, the apparent treatment effect. Even if it was 50 percent of the 87 percent, a strong relationship between treatment and onset of effect, it was a fairly hard endpoint and no safety signals that was of concern.

MS. KANDELL: Ellen Kandell. I voted Yes for the reasons I previously stated.

DR. ANDERSON: Britt Anderson. I voted Yes.

DR. GREEN: Mark Green. I voted Yes based on the first study and the ability, probably unique ability, of the agent to appear to jump-start therapy.

MS. VEGA: Marielos Vega. I voted Yes

DR. KHANNA: Prerna Mona Khanna. I voted Yes primarily because of the high success rate and the temporal relationship of the success after the medication was given, also because of the very low p-value in the study. I thought it showed that it was efficacious.

DR. FRANK: Samuel Frank. I voted Yes. I think that the pivotal study, 01, study did demonstrate effectiveness. Even though the supportive and the additional study weren't necessarily positive in terms of their own outcome, I think that it still was above and beyond historical controls.

I also thought that the evidence that was presented and summarized today wasn't so poor and minimally significant that we can recommend reversing half a century of clinical practice given that it is a rare, devastating disease.

DR. KHATRI: Pooja Khatri. I voted Yes. I did think that the treatment effect lacked precision in the

total trial, it did seem that the treatment effects were consistently seen in several of the confirmatory studies whether numerically or statistically.

DR. PEARL: Phillip Pearl. I voted Yes. I would like to address one concern about supportive evidence, confirmatory evidence, because I had the same caveat. When Dr. Katz opened, he said really not to use, I think, historical precedent, practice experience, advocacy pleadings as the reason for this approval, as tempting as those things are.

But when I also learned that the blanket of confirmatory evidence was broad and that one in fact could use a cohort within a study to support that, I thought of how the non-responders did in the Baram study to prednisone, and they actually did pretty well when they were given ACTH, and so I was satisfied that going within that study met the FDA criteria for confirmatory evidence and felt comfortable voting yes.

DR. MIZRAHI: Eli Mizrahi. I voted Yes.

DR. DURE: Leon Dure. I voted Yes.

DR. SNODGRASS: Wayne Snodgrass. I voted Yes.

DR. GORMAN: Rich Gorman. I voted Yes for a lot

of the reasons already stated. I was taught in Statistics that if you have small numbers and a very diverse population, you have a hard time proving your out points, and they did, and the outcomes were hard outcomes.

The other point that was incredibly convincing to me was in the statistical analysis, Chart 11, which showed that there was a dose-response for these agents across the three trials that were done.

DR. ANDERSON: I am supposed to also summarize just in case people wonder what I am doing. So, the Committee's vote largely reflected the standard of a single, well-controlled clinical investigation with confirmatory evidence. The confirmatory evidence represented analysis of the crossover populations, the aggregated data across several studies showing evidence of a dose-response curve.

The dissenting vote reflected not being persuaded that the secondary supportive studies were, in fact, studies of a positive effect.

I think we have already answered (b) pretty much through our discussion of that first question.

So, we can now move to Question 2, which is another discussion question, and since it has several parts,

maybe we ought to fractionate it a little bit, but it says, If the answer to Question 1 is Yes, has effectiveness been shown in cessation of spasms, amelioration of the EEG, prevention of other seizure types, improvement in long-term developmental outcomes, or (5) other outcomes?

To me, there seems like there might be a couple of easy ones for us to tackle. Does anybody feel that there has been persuasive evidence that this treatment prevents the development of other seizure types?

Okay. How about anybody who feels that these studies provide evidence for the improvement in long-term developmental outcomes?

Okay. I guess we will do this one. Besides the spasms cessation or the EEG resolution, are there any other outcomes from these studies that somebody wants to make the case has been persuasively presented or--you know what I mean.

Okay. So, our discussion can pretty much focus I think on the two first ones of cessation of spasms and amelioration of the EEG.

Would somebody like begin with a pro or con against--well, we must have some reason for our decisions,

so I will start out.

I think the spasm evidence was stronger, because at least there was evidence within subgroups of one of the other trials that showed a statistically significant, nominally, statistically significant, benefit for spasms. So, that one, in my own case, seemed to be one of the reasons I used it, and also the EEG evidence seemed to me, second-hand, to be reasonable. So, I felt there was evidence for those endpoints.

Does anyone else want to add anything?

Do you feel like you need to hear more discussion on that? Okay.

So, Question No. 2 is a discussion question, so that has been discussed, and it seems like the Committee's general consensus is there was evidence in favor of the first two endpoints having been demonstrated, and no persuasive evidence for the second set of three.

Yes, Dr. Frank.

DR. FRANK: Just a question. Was this question posed to us in terms of what to look for postmarketing if this drug gets approved?

DR. ANDERSON: I think the question is basically

if you voted Yes on Question 1, you must have felt it was effective in some way, and what were those ways that you sort of felt it was effective, and you used to support a vote of Yes.

DR. FRANK: So, not using this question, the discussion to move forward once it's--

DR. ANDERSON: I think it's looking more for our rationale and justification for our Yes votes than sort of what should be done next.

Dr. Katz.

DR. KATZ: Just to clarify, this wasn't intended to start a discussion about what additional information we should obtain postmarketing if it's approved. It really was largely driven by what do we think it is appropriate to say in labeling if it's approved. Can we say that there is evidence that this treatment decreases the developmental sequelae or decreases the possibility of having other seizures? That is really what it was intended to do.

DR. ANDERSON: We will skip Question No. 3 since it's not pertinent, and we move to our next voting question.

The sponsor wishes to recommend a two-week course of treatment, followed by a two-week tapering regimen. Has

the sponsor submitted evidence to support the view that a short course of treatment provides sustained effectiveness?

There were several people who had dosing issues, so maybe one of you would like to begin this discussion.

Dr. Clancy.

DR. CLANCY: Well, the question is whether there is sustained effectiveness, and the question is what does sustain mean over the two weeks of the study, a month later, a year later, and I didn't see the data that supported the concept that it sustained. It is really a short-term study.

Whatever the specifics of the dose regimen, I don't know how we can answer this.

DR. ANDERSON: I guess you could also use sustained just--you know, I give you the dose, something stops, the drug runs out of your system, and immediately everything starts up again. So, like you say, there is an issue of time course, sort of what is the time course of effectiveness. Do you have some sense of what you would go out on a limb for, what sustain should mean in the context of the data we have seen?

DR. CLANCY: Well, I mean taking the data at face value, if you follow that recipe that they give, the

duration, the taper, and so forth, it's an effective treatment. I am very comfortable with that. But they ask the question how long does that sustained benefit, six months later, a year later--there just weren't data that provided for that.

DR. ANDERSON: Dr. Mizrahi.

DR. MIZRAHI: I guess the other issue with this question is the two-week followed by the tapering schedule, and the question is, is the data adequate for the two-week and two-week tapering, or is the question is this the best schedule. So, if it's just this particular schedule and the snapshot of this particular schedule, then, I think that there probably is information to suggest that there is some effect.

I guess the real question is about what Dr. Clancy was talking about, is what does sustain mean, does sustain mean relapse rate, and then that represents a different question. But if, as you suggest, it's a matter of drug taper, is everything back, then, I think you could say that with that definition of sustainability, probably yes.

The issue is if, by looking at sustainability, you are looking at, for example not EEG-video monitoring but

parental observation. Some of the studies, in one of Hrachovy's studies, looking at EEG-video monitoring and parental reporting shows that parents are really pretty good at saying their children have spasms. But they are not very good at saying they don't.

So, you know, just a report of success is not going to be good enough.

DR. ANDERSON: Dr. Katz.

DR. KATZ: Again, just to clarify what we were trying to get at with the question. Remember if the drug is approved, we have to write labeling, and part of that is dosing recommendations. I think the expectation or the implication of the company's proposal is you treat for two weeks, you taper for two weeks, and you are done. You know, the patients are either going to respond or they don't respond, and then they don't respond to the treatment.

But what are we supposed to write? What is the evidence that have been submitted? Again, you can take whatever evidence that you have been presented into consideration when you try to answer the question.

But if you had to write dosing recommendations for this, what do you write, treat for two weeks, taper two

weeks, watch for two weeks, and if spasms recur, treat again? It's not like we have actually evidence of the safety or effectiveness of multiple treatment regimens.

So, we have to try to figure out how to explain to practitioners how to use this, and that is really what we are trying to get at.

Pretend you were us for a minute.

DR. ANDERSON: To present a fixed point against which others can argue, I guess my logic would probably be similar to what I surmise may have been the corporate logic, which is if I think it's effective and I have to pick a dose, I might as well pick the dose for which the p-value was the biggest and the effect was the strongest without necessarily claiming optimality, So if I had to write the label, I would pick the dose that they picked.

Does someone else want to pick another one or argue against that rationale?

DR. KATZ: Again, to clarify, it is not so much what specific amount of drug--for example, when we talk about dose, your conclusion is perfectly reasonable as far as what specific dose. But it isn't enough to say that the treatment is effective.

As I say, we have to write labeling, we have to be able to tell the practitioner how to use this, how many of these treatment courses can they give, should they give, how long do they observe the patient after this first course before they give another course, and is there evidence that that other course is going to do anything.

So, that is really the question we are trying to grapple with here.

DR. ANDERSON: Dr. Gorman.

DR. GORMAN: I have always tried to be someone to tell people what I actually know, so I think if I was writing this label, I would go with this two weeks with a two-week tapering regime, and then say, in long-term follow-up studies, the relapse rate after treatment with this dose appears to be at least 20 percent and the efficacy of repeated treatment is unknown.

I am not saying that is what you should write, because somebody might think that is too permissive. But that is what I would write.

DR. KATZ: That's fine, I mean that's a specific recommendation. You have to decide, or we would like you to think about the question of, whether or not writing labeling

like that is adequate.

DR. ANDERSON: Dr. Green, I think you are next.

DR. GREEN: Well, I am probably saying the same thing, but I think you can't say anything more or less than the safety and efficacy of retreatment has not been established, which is probably different from not saying anything about retreatment. But that is all we have based on the data that we have been given.

DR. ANDERSON: Dr. Dure.

DR. DURE: I think there are a couple of things here, and I hate it when this happens, but I mean the statement here, has the sponsor submitted evidence to support the view; sure they have. I mean why would they submit evidence that's against the view to provide a short course of treatment.

So, unless you want a different answer, we need to reword that. But I think that the details here are really going to be tough because, as Dr. Gorman said, yeah, that's right. You could write something with respect to, you know, we don't know the efficacy of a repeated trial or--yeah, repeated course, but what do most people do.

A lot of times they do go ahead and give them a

second course. So I think this is going to be tough to write this in terms of what to write in the label.

That is why I say I think there really needs to be more discussion, maybe on the front end, about dosing and specific regimens, because we are all basing this on 16 patients.

DR. ANDERSON: So, what is your recommendation and then we will get Dr. Gorman's response.

DR. DURE: Well, I think that has the sponsor submitted adequate evidence to support the view of a short course or a single short course provides sustained effectiveness. That will give you an answer that, well, some people are going to say yes and some people are going to say no, and that might give you someplace to go from there.

DR. ANDERSON: What about the sustained effectiveness or the issue of relapses? I mean what are you going to tell the residents? I mean what is the advice that we should give the community I mean beyond whether they simply established effectiveness, what should the label say?

DR. DURE: I mean I am the one child neurologist here who is not an epileptologist, so I would be asking

epileptologists as to what is the sort of standard there. I mean because I quite honestly don't know what the standard would be.

DR. ANDERSON: I will get Dr. Gorman and then I will come back over to this side.

Dr. Chapman?

DR. CHAPMAN: I sort of agree that in the absence of better data, I think that the two-week course and followed by a two-week tapering regimen seems reasonable to me. I mean if you have to put something in a labeling as a guideline, it seems like a reasonable guideline.

I think you would like to have some harder data but, in the absence of it, I think it's a reasonable course of action. I do think you would have to probably specify in there to watch closely for relapse rate. I mean if it's going to be 20 percent, maybe you need to counsel the physicians about that, as well.

DR. ANDERSON: Dr. Cohen, you are next.

DR. COHEN: Most of what we do unfortunately, in clinical neuromuscular medicine, is not well documented, the use of IVIG, the use of steroids, et cetera, and some of it is on label and some of it is off label. So I agree with

Dr. Gorman that I would try to keep it loose, because also there are issues about insurance reimbursement, but also the idea of perhaps since one of the gold standards that we are using is video-EEG monitoring to recommend or suggest something about that, and clinical observation.

But, you know, I was just thinking about this and treating CIDP or myasthenia gravis, or muscular dystrophy, I really couldn't write a label on most of what I do.

DR. ANDERSON: Dr. Felner is next.

DR. FELNER: I think the first question we all, for the most part approved, all you can really go on is what we have, which a lot of people are saying, and I think the discussion ends there except for what are the postmarketing studies or what are the other studies that everybody here has been talking about, we want to see six weeks, we want to see three weeks. Whatever it is, that can all come up later, because I think just to answer this question, to say this is what we have seen, this is what it is, we agree with it.

Is everybody happy with it? No, but you can be happy with it if we know that the sponsor can do some studies in the future which will hopefully discuss a design

in the next few questions.

DR. ANDERSON: Dr. Pearl.

DR. PEARL: I propose that the labeling be very clear that this course is based on a study of 29 randomized patients. I think you can't get away from that, because there are a lot of very experienced child neurologists who are not going to be satisfied with the two-week taper.

A lot of people think you have got to go longer to prevent relapse just based on their personal experience. There has been a lot of discussion today about personal experience. There is a protocol some of us are using, not just in my hospital, but other big children's hospitals, using an every--other-day-taper, finding that it is better tolerated, parents like it better because there are less injections, less side effects. It hasn't come up for discussion today.

The course of ACTH is so variable, it is so unknown that to put this out there that this should be a two-week course and a two-week taper is based on such a small, tiny study that I think it's okay to put it in the labeling but it has got to be specified what it is based on.

DR. ANDERSON: Dr. Snodgrass.

DR. SNODGRASS: To follow up with that further, and what Dr. Gorman has said as well, you could in some fashion address. What I recall hearing earlier that, by six months and by a year, you had some idea from clinical experience of what the relapse rate might be, perhaps, and you could address that, and that way give some further information in the label.

DR. ANDERSON: Dr. Gorman.

DR. GORMAN: Dr. Katz, do you have the same latitude in this situation as you would if this was a BPCA or PREA label where you have the ability to put both positive and negative studies and an interpretation on the label, or is that ability for pediatric labeling restricted when those two laws are enjoined?

DR. KATZ: With BPCA, it's a requirement I think. We can certainly do that. We don't typically, at least in my experience, describe negative studies in the label outside of BPCA. You could, I mean to the extent that we felt it was informative. I think we have the latitude to do it. It just isn't typically done.

DR. TEMPLE: There is something to be said for it in this case, Rusty, because it gives you data on what a

lower dose did. I mean these three studies.

DR. KATZ: Yes, it's possible. Again, we certainly have the latitude, as you said, to do it if we thought it was useful.

DR. GORMAN: Thank you.

DR. ANDERSON: Dr. Frank.

DR. FRANK: First, can you expand on what BPCA is?

DR. GORMAN: Yes. The Best Pharmaceutical for Children's Act. It has gone through several iterations, but basically it is a mechanism to incentivize the pharmaceutical manufacturers to do clinical trials in children to produce labeling.

Its sister legislation is PREA, the Pediatric Research Equity Act, which requires pharmaceutical companies to do research in children when they ask for pediatric labeling.

DR. FRANK: Actually, that wasn't my question. But this is more of a comment about our voting question. I think that there are really two issues here, and it's in the two sentences. The sponsor wishes to recommend a two-week course of treatment, followed by a two-week tapering regimen.

I think that we just voted yes to Question 1 based on that data. So I think if that was the question, that's the dosing recommendation, I think most of us would say yes.

But have the sponsors submitted evidence to support the view that a short course of treatment options provide sustained effectiveness, I think that is a different question that I think we are struggling with that we don't have the data for.

DR. ANDERSON: I have been generally instructed that we should try to vote on the questions as they are written, acknowledging that some of them don't completely express our own views or may not be sort of sharp in terms of their delineations.

I will get the last comments from everybody, and then we can move on to vote here, and I think after your vote is recorded and you sort of give the chance to sort of say what you vote, then, it would be probably helpful to hear what sort of metric of sustained effectiveness you have sort of considered, and when you voted pro or con.

Dr. Felner.

DR. FELNER: Just answering the question, you can actually ignore the question and move quickly to 5 where it

says if your answer is no, come up with a dosing regimen. So it's either (a)--I mean if you read them the way they are, you agree with it or if you don't. Give something real that is not the sponsor has done this and that.

I mean to answer the question, you need to give something objective, and I think the only thing that we have to go on that is objective is what has been studied and what we read. Then, we can move to giving them suggestions on how to do this.

I mean, in endocrinology, there are a fair number of pediatricians that use some of our medications without sending the patients to us--I don't know if it is like that in pediatric neurology--and if you leave an open window for family practitioners, internists that see kids, that have the ability to write this, I mean you are digging yourself a grave there for some of these physicians.

So, give them the logistics of what should be on there. I mean give them the exact regimen that you want, and then let us figure out or let the FDA figure out how to come up with better studies.

DR. ANDERSON: Dr. Clancy.

DR. CLANCY: So, if we are going to use the single

Baram studies as the pivotal study and say this is the study on which we are going to base the decision of ACTH effectiveness, then, it seems illogical to me to do something other than their dosing regimen. It is effective at this dose on this schedule, and so forth.

Now, of course, there might be lower doses, higher doses, longer times that could also be effective. But, in terms of labeling, it just seems illogical to me to separate the two parts of the study. We are going to vote yes on the ACTH, but no on that schedule.

The question is really a compound question because you are sort of saying, well, you like the dose and does it cause sustained effectiveness, and I might like the dose because I am not going to disagree with their schedule, but again there is no data provided on sustained effectiveness.

DR. ANDERSON: The question is as written, so I think, you know, noted, and then we will have to vote, we will have to clarify the basis for our votes and interpretations.

Other people want to weigh in here before we move to a vote on this one? Yes, Dr. van Belle.

DR. van BELLE: Just one quick question. What is

the current clinical practice of the Commission sitting around this table when they deal with infantile spasms? What is your current practice with respect to using ACTH?

DR. ANDERSON: Dr. Chapman, do you want to give us yours?

DR. CHAPMAN: Actually, I use the Baram protocol, so I mean I think a two-week course is appropriate, and if they relapse, we put them back on.

DR. ANDERSON: Dr. Pearl.

DR. PEARL: I normally start with ACTH 150 U/m². After a week, if there is a clinical and EEG response, I taper down then to 75, and then the third week I go to an every other day, and the fourth week an every third day, and try to spread it out over about six weeks total. By the time I am in Week 4, it is every three to four days and every week for a couple of weeks. But it varies from patient to patient.

DR. ANDERSON: Dr. Dure.

DR. DURE: Carter Snead was at UAV and so we are a high-dose group. But I also have some new faculty who have come who are lower-dose people. And so within the same group we are not at all consistent and our taper is more

like Dr. Pearl's, where we take our time.

DR. ANDERSON: At this point, we will move on to vote on this question with the same process as last time, probably the same efficiency. I will read the question one last time.

The sponsor wishes to recommend a two-week course of treatment, followed by a two-week tapering regimen. Has the sponsor submitted evidence to support the view that a short course of treatment provides sustained effectiveness?

[Electronic voting.]

DR. ANDERSON: Still missing one, so give it another press, please.

The votes are 16-4, 7 against, and 0 abstentions, and I guess we will go around in the opposite order this time. Start with Dr. Gorman on this side.

DR. GORMAN: I voted Yes, and I voted yes because I thought that the course presented gave relief of the symptoms using hard out points. I don't think the studies that were presented in the efficacy data dealt very effectively with long-term sustained relief, but I thought the safety studies did and the relapse rate for successful converters was low enough to convince me that the effect was

sustained.

DR. SNODGRASS: Wayne Snodgrass. I also voted Yes and for the same reasons that Dr. Gorman did.

DR. DURE: This is Leon Dure. I voted Yes for pretty much the same reasons. I think, though, that sustained doesn't bother me as much because I know what they mean. I mean they mean what you had mentioned before, Dr. Anderson; sustained is once you withdraw the drug, the spasms typically don't recur.

I don't think the question is very good, though, because--so, I just voted on it that way. And I would agree that there needs to be a lot of room for ambiguity in terms of how this drug is used, if approved, or else it will backfire and the availability issue will become a problem if people aren't using it "appropriately."

DR. MIZRAHI: Eli Mizrahi. I voted Yes and I considered the term sustainability in terms of whether or not we think this works as opposed to the issue of late relapse.

DR. PEARL: Phillip Pearl. I voted Yes. I think the answer to the question is Yes, but again I think that it is based on a small study and that needs to be specified

with lots of room for variations in the dosing regimen.

DR. KHATRI: Pooja Khatri. I had an emphasis on the word sustained, so while I do think it is the most appropriate dose to use the one with the pivotal trial that substantiated effectiveness. I don't think there is any evidence for sustained effectiveness.

DR. FRANK: Samuel Frank. I voted No for the same reasons. I feel that the statement part of the question is correct based on the evidence that was presented, but I don't think that there was enough evidence to support a sustained effect.

DR. KHANNA: Prerna Mona Khanna. I voted Yes. I think that the answers to the question that I asked about cure of infantile spasms versus symptoms, et cetera, were enough to satisfy the requirement of sustained effectiveness

MS. VEGA: Marielos Vega. I voted Yes, but I have a conflict between the sustained effectiveness statement because I think there is a big difference between short-term sustained effectiveness and long-term effectiveness. But I think this is something that we can take a look at post development.

DR. GREEN: Mark Green. I voted No. I don't

believe that we have documented sustained although admittedly, the term is ambiguous, and I think it becomes very important going forward to develop immediately safety and efficacy data on re-treatment protocols.

DR. ANDERSON: Britt Anderson. I voted Yes. In the short time frame interpretation of sustainability, and I feel that there is not data for the longer term effects from what we have seen today.

MS. KANDELL: Ellen Kandell. I voted Yes for a lot of the reasons that have already been stated.

DR. LESAR: Timothy Lesar. I voted Yes for the reasons that have already been stated.

DR. GARDNER: Jackie Gardner. I voted No because I too focused on the issue of sustainability and the word evidence. But I am trusting that our conversation about this will give the FDA the guidance they need about our thoughts on it.

DR. CRAWFORD: Stephanie Crawford. I voted Yes and I just say, in terms of what others said with a Yes vote, ditto.

DR. CHAPMAN: Kevin Chapman. I voted Yes because I realize the difficulty that the FDA has as far as the

labeling. I don't have a better alternative plan and, as far as sustainability, it's open enough that I think I am okay with it.

DR. CLANCY: Bob Clancy. I voted No for the reasons people gave, and I would just want the FDA to think about not using the word sustained in the labeling, but rather short term.

DR. FELNER: Eric Felner. I voted Yes for the reasons I discussed previously.

DR. AOKI: Tom Aoki. I voted Yes. I think the fact that in most of the instances the Acthar at the high dose promptly relieved the spasms and reversed the EEG change abnormalities. If it lasted a week, two weeks, three weeks, as far as I was concerned, that was sustained. It didn't pop right back up. The relapses I think took longer to occur.

DR. van BELLE: Gerald van Belle. I voted Yes, because that is the evidence from the clinical trial.

DR. LU: Ying Lu. I vote No also because of the clinical trial and found that the pivotal were designed at Week 2 confirmed the response rate. But there is no evidence that there is no--and there is an assessment. So I

can't say it's sustained.

DR. COHEN: Jeffrey Cohen. Like most discussions of neurologic therapeutics, this becomes a Talmudic discussion. But the important thing is I think that there needs to be a wide range of dosing as far as time. It is sustained in the sense of most of our treatments that we do get benefit after cessation of therapy.

What that sustainability is obviously varies from patient to patient, treatment to treatment.

DR. TODD: Jason Todd. I voted No for similar reasons as others have already stated.

DR. ANDERSON: I realize often there is a desire among some that we just sort of blast straight ahead, but we do need to take a break, and so this seems a convenient time to do so.

We will take a 15-minute break at this point and then resume for the remaining questions. That will be 3:20 by my watch.

[Break.]

DR. ANDERSON: I neglected to provide my summary after the last question, so I will do that here.

The summary of the Yes and No votes seemed to

center more on the issue of defining sustainability and exactly what that meant in terms of its duration and also the quality of the evidence for its demonstration. That explains the heterogeneity.

Because a majority voted Yes on Question 4, we could skip Question 5, but since most of our discussion focused not on whether it was two weeks or whether the taper should be two weeks but more on the issue of sustainability, I wanted to give an opportunity for anybody who felt that there was important information about changes or other or alternative dosing regimens that should be specified or had comments on that issue because we didn't really treat them fully.

Was there anyone who wanted to pursue further the issue of whether they wanted to make a recommendation for some other alternative dosing regimen?

DR. DURE: Are you speaking in terms of duration or actual dose itself? When you say dosing regimen--

DR. ANDERSON: The way Question 5 reads, it sounds like it perhaps was interested in other aspects than we treated in Question 4 where it says specifically; for example, is there evidence that continued treatment beyond

two weeks is appropriate, or is there evidence that repeated intermittent short courses of the treatment are useful.

DR. DURE: That refers primarily to timing, not actual, you know, 75 versus 50 versus 10; right?

DR. ANDERSON: That was the way I was reading it.

DR. DURE: Okay.

DR. ANDERSON: Dr. Snodgrass.

DR. SNODGRASS: This might come up for discussion about postmarketing studies, it might be considered.

DR. ANDERSON: Yes, we have a Question 10 that will ask--well, it asks us about recommendations for specific adverse events, so we are kind of moving to the adverse events series of questions here. So, I would say this is sort of people's last opportunity to comment if they feel they have a strong point they want to make on recommending doses issues, or duration issues, or taper issues at this point.

Dr. Felner.

DR. FELNER: This may be a surprise, but the actual tapering using ACTH at least from an endocrinology standpoint may even be wiser to taper with a glucocorticoid rather than ACTH for some reasons that maybe aren't that

clear.

But if you look at when the adrenal gland actually comes back, if you were to treat somebody initially with high-dose glucocorticoids, we know at least from my own studies that I have published that it takes at least a month or so on high-dose steroids to get recovery of that adrenal gland, and we assume that the ACTH, pituitary and the hypothalamus recover quicker.

But if you give ACTH, which we--you know, we know the half-life on it or the Acthar, we know the half-life, but we don't really know the true effect of what is going on with the cortex, the adrenal cortex.

If you actually just taper with ACTH and a patient were to come under a stressful event that they would be unable to counter enough glucocorticoids, because the ACTH itself may not be beneficial. But you put them on glucocorticoids, instead, you almost always have them covered and to know that when they hit a stressful response, they can just be bumped with a stress dose of glucocorticoids.

I know nobody was really prepared for this, and it probably has never come up, but I think the whole reason why

we taper is for the fear of being adrenally insufficient. And the ACTH, itself, what its action is we don't really know, and we don't understand very well.

But the main point to make is if anybody who is undergoing a taper or shortly after coming off this ACTH encounters fever and illness, any stressful event, and has to go to the OR for a PICC line or for whatever it is, they need to be given a stress dose of glucocorticoids.

That would bring back the possibility of tapering with glucocorticoids instead of ACTH unless you think you are getting a beneficial effect from the tapering of the ACTH.

Many times in lupus and pulmonary disease, when you use glucocorticoids, they are tapering them, but they are still getting a pretty good effect because it is superphysiologic. So that was the only thing I wanted to bring up.

DR. ANDERSON: Thank you.

We will move on then to Question 6, which is another voting question. So I will read it, and then we will have an opportunity for discussion.

Acthar Gel has been shown to cause serious adverse

effects, and the sponsor concludes that they are predictable, easily recognized and manageable, and reversible upon drug continuation.

Has the sponsor provided evidence that the adverse events are manageable and reversible?

Thank you, Dr. Crawford.

DR. CRAWFORD: Thank you. Before I could answer that question, I have to state my concerns about where the qualifiers are in that sentence that you read for us, Mr. Chairman, that the serious adverse effects are easily recognizable.

As I look at the information that the sponsor kindly provided to us as part of the NDA was based on integrated safety data from some of the studies in a retrospective study, Study 4, and postmarketing surveillance data. The postmarketing surveillance data was simply spontaneous reports. They acknowledge those are highly under-reported.

On top of that, if you look at the patient-reported adverse effects versus those from some of the study investigators that were done after the fact, we are not sure how it was collected in the initial studies, but they didn't

match. So, I don't necessarily expect that they are all easily recognizable, although this gets a little into the Question 10 that is coming up.

The part that concerns me the most is the lack of a known plan to look at more safety issues with this product if it were approved for this additional indication, and again it seems as though the answer is that we have 50 years experience with the product and we think we know everything.

But unless it is collected in a more systematic, scientific fashion, I am a little concerned about that, and especially since there is a closed, fairly closed distribution outlet right now. There is an opportunity for much more active data collection on safety.

DR. ANDERSON: I think it is an excellent contribution. Does anyone else want to make a comment on whether they feel that the evidence regarding the recognizability, reversibility and predictability has been established by the sponsor's submission and data? Dr. Dure.

DR. DURE: Well, i would probably agree with the last comment, but it reminds me of the vigabatrin meeting a year ago. I mean infantile spasms is a bad disease and I think one of the other comments that was brought up in the

public forum was that people are willing to bear a larger burden.

So, I agree with you. I am probably going to vote No on this. But it may not necessarily play out in terms of what ultimately happens because this is a really bad problem. And when you consider who is actually prescribing ACTH, there are probably only about 400 to 500 people that do that a year.

Most people are probably pretty well aware of the problems.

DR. ANDERSON: If I understand you correctly, when you say you are probably going to be voting No, you are going to be voting No sort of on the issue of whether the sponsor has provided the evidence rather than sort of whether you feel the risk-benefit sort of ratio is an advantage.

DR. DURE: Correct. What I heard during the presentation was we don't have very much data, and the data we have wasn't collected in a way that we would like, and it is just not very good data.

So, I thought that was pretty much a self-admission from the sponsor.

DR. ANDERSON: Dr. Khanna.

DR. KHANNA: I am unclear about the adverse event of death. I mean clearly, it is not manageable or reversible. It is an adverse event; correct? okay.

DR. ANDERSON: You are raising a serious point, but obviously --

DR. KHANNA: Right. I am confused why everyone was laughing. So, we had two examples that were given to us of two deaths actually that occurred. There were multiple medical complications in those two patients which is understandable that that could be a correlation with death, not the temporal relationship with the medication.

But could I ask the McLaughlins actually--I am very sorry for your story, sorry for the death of your son--what the temporal relationship was? Can I clarify with our public presenters?

DR. ANDERSON: We can invite comment from anybody that we would like, and if that would help you to address your response to this question. There is no reason we can't. They may choose not to respond.

If the McLaughlins would like to respond, we would welcome you to help us out here.

Do you want to repeat your question?

DR. KHANNA: I know your son had a protracted relationship with this terrible medical condition. My question is, along the course of his struggling with it, when was this particular medication administered?

MR. McLAUGHLIN: He received ACTH at about between four and five months of age, and it lasted for about--I think we had an initial course of two to three weeks, and then taper, so, until approximately seven to eight months. He passed away when he was seven years old.

Don't really think there was any effect, and I don't think he had really any--other than some of the typical side effects that were described earlier, I don't think he had any negative impact.

I just would have been very happy if it would have worked.

DR. KHANNA: Thank you. We all I am sure would have felt the same. That was the clarification I needed. There were so many stories that were told about positive and negative experiences with the medication that I had forgotten the exact details.

So, that would be my comment is, I am not sure

that, you know, we have heard enough about the adverse event of death in this case except for those two situations, and if the company wants to clarify, that would be my request.

DR. ANDERSON: I would like to thank the McLaughlins for taking the time to respond to that.

Dr. Clancy.

DR. CLANCY: So, the data that was presented actually is more the litany of what kinds of things can happen.

DR. ANDERSON: Can you share with us where you are looking? Maybe we can join you on that page.

DR. CLANCY: Yes, I am looking at page, it is CS-48 within the handout. It describes adverse events in more than 2 percent of patients by treatment group. I don't think that any child neurologist would be surprised at a prolonged course of steroids, whether it be oral steroids or injected ACTH, would predispose patients to infections, irritability, Cushingoid, and so forth.

So, I think the data does sort of secure the notion of who are the players, how common are they, and so forth. The question, though, as stated, says are they manageable. So, for example, let's imagine a patient who

has hypertension, and there is no data provided that says that if you give a diuretic or an antihypertensive, that you can manage it.

How do you manage the irritability? How do you manage the increased appetite? Rather than toughing it out, there is really no data one way or the other that supplemental medications or anything short of discontinuing the medication actually manages it.

I certainly agree that once they are off of the course that these side effects disappear. I don't want to overly focus on the word manage, but I didn't see any data suggesting that they are manageable.

DR. ANDERSON: Thanks. Dr. Green.

DR. GREEN: I am not familiar with it being a usual responsibility of a manufacturer to give us advice as to manage all the side effects.

DR. KATZ: Let me try to clarify this. ACTH can cause some serious adverse events. The thrust of this question is, look, the sponsor says that yes, sure, there are serious side effects, but we can deal with them, nothing goes on to progress that is irreversible and irretrievably dangerous. That is what we mean by manageable. Stopping

the drug is managing.

We just really wanted to get a sense of whether or not you thought there was something very bad that the drug caused that we can't do anything about, and that is going to result in some significant sequelae. That is really what we are trying to get at.

DR. ANDERSON: Dr. Pearl.

DR. PEARL: Phillip Pearl. I want to apologize for my laryngitis. I hope you can still understand my diction.

I am very concerned about soft pedaling the toxicity of this drug. This is a toxic drug. Dr. Sheridan did a wonderful analysis. He has a table of eight deaths with a lot of details, so there are a lot more than two deaths reported in what we received. This drug has been associated with sepsis and death. It causes cerebral shrinkage on imaging, hypertension, hypokalemia, hyponatremia, glucose intolerance.

I mean if you think back to the felbamate fiasco, when that was approved in 1993, it was felt to be so safe, like meprobamate, it took 100,00 patient exposures to realize to put the brakes on that drug because of the

aplastic anemia and liver failure.

So, we are getting adverse effects data on 300 and some patients, 319 patients. I mean that is woefully small to say that these side effects are easily recognizable and manageable. There is nothing easy about using ACTH.

For those of us who have a lot of experience with it, and frankly, I do, it is not an easy drug to give, and you can get into all sorts of trouble. If non-pediatric neurologists start using this based on this label--and I am for the indication, and I voted for the label--we are going to have more adverse effects than we ever dreamed of.

So, I don't think it's a good idea to say only 400 people in the country are going to prescribe this drug, because that is how many pediatric epileptologists there are.

So, I am very, very concerned. I think this issue has to be taken very seriously because kids are going to get into trouble with this drug, and it is going to come back to haunt us if we don't deal with it right now.

DR. ANDERSON: Dr. Snodgrass.

DR. SNODGRASS: Yes. This addresses again the issue of some degree of postmarketing surveillance, and of

the top four or so that are in that slide we just looked at, CS-48, the ones that concern me as a pediatrician or that I think needs a low focus on postmarketing is simply infections, particularly pneumonia, and particularly since these are younger infants.

The others are in a sense, yes, reversible. You can reverse your drug, but pneumonia is something that probably needs to be, among others, looked at a little bit more closely on follow up.

DR. ANDERSON: We have heard several experts, and we have also heard the FDA clarify slightly what they meant by the issues of sort of manageability and reversibility, so at this point, if there is no objection, we will go ahead and vote on the question.

Let me read it one more time, and then we will push our buttons.

Has the sponsor provided evidence that the adverse events are manageable and reversible?

[Electronic voting.]

DR. ANDERSON: The votes are 10 Yes, 12 No, and 1 abstention.

This time we will start back again on this end,

please.

DR. TODD: Jason Todd. No. I think the safety data is weak. Actually, it was the only center on the efficacy, but certainly a potentially toxic drug. Even though I voted No on Question 1, if I accepted the effectiveness overall, the safety profile would not keep me from using the drug.

DR. COHEN: Jeffrey Cohen. I voted Yes. The reason why is we have 50 years of experience with ACTH. We use steroids fairly frequently in neurology. We use it chronically, which is something that I think is much more worrisome than doing a four-week pulse of ACTH. We used to use ACTH, by the way, in multiple sclerosis when I was a resident and attending, so had years of experience with that.

Also, the definition by the FDA of irreversible. Most of the side effects we handle.

DR. LU: Ying Lu. I vote No partially because the data was collected retrospectively, and I have some worry about completeness of information, but particularly when I hear the panel's discussion and from clinicians and I vote No.

DR. van BELLE: Gerald van Belle. I abstained. This is a very clinical question. I don't feel competent to make a judgment.

DR. AOKI: Tom Aoki. I voted Yes. I think that the side effects are manageable. I think you have to be alert for them, but I think I think the benefits far outweigh the risks.

DR. FELNER: Eric Felner. I voted Yes. I think again the short course really is what takes precedent here, because you can manage all of these things and many other conditions that are dealt with, with either steroids or ACTH for that matter.

DR. CLANCY: Bob Clancy. I voted Yes. When I start patients on ACTH, I tell them that this is a bitter pill, and that we have to look out for trouble, and so we do carefully monitor the patient. I think the risk-benefit is adequate. After the clarification about what they meant by manageability, I was willing to vote Yes on this.

DR. CHAPMAN: Kevin Chapman. I voted yes once again because of the clarification by Dr. Katz, and I have to agree with Dr. Pearl, ACTH is the scariest drug that I use. But I also, because of that respect, I do follow them

quite closely. But I think they are manageable side effects.

DR. CRAWFORD: Stephanie Crawford. I voted No because the evidence presented to us by the sponsor on safety for me was lacking.

DR. GARDNER: Jackie Gardner. Similarly, I voted No on the basis of the word "evidence." In trying to separate evidence from clinical practice, which is part of our job. It doesn't mean that I don't favor approval, just that we need to think about what to do next.

DR. LESAR: Timothy Lesar. I voted No based on the reading of the question that we are asking about not so much are they adverse effects that we know are reversible, and the fact that we don't know what all the adverse effects are. Again, I wouldn't preclude by looking at it that it doesn't have a positive risk to benefit.

MS. KANDELL: Ellen Kandell. I voted Yes because it appeared, in my lay opinion, non-scientific background, that the benefits outweigh the risks, and I didn't hear anything about sepsis or any of that at least in the presentations, or holes in the brains of people, that was presented by Questcor.

DR. ANDERSON: Britt Anderson. I voted No. Sort of a fairly literal reading of the question, not so much an assessment of risk-benefit, but I felt the number of subjects was small, the data was retrospective in its collection, infection in a child who may have multiple issues to start with, may not be trivial nor reversible, and so. without commenting on whether there is a positive risk-benefit ration, I didn't feel the evidence of sort of manageability and reversibility had been established.

DR. GREEN: Mark Green. I voted Yes. The reported side effects were all in line with those which we have all experienced over many years of experience with this agent.

MS. VEGA: I voted No and I don't have the clinical background that other people here have in prescribing this medication, but I was most concerned with the fact the small sample sizes, and then we really don't have enough evidence if they are reversible, some of the serious side effects, adverse events.

DR. ANDERSON: Can you read your name into the record.

MS. VEGA: Marielos Vega. I voted No.

DR. KHANNA: Prerna Mona Khanna. I voted Yes despite the fact that the N is small and I think there is a selection bias because of the retrospective nature of the data and also because of the desperation of parents who are looking for a treatment success.

I also have concerns if that is under-reported or had been under-represented here. Despite all that, I voted Yes, because all of the adverse events that I saw listed are either treatable or they regress with discontinuation, and since most of these adverse events are known, they can be managed if they are expected.

DR. FRANK: Samuel Frank. I voted Yes because, even though the number is small, I think it is actually fairly large for a rare disease, and even though the data isn't perfect, there was nothing that was unexpected in terms of the side effects.

I also think that pediatric neurologists don't work in a vacuum, and they can get their colleagues to help them manage some of the side effects. I do think that in terms of the adverse events that were reported, they are manageable.

DR. KHATRI: Pooja Khatri. I voted No primarily

for some of the same reasons others have said, specifically, patient numbers, the lack of systematic prospectively collected data to truly know what the adverse events are in this population and then, finally, a particular concern about sepsis infection, and death is a real risk with this treatment.

DR. PEARL: Phillip Pearl. I voted No. The safety data is small. It's retrospective. Steroid use in infants is a different matter than using it in adults even though it is widely used in neurology. We heard some endocrine information that hasn't even come up that we really don't know what to do about the taper and what product we should use for the taper, and that is when people are going to get into trouble with adrenal insufficiency and infants and children being exposed to other infected kids.

So, I think the safety data still needs a lot more attention.

DR. MIZRAHI: Eli Mizrahi. I voted No primarily for some of the reasons Dr. Pearl mentioned, particularly about the so-called potential soft selling of these potential adverse effects. I think also the vote with a look towards what might be postmarketing surveillance.

I think this, though, is a different issue than what we are going to be talking about next, and so I really didn't see it as a risk-benefit ratio calculation, but just specifically related to ease of recognizability, recognition, and management.

DR. DURA: Leon Dura. I voted No because of a literal reading of the question and the other comments that I made before.

DR. SNODGRASS: Wayne Snodgrass. I voted No. I could have easily voted Yes. I think the adverse events as identified are--typically we consider them manageable and generally speaking reversible, so I don't think that to me is much of a question. But since the question was, "provided evidence," I tried to answer it on that basis.

DR. GORMAN: Rich Gorman. I voted Yes, a little reading that caught my eye was has been shown to cause serious effects, and that was the premise on which the rest of the question was based. So, it started with that and I agreed with that statement, and I agreed that they are mostly manageable and mostly reversible.

The side effects are adverse effects that were mentioned do have management strategies.

DR. ANDERSON: Again, I think the summary is that there perhaps may be more consensus than the vote reflects. It sounds like people emphasize sort of different aspects of the questions. There was a recognition that there are serious effects associated with the use of the drug. Whether they are manageable or reversible, or whether the numbers were sufficient to demonstrate their manageability and reversibility were some of the issues that panelists mentioned in describing their different votes.

Now, we move on to Question 7. Has the sponsor submitted sufficient evidence of the safety of Acthar Gel at an effective dosing regimen?

This seems to be a little bit more to the issue of sort of the risk-benefit ratio. Is that what you were looking for here?

DR. KATZ: Right, again sufficient to support approval.

DR. ANDERSON: In this case, I think we have heard some already people have made comments of their opinion on this matter. Maybe we could sort of have some restatement of whether--well, maybe Dr. Todd, since you were one of our earlier dissenters, do you want to start off by your opinion

as to sort of how the sponsor's evidence stacks up in terms of the safety and efficacy tradeoff?

DR. TODD: I think the quality of the safety data is pretty weak and taken mostly from a different population, from the population on what we are basing the efficacy on primarily. Having said that, if I accept the group opinion that there is sufficient evidence of efficacy, acknowledging that it is potentially a toxic and dangerous drug, I think that the benefits do potentially outweigh the risks.

DR. ANDERSON: Dr. Belle, did you have something?

DR. van BELLE: My question is how does Question 7 differ from Question 6? Maybe I could get some explanation, because I would be inclined to vote exactly the same way for Question 7 unless I am told what the difference is between the two questions.

DR. ANDERSON: Dr. Katz, could you clarify what the different perspectives were here?

DR. KATZ: I think Question 6 was sort of intended to get at the aspects of the adverse events that we talked about. You could feel that there are some adverse events that are irreversible or unmanageable, however you want to define that, but yet still think there is sufficient

evidence to approve it.

So, Question 6 was trying to get at the specific events and what you think about the specific panoply of events in terms of what you can do about them or how serious do you think they are. But Question 7 is asking, given all of that, do you think there is sufficient evidence of safety to support approval.

DR. van BELLE: Thank you.

DR. ANDERSON: Perhaps then we have already sort of had sufficient discussion in terms of the preliminaries to sort of proceed to a vote unless there is somebody who strongly feels they would like to address something.

Okay. Then, why don't we go ahead and move on to our vote on Question 7, sort of treating it as more of a sort of risk-benefit tradeoff; has the sponsor provided sufficient evidence of safety of Acthar Gel in an effective dosing regimen.

[Electronic voting.]

DR. ANDERSON: There were 20 Yes votes, 1 No vote, and 2 abstentions. I think this time we will start on my left again with Dr. Gorman, please.

DR GORMAN: I voted Yes, and I just wanted to add

something. I wanted to add to the last statement, which is this drug strikes me as having a large number of toxicities, and I feel like many of my neurological friends that this deserves to be limited to a group of places where there those toxicities can be monitored.

DR. SNODGRASS: Wayne Snodgrass. I voted Yes.

DR. DURA: Leon Dura. I voted Yes.

DR. MIZRAHI: Eli Mizrahi. I voted yes.

DR. PEARL: Phillip Pearl. I voted Yes. I think the benefits outweigh the risks.

DR. KHATRI: Pooja Khatri. I voted No. I remain concerned about the risk-benefit profile and how much we really know about that.

DR. FRANK: Samuel Frank. I voted Yes. I do think that the benefits outweigh the risks, and that the patients that are going to be getting it and their families are willing to tolerate a little high risk given the benefit.

DR. KHANNA: Prerna Mona Khanna. For the same reason, I voted Yes. I think in rare disorders such as this, such a devastating disorder, that families need to be given every shot that they can.

MS. VEGA: Marielos Vega. Voted Yes for some of the same reasons that people just said.

DR. GREEN: Mark Green. I voted Yes.

DR. ANDERSON: Britt Anderson. I voted Yes for the reasons we have heard.

MS. KANDELL: Ellen Kandell. I voted Yes for the same reasons that Dr. Frank and Dr. Khanna mentioned.

DR. LESAR: Tim Lesar. I voted Yes, but I believe there needs to be postmarketing surveillance or follow up.

DR. GARDNER: Gardner. Yes.

DR. CRAWFORD: Crawford. Yes. The Yes would be a lot more enthusiastic if I thought there would be some type of ongoing monitoring.

DR. CHAPMAN: I voted Yes as the others.

DR. CLANCY: Bob Clancy. I voted Yes.

DR. FELNER: Eric Felner. I voted Yes.

DR. AOKI: Tom Aoki. I voted Yes.

DR. van BELLE: Gerald van Belle. I abstain for the same reason as Dr. Todd.

DR. LU: Ying Lu. Yes.

DR. COHEN: Jeffrey Cohen. Yes.

DR. TODD: Jason Todd. I abstained, had some

problems with the data on both sides of events, and I couldn't really resolve that.

DR. ANDERSON: The consensus of the panel seemed to be that although there were significant risks and a significant amount of uncertainty about the magnitude and extent of those risks, the understanding of the disorder led the majority of the panel to believe that the risk-benefit ratio was favorable.

So, for Question 8, not to put you on the spot, but Dr. Khatri, what sort of additional safety data would you like to see in order to sort of change your opinion?

DR. KHATRI: I think that it would be helpful to see subpopulations, cryptogenic versus symptomatic particularly, and I think that we don't really--while this is a devastating disease, we can't predict who those people are that do well, that are unnecessarily exposed to the risk of ACTH.

Particularly and related to this decision which I apologize if this is a bit of a tangent, but I also think that we don't know whether--I think it has been well established in this discussion that we don't know whether cessation of infantile spasms and amelioration of the EEG

actually improve long-term outcomes, so perhaps we are introducing risk without any clear benefit in the long term.

So, I think postmarketing safety would make me much more comfortable.

DR. ANDERSON: That concludes Question 8. We have two more questions, one fairly specific and then one, I think, more of an open opportunity.

So, Question No. 9; are there patients in whom Acthar Gel should be contraindicated, for example, infants with hypertension, infections, or metabolic disorders?

This is a discussion, not a voting question. Does anybody want to nominate a particular category of patient that they feel or they would advise the FDA should be listed as contraindicating this medication? Ms. Vega.

MS. VEGA: One of the issues I have, we got some data in terms of the two children who died, some with medical problems that they have. But in regards to the other children who were in the other studies, we have no idea of what other medical issues they had. There was no health profile in general, a general health profile, if they have other conditions, if they were taking other medications for other reasons.

So, for me, this question is difficult to answer because I didn't have any evidence of what those children who were part of the studies--what other issues they have.

DR. ANDERSON: I am not sure which one of you got your hand up first here, but we will go to Dr. Snodgrass, and then we will go next door.

DR. SNODGRASS: I think contraindications is a really strong word, and it might deny some patients in therapy. I think it would tie the hands of what might benefit patients.

DR. ANDERSON: Dr. Gorman.

DR. GORMAN: I would recommend the word "precaution" rather than "contraindications." We treat other terrible diseases in both infants and adults with these complications, and it is again an issue of--you might put in something about risk-benefits.

We do have another approved drug for this agent. You might say consider the use of other approved agents. There is wording to use, but contraindicated, no.

DR. ANDERSON: So, is there a specific category or patients for whom you would recommend that that language regarding consideration of alternative therapy would be

particularly advisable for? Did you have a specific subgroup of patients in mind?

DR. GORMAN: I think the group up there, two of the three make some sense to me. Infections, I don't know a pediatric patient without infections after 25 years in pediatric practice, so I might change that to people with immune deficiencies.

DR. ANDERSON: Dr. Clancy.

DR. CLANCY: Here is the other side of the coin, I would just like to bring up. When Dr. Pellock gave his presentation earlier, he had mentioned that 40 percent of patients with infantile spasms were treated with ACTH, and we don't know the reasons that 60 percent weren't. Some may have been availability, and so forth, but there has to be some element of the perception of the treating physician that the treatment may lead to some meaningful improvement.

I know that, within discussions in child neurologists, there may be some types of children who have horrific brain malformations or neurodegenerative diseases that are leading them to their death, if they go through a phase of hypsarrhythmia. The question is whether treatment can really make a difference in them.

That is a very personal decision and I think that whatever the wording is on the labeling if this gets approved, that we should not be sort of automatically compelled, in each and every human being who has this to, you know, knee-jerk reflects, that we are compelled to administer ACTH because there probably are within individual doctors, opinions that some children who really shouldn't be treated for whatever the reasons are.

So, it is not a contraindication so much, but again I am just worried about the labeling where I am somehow malpracticing if I don't do this if, in my best judgment it is not in the best interest of the patient.

DR. ANDERSON: You will probably never have a better chance to sort of have an influence on not having your hands tied in that way. How would you word that? How would you try to capture that concern that could be included in a label or could give the sort of guidance that would allow you that sort of flexibility and protection?

DR. CLANCY: Even if it was worded that, if, in the opinion of the treating physician, that this could benefit the patient, just give a little wiggle room rather than hypsarrhythmia equals ACTH treatment.

DR. ANDERSON: Does anybody else want to suggest a group in which the medication should be contraindicated or otherwise warned against?

All right. All right. So that concludes Question No. 9, and now the last question for discussion is No. 10.

Does the Committee recommend any specific monitoring for specific adverse events, and if so, should these be made mandatory under a REMS program?

So, lots of people have had, I guess, requests or things they think would be desirable to be learned in a postmarketing situation, but are there any that they feel should be specifically recommended or mandated?

Yes, please, Dr. Gardner.

DR. GARDNER: If the sponsor plans to continue with the specialty pharmacy or other kinds of limited distribution that represents the opportunity for some kind of registry of each patient for whom the drug is made available, we would have to think--or the FDA would have to think--about how to manage that hospital sampling program.

But certainly from the specialty pharmacy's distribution, even if there is more than one specialty pharmacy, it opens the opportunity to do some prospective

monitoring of people at least who get the product.

That doesn't set you up for a control study, but it does give you some answers to how it is being used, what is the outcome, and what are the dosing and--you know, the opportunity to identify and follow up, and what were the adverse effects.

I would certainly recommend that, whatever the questions being asked--and many of the ones that came around the table today might be considered for a prospective registry of patients receiving this through the specialty pharmacy.

DR. ANDERSON: Dr. Pearl, you have had a lot of sort of words of warning. Is there something specific that you think should be mandated or strongly recommended?

DR. PEARL: Well, on the one hand, I think it would be very important to be clear in the package insert what needs to be monitored--blood pressure, electrolytes, I think mention of atrophy on imaging, cardiomyopathic changes. I think these things need to be clear, not soft-pedaled.

On the other hand, I actually don't want to put too many obstacles in front of prescribers. It gets to be

cumbersome. Having the pharmacy that you mentioned with the registry is probably enough. Just as a case in point, the vigabatrin, there are a lot of obstacles in using it. You have to have a form filled out for the ophthal exam every three months. It is not so easy, and I don't want to make using ACTH harder than it already is.

So, I am on both sides of this a little bit.

DR. ANDERSON: So, from the two people that mentioned the registry, I want to know if they are suggesting that, as opposed to sort of a convenience sample, because there is a pharmacy being used now that they really feel like a registry, it is something that should be mandated for this medication for this indication because of their concerns, or are they just saying take advantage of it if you can.

Dr. Chapman.

DR. CHAPMAN: I think most of us that use ACTH are pretty cautious with the medication, and I will say that I require that the patients be seen every week while they are on the drug; if not by me, then, by their pediatrician.

I mean I don't think you should necessarily word it so it's forced in there, but maybe a suggestion that they

are frequently evaluated. So, in other words, it is not you start them on the drug, four weeks later when they are uroseptic, they come in, or they have cardiomyopathy.

I mean I am sure there are different regimens for different people, but I tell the families they have to be seen by their pediatrician. They see me one week, the pediatrician the next week, me one week, the pediatrician the next week. So, that may be something that might help address some of the issues about what to check and what to follow, at least they are seen by somebody.

Dr. Khanna.

DR. KHANNA: Thank you. I don't treat pediatric patients, but it seems to me, from the comments that we have heard today, that I would recommend that for this particular medication, we put it in the category that is the highest surveillance or registry.

I don't know what the difference is between a registry and a REMS program. I don't know what a registry is, if that current exists, but whatever it is, we put this one in the highest category of monitoring and surveillance, and in terms of risk communication and risk mitigation.

DR. ANDERSON: Ms. Vega.

MS. VEGA: I think it is also important to have a plan of action for educating the public especially parents in a way that they can understand, the littlest level they can understand. Then educational materials be available for people other than those who speak English, because they say how complex this is, so you want to make sure that even the person who can read at a grade level of 6 can understand what is being told. So, I think it is very important to have that plan of action.

DR. ANDERSON: Dr. Crawford.

DR. CRAWFORD: Thank you. As I read the question, I am hearing the comments around the table, I think we are looking at monitoring in two ways, as we should, both in terms of the clinicians who are prescribing and/or administering as well as the caregivers, of course, and differently from the sponsors, so my comment is a bit more of the sponsor.

So, I get back to -- it's a subquestion under there in terms of the mandatory REMS, and one of the questions was what is the difference between a registry and a REMS. A registry could be part of a REMS. REMS could have many different components.

I don't advocate one way or the other whether there should be a registry. I strongly agree, yes, we should take advantage of the fact that the sponsors are choosing to use the specialty pharmacy. I am not saying I necessarily agree with that, but I really feel there should be mandated postmarketing study of safety for this drug as part of a REMS.

DR. ANDERSON: Dr. Gorman.

DR. GORMAN: One of the most specific adverse events I would like to be monitored is relapses, and I think that, if there is a single specialty pharmacy that is associated with distributing all these drugs, they should be able to identify people who get this more than one course of this drug if it's done that way, and they could then be required to query about the outcome of the second course.

DR. ANDERSON: Dr. Dure.

DR. DURE: I agree with most of the comments that have been made. I mean I think with respect to what Dr. Pearl was saying, he doesn't want to make ACTH any harder to use. That is true.

I don't think it needs to be any harder to use for him. But, on the other hand I would like to be sure that

other, say, child neurologists or other people are adequately aware of the issues relating to dosing and clinical trials, et cetera. So one could make a reasonable argument for some type of up-front education, sort of like with vigabatrin; you kind of have to sign on the dotted line that you have read and listened to the information that is available.

I think that I would agree that there need to be postmarketing studies. The FDA can tell me if it fits under a REMS. But, again, I think there is still a good deal of-- I do not have confidence that this dose is the dose, and we could mitigate a lot of risk if we were able to find a dose that might be lower and better tolerated.

So, I think that that should be a goal is to try to look and see what other doses--sort of what Dr. Chapman mentioned before. I mean you could probably treat somebody with 37.5 units twice a day for two weeks, and see how they do, and then you could increase the dose. I don't see any problem with that.

DR. ANDERSON: Dr. Clancy.

DR. CLANCY: Just a practical suggestion. I think when pediatricians monitor infants, they don't typically

think of hypertension as something that they zero in on, and yet in these adverse event sheets, up to 20 percent of the patients are hypertensive. The studies differ because maybe the criteria to define hypertension can vary by institution to institution.

So, I think it might be just worthwhile to have a link or some source of data to provide like the NIH guidelines for allowable hypertension as a function of the infant's age, at least so that we are all on the same criteria for what is and what is not hypertension. That would be useful if the people don't know how to access that.

DR. ANDERSON: I have heard recommendations for hypertension, for tracking patients for relapse rates and re-use of medicines and outcome measures, and programs for sort of physician education prior to sort of dispensing the medicine.

Other comments? Dr. Lesar.

DR. LESAR: I would just put a word in. I think a registry in this case is probably more appropriate than many other drugs when it is a small population. Number two, it's a drug which might be approved on very little data, and unlike many registries, they are sort of designed to protect

the patient.

In this case, the registry is really designed to make sure that the right decision was made related to the marketing of this drug in terms of what happens to patients who subsequently receive it.

I believe the REMS should include those things about patient and caregiver education, but also include a registry that allows us to see what happens subsequent to the decision, and that is something you might be able to get through postmarket surveillance, but with such a small population, you have a hard time seeing how that could be done in a timely manner.

DR. ANDERSON: Dr. Felner.

DR. FELNER: I guess just to get back along the lines of adrenal insufficiency, if there is a way to--I don't know--to put something in the label that anybody, any child that is receiving this medication either at the proper dose--I mean at the scheduled dose or the tapering dose--in some fashion, if they present with illness or they have a procedure, assume they are adrenal insufficient.

So if a child comes in with a raging infection who either just started the medication, who is actually in that

third or fourth week of being tapered, if somebody called us and said--called the endocrinologist and said we have a hypotensive kid who is septic, we are just going to assume they are adrenal insufficient based on this history, because we have no clue--at least I don't have any idea what the responsiveness of the adrenal gland is, or at least the cortex is, to this dose or this type of ACTH, as well as somebody who is weaning off of it, or tapering off of it.

So, those, you have to have a high suspicion for the kid having adrenal insufficiency.

Again, you guys treat them all, and it doesn't sound like you have too many issues with that, but I know if--and I don't see any of these kids. I have been called one time in 15 years for a child that received 10 times the dose, and still didn't have a lot of plan formula other than to watch him for a few hours.

But I think the key is, is keep that in mind. That, to me, is going to be the main thing that puts these kids in trouble--not the GI problems, not the fatigue, not the weight gain for a few weeks. Those are non-issues as far as I am concerned.

The issue is the child that is going to die

because they are adrenal insufficient and didn't get a big slug of glucocorticoids when it probably would have taken care of the problem.

DR. ANDERSON: Would the FDA like to get us to address anything further or more specifically, or have we gone through things? Okay. Dr. van Belle.

DR. van BELLE: I notice that we did not approve or did not agree that the long-term developmental outcomes have been demonstrated, which I think is right. So, I think it would be--and many of the parents that are here, that is, in fact, why they are here, because of the long-term developmental outcomes.

So, whether we should encourage the sponsor to maybe, through a carefully controlled cohort study, get some assessment of the long-term developmental outcomes, I think that that really would benefit all of us and would benefit the company, as well. It may not pay off in terms of money, but it would certainly pay off in terms of good will.

So, I would like to encourage somehow or other the company to think about that, and maybe there is a research project here for some academic researcher, but I do think we should pay more attention to the long-term developmental

outcomes. Thank you.

DR. ANDERSON: Dr. Aoki.

DR. AOKI: Just a quick aside. When we were talking about what studies we would want to do, one study that I thought of is that rather than giving shots of ACTH by IM injections, which I think correctly reflects when it was started, which was 1958 or earlier, we now have means of giving any hormone, either subcutaneously or intravenously using pumps.

I just don't know why it hasn't already been done, but it seems to me why are we still using a crude approach of giving twice a day IM injections when you could literally create almost any pattern you want of ACTH with a subcutaneous or an IV infusion.

I think that perhaps Questcor might consider encouraging an investigator-instigated study to actually not just--I think we were talking about comparative treatment regimens. I think giving it IV, for example, or even subcutaneously using various types of patterns would actually have a superior outcome than the one that they are getting now with the IM, so that when you approach a patient to be a participant in a project, it is not that they

wouldn't be denied access to a good protocol, they could actually be exposed to a superior one.

DR. ANDERSON: Dr. Snodgrass.

DR. SNODGRASS: To follow up with Dr. Felner's statement regarding adrenal insufficiency, I just would add to that, associated with that perhaps would be risk for infection. Again, I think in the data we have so far, perhaps sepsis, certainly some degree of pneumonia, that could be specific to be considered in some follow-up studies.

The other issue--I agree with Dr. van Belle about the developmental follow-up, but I think you have to be very careful about what you really mean by that.

If you are talking about very in-depth, you do age-related appropriate, various kinds of psychological testing, for example, developmental testing for X number of years, that is going to be extremely, not only expensive, but nearly impossible to do.

So, you would have to define something that is at a level that can be realistic to be done.

DR. ANDERSON: I hope those suggestions are all of use to you.

DR. YOUNG: I want to thank the Committee for everything they have provided here and all the information, and the feedback. Questcor appreciates it.

DR. ANDERSON: Thank you, Dr. Young.

With that, on behalf of myself and the sponsor and the FDA, I would like to thank everybody for their contributions and time today.

We stand adjourned.

[Meeting adjourned at 4:16 p.m.]

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