ORIGINAL

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

Volume II

Pages 1 thru 308

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

# PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

Volume II

Friday, June 7, 1996

8:30 a.m.

Holiday Inn Bethesda
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Versailles III and IV Ballrooms
Bethesda, Maryland

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PARTICIPANTS

Sid Gilman, M.D., Chairperson
Michael A. Bernstein, M.P.H., Executive Secretary

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Harold P. Adams, Jr., M.D.
Peggy J. Copple, M.D.
Patricia K. Coyle, M.D.
David A. Drachman, M.D.
Chris Gennings, Ph.D.
Claudia H. Kawas, M.D.
Zaven S. Khachaturian, Ph.D.
Ellyn C. Phillips (Consumer Representative)
Orlando C. Snead III, M.D.
Justin A. Zivin, M.D., Ph.D.

FDA

Russell Katz, M.D.
Paul Leber, M.D.
Robert Temple, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

**WELCOME AND INFORMATION**

DR. GILMAN: I would like to call this meeting to order and welcome everyone to the 43rd meeting of the Peripheral and Central Nervous System Drugs Advisory Committee.

My name is Sid Gilman. I am from the University of Michigan Medical Center in Ann Arbor, Michigan. I am Chair of this committee.

I would like to introduce you to those seated around the table. I will start with Dr. Harold Adams. Please identify yourself, your institution.

DR. ADAMS: I am Harold Adams. I am Professor of Neurology at the University of Iowa.

DR. DRACHMAN: David Drachman, U. Mass Medical Center.

DR. COYLE: Pat Coyle from SUNY Stony Brook.

DR. SNEAD: Carter Snead from the University of Toronto.

DR. ZIVIN: Justin Zivin, University of California at San Diego.

MR. BERNSTEIN: Mike Bernstein, Executive Secretary, FDA.

DR. GENNINGS: Chris Gennings, Medical College of Virginia.

MS. PHILLIPS: Ellyn Phillips, Consumer Representative.

DR. COPPLE: Peggy Copple from the University of Arizona Health Sciences Center in Tucson.

DR. KHACHATURIAN: I am Zaven Khachaturian, Director of the Ronald and Nancy Reagan Institute for Research.

DR. KAWAS: I am Claudia Kawas, Johns Hopkins School of Medicine.

DR. KATZ. Russ Katz, FDA.

DR. LEBER: Paul Leber, FDA.

DR. GILMAN: Thank you all.

I just wanted to make a few remarks to the audience and also to the members of the panel. First, we will follow the agenda. There is an agenda available for you. If you don't have one, it is on the table outside.

I would like to delay voting on the issues on before us until the very end of the day. First, I would like to have our committee hear the evidence to be presented, both from the sponsor and from the FDA panel.

Then, we will have deliberations by the panel about the evidence that we have heard. Next, we will have an open public hearing. Finally, we will resume our deliberations and at the end of the day we will vote.

To the speakers from both the sponsor and the FDA,

I would ask that we be allowed to interrupt your presentations. Any member of the committee who wishes to interrupt, please do so. It is important that we have our questions answered at the time that you are presenting your data.

I wish the committee members, though, would raise their hands to be recognized before they speak. If the lights are out, of course, you can simply interrupt the speaker and speak into the microphone.

At this point, I would like to introduce Mr. Michael Bernstein, committee Executive Secretary, who has asked for time to make a number of administrative announcements.

**OPENING COMMENTS**

MR. BERNSTEIN: Thanks, Dr. Gilman.

I would like to welcome each of the committee members and especially our new members to this 43rd meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. My name is Mike Bernstein and I am the Executive Secretary of this committee, which functions within the Division of Neuropharmacological Drug Products.

Please bear with me while I make a few administrative announcements.

On the table by the entry are handouts of the agenda, question lists, and roster of committee membership.

I hope that everyone has picked up a package.

We ask again that all speakers speak directly into a microphone. Individuals from the audience, following recognition by the Chair, should come forward to a microphone. Unless one speaks directly into the mike, comments cannot be heard by our transcriptionist or those sitting in the back of the room.

If anyone in the audience describes to make any comments in the open public hearing, we ask that you wait until you have been recognized by the Chair before coming forth to a microphone. Please identify yourself and your affiliation before you begin your statement.

Statements made in the open public hearing must relate to the issue being considered at this meeting and be of general interest to the committee members.

A lunch break will be determined according to our schedule. There is a lunch break on the agenda, but that may have to fluctuate a little bit according to discussions.

As this is an open meeting, a reminder that the proceedings may be tape recorded, but that the recording is considered to be unofficial until it has been approved by the Commissioner of the Food and Drug.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made part of the record to preclude even the appearance of such

at this meeting.

Based on the submitted agenda made and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exception.

In accordance with 18, U.S.C. 208(b)(3) a full waiver has been granted to Ellyn Phillips. A copy of this waiver statement may be obtained by submitting a written request to FDA's Freedom of Information Office located in Room 12A-30 of the Parklawn building.

We would also like to disclose for the record that Ms. Phillips, through her affiliation with the ALS Association, has been actively involved with Cephalon, Inc., one of the sponsors of Myotrophin, the product at issue today, and with Rhone-Poulenc-Rorer Pharmaceuticals, a competing manufacturer to Cephalon's Myotrophin.

Ms. Phillips has been actively involved in educating Cephalon, Inc., and Rhone-Poulenc-Rorer Pharmaceuticals concerning the ALS patient population and its needs.

Although these past involvements do not constitute a financial interest within the meaning of 18 U.S.C. 208(a), they could create the appearance of impartiality. However,

the agency has determined notwithstanding these past involvements that the interest of the government and Ms. Phillips' participation outweighs the concern that the integrity of the agency's programs may be questioned.

Therefore, Ms. Phillips may participate fully in today's discussions.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are ware of the need to exclude themselves from such involvement, and their exclusion will be noted on the record.

With respect to all other participants, we ask that in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Lastly, IND 39-927, Myotrophin, will be the only issue discussed by the committee at this meeting.

Thank you for your attention, and this concludes my comments, Dr. Gilman.

DR. GILMAN: Thank you, Mr. Bernstein.

**IND 39-927: MYOTROPHIN: TREATMENT USE UNDER AN INDIVIDUAL TREATMENT PROTOCOL FOR AMYOTROPHIC LATERAL SCLEROSIS (ALS)**

**FDA PRESENTATIONS**

DR. GILMAN: As you heard, the topic for today's meeting is IND 39-927 Myotrophin.

Dr. Paul Leber, Director, Division of Neuropharmacological Drug Products, has a few opening comments.

Dr. Leber.

**WELCOME AND OPENING COMMENTS**

DR. PAUL LEBER: Thank you, Sid.

Good morning, everybody. I would like to welcome you, particularly the new members who have joined the committee. Some of you we have known from the past, in particular Dr. Drachman has served so often as a special consultant to the agency that he almost feels like he has been on the committee before. But to everyone, welcome, and thank you for joining us.

This, I believe is a relatively unusual question for an advisory committee because it concerns the treatment use of an investigational drug. Therefore, although many on the committee who are old hands probably know what we do with NDAs, there is a necessity that I take some time to try to explain, as we have done in our briefing manual, what it is that makes treatment use different and what it is that makes it comparable to NDA decisions.

In order to do that, I have to tell you something about the Act and something about the way in which we

interpret the regulations under that Act that deal with treatment use of a drug that is an investigational drug.

I would also like to take a little bit of time after I do that to explain who we happen to choose to come to the advisory committee, because we do not always do so in the case of a treatment NDA decision, but that comes later.

Finally, I would like to acknowledge before I begin that is in any institution those who sometimes make the presentation are not those who do the work. In this particular occasion the lion's share -- and I take it in its full meaning, meaning almost all the work here -- has been done by Dr. John Feeney. He is a senior medical reviewer who has dealt with ALS products.

And Dr. David Hoberman, a mathematical biometrician on our staff, who have worked to examine the evidence in this particular case. And to them we owe really most of what was done. Russ Katz and myself, of course, have played our usual role as the "executives." I will use that in quotation marks.

To begin with, let's talk a bit about why we have INDs. As many of you know here, the law of the land as regards drugs deals with issues of premarket clearance. The mechanism used is to require that no drug be in circulation unless it is safe for use and effective in use, and the device used in the 1938 version of the Federal Food, Drug,

and Cosmetic Act is the requirement that sponsors do test, submit reports of those tests to the agency in the form of something called a New Drug Application, and initially it became effective if the FDA didn't work, but since '62, it has been required that the FDA review it and approve it unless it finds that it does not meet the requirements of the law.

Accordingly, if you don't have an NDA, as a sponsor, you can't ship a drug in interstate commerce. But clearly, what do you do about investigational drugs? So, since the 1938 version of the Act, there has been something known as a Notice of Investigational Exemption for an Investigational Drug or something to that effect. Obviously, I am fumbling on it and over the years its use has changed and it has been called an Investigational New Drug Application.

This is a device that allows someone who wants to conduct trials with the drug, experiments, to obtain supplies of drug that moves in interstate commerce. This is where the Federal Government's hook comes in, because it is interstate.

Well, in 1962, the IND, which between '38 and '62 was largely a notice issued by someone who was going to move the drug that they were going to do so, the only provision is at that time that they had to label the drug as

investigational and keep records of what they had, got changed because of a number of events that I don't have time to go into, but many of them concerned the widescale, unsupervised distribution of thalidomide at the time the thalidomide story broke.

It also probably concerned developments in the issue of human rights, knowledge of basically violations of human rights in research, putting patients at risk for the interest of society without due attention to the rights of individual patients that led to a whole new introduction or respecification, I should say, of the IND requirements.

[Slide.]

So, in '62 you see a set of rules that give the FDA authority to monitor research that is going on and to specify and set forth in regulation, requirements that sponsors have to meet to set it.

This whole thing, as you know, you have to do testing before you put patients at risk. You have got to do some testing. It doesn't specify what it is, but you have to do something. Control supplies of the drug, don't give it away to your neighbors, your friends, or anyone you want, because then you have widescale distribution. Keep records, so we will know what is going on in cases there is a disaster that happens in three patients, tell everybody, obvious reason protect us. Finally you see the beginning of

informed consent.

Now, the requirements of this particular IND are interesting because they show how far we have come. At that point, a physician, in their judgment, could decide it would not be in the interest of a patient to give informed consent and could suspend it. Clearly, that is not the rule today, and today we only have one exception under very, very careful circumstances where you can't have informed consent.

Well, if you look at this regulation as it actually is in the Act, not the regulation but the law, it appears to be an exemption solely granted for investigational use. But clearly, since 1962, when controls became fairly demanding, people have used the investigational exemption as a device to treat patients who are sick. In the brochure, we have given you an article published in '88 or '89 that gives some of the history, but basically, it is obviously so that many drugs are not pursued commercially and they end up in this sort of never-never land state, having some evidence supporting their value, but they can't be moved in interstate commerce.

So people gave them INDs, and this was known as compassionate use, single investigator treatment use, and the like, but it was in sort of a limbo regarding the law. So when the FDA began in the early eighties to take a very serious look at what its regulations were in regard to

investigational use, a rewrite effort, it decided to settle once and for all treatment use under investigational exemptions, and it came up with the notion and the device of something called the treatment IND or the treatment protocol under an existing IND that allowed the use of an investigational drug.

Now, this is very different. It was done. It was in fact challenged as not being consistent with the law by some commentators, but the FDA decided that it was, and we now have the regulation that is critical to today's discussion.

[Slide.]

Now, this regulation lays out the conditions very carefully of when you can in fact have treatment use. The reason for this is that we have a standard of an Act which we believe ensures the quality and performance of drugs that are in the armamentarium. That is set by the Act and we go through a process of approving NDAs that is supposed to guarantee that drugs are safe in use, effective in use, and labeled appropriately.

If we were to allow treatment use, we could generate in perpetuity the marketing of a whole new class of agents that had not met the test of law and would clearly violate the interests of society supposedly in the defending that Act.

So treatment INDs are set up under fairly stringent conditions that have to be met in order to allow treatment use, also important to recognize that they are intended not to allow use forever, a point I will come back to.

Anyway, here are the conditions. This is all part of concern that drugs that are going to be effective are denied because of bureaucratic sloth and the like -- which I deny, but that certainly was the assertion -- availability of drugs. It takes too long to get them.

So here are the conditions. The drug has to be intended to treat a serious or immediately life-threatening illness. There is no comparable or satisfactory treatment available, marketed, to treat that condition.

And here is an important thing. The drug is under investigation in controlled trials or all controlled trials, and it doesn't say it, but it means necessary probably for the submission and approval of an NDA have been completed and the sponsor is actively pursuing with diligence this development of the product so we are going to get an NDA.

All of this points again to the point that this is a transient state, it is not supposed to create a new drug class.

[Slide.]

Now, it is important, as always, to consider

definitions when people throw words around without defining them. Remember, you have got to define what you mean by serious disease and a life-threatening illness. Without doubt, ALS is a serious or life-threatening illness, but by this test of regulation, it probably qualifies as a serious disease.

If you look at the definitions, immediately life-threatening, it is down at the very bottom, it is a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or which premature death is likely without early treatment.

You could argue that ALS even fits that, but for purposes of the typical patient at the time of presentation has been treated with Myotrophin, I would argue we are at the stage we are talking about what would be classified as a serious disease. It is a minor point, but therefore, the test would be that no one can deny a request for treatment use those first four conditions having been met if there is insufficient -- you can only do it if there is insufficient evidence, which means you need sufficient evidence.

[Slide.]

Now, here is the rub which is always true. Sufficient and substantial, they like to say are terms of art. What does that mean? It means that if you read the legislative history, the regulatory history, you may have an

opinion about what they mean.

Substantial evidence, just to set where we are, which is the requirement for approval of an NDA, has been characterized as just such a term of art, but it has been long used and I can tell you what its salient points are.

It basically says that in order to reach an affirmative decision that a drug will be effective for use, experts qualified by experience and training in the management of the illness for which the drug is being proffered, have to be able to conclude, not on the basis of this opinions, beliefs, prior experience, but on the basis of evidence adduced in adequate and well-controlled trials, that the drug will do what the labeling the sponsor is going to use claims it will do.

That is very important because it is not seeking testimony or belief, it is seeking a judgment by experts qualified to make such judgments that evidence exists from a trial, which is deemed adequate and well controlled, that is, scientifically bona-fide trial, that supports the claims the sponsor makes.

Now, that cuts two ways. It means you need evidence that comes from investigations that are scientifically valid, but it also means that you don't have to have a drug that work in everyone or in all conditions. You need only meet the requirements that the sponsor has

claimed for the drug. So you can have very narrow. That allows you to make decisions. I mean you did one yesterday. You don't think that that product works in every patient with stroke. You think it works in a selected subset, and this is perfectly legal under substantial evidence.

[Slide.]

Okay. What is sufficient then? The only thing I can tell you about sufficient is that it has to be less than or equal to substantial. However, as a matter of practice, because we know where we are going and because you know what the intent of the regulation is, sufficient usually means that one component of the evidence that we intend to rely upon has probably already been generated at the time we make the decision. It needn't always be true, but in practice, in previous treatment INDs that has been the case, and it has often been the case that we have an expectation, a good one based on the fact that trials are ongoing, that we will shortly have results -- it could be a matter of a couple of years -- of another trial of equal structural validity and the likelihood of success that will confirm the first, so we will have our investigations, plural, as required in most cases under the current Act. That is the best I can tell you.

[Slide.]

Actually, if you go back and saw what was going on

in June of 1995, Cephalon informed us that they had the results of Study 1200 -- this is the North American trial -- in hand, and they were persuaded that they had met the test of what would contribute to substantial evidence.

Upon review of that, we agreed. In fact, we were the ones, the agency, who encouraged the sponsor, as part of your role of trying to accelerate the availability of promising drugs, to submit a treatment protocol, and the sponsor agreed to do so.

[Slide.]

We didn't get that submission until October of '95, and the points I probably should just reemphasize, what is probably obvious to all of you, the reason that we were able to make this suggestion and the sponsor could agree, is that it is a serious illness or worse, certainly a devastating one. There was no fully satisfactory treatment available. That remains true to this day.

We had the second trial underway. It wasn't completed yet, but we knew it was going to complete, and we had every reason -- and I still do -- to believe that the sponsor is pursuing the development of the drug in the sense that they will submit an NDA or want to submit an NDA.

[Slide.]

Now, in October of '95, however, just about at the time that we are going through the necessary internal

documentation to make a recommendation to the authority in FDA that can grant permission for a treatment IND, I believe three or four days prior to the time this action had to be taken, we received a copy of a press release that Cephalon had issued.

In reviewing that, it basically said that the results of the European trial, 1202, formally and strongly confirmed the results of 1200. I have to admit we were happy that was the case, but then we read it and we found that there appeared to be -- in fact there was -- a relative excess of deaths in Study 1202 among patients assigned to Myotrophin as compared to those assigned to placebo.

Well, that could always be due to chance. In fact, on straight statistical analysis, it was, but one must remember that imbalances that aren't even statistically significant can have an impact on the interpretation of other results because of the net effect that someone who dies may, in fact, have a score attributed to them, and there was a possibility, if one looks seriously, since there was a slight excess in Study 1200 of deaths, that something wasn't awry, and so we delayed making a treatment IND decision.

We asked the firm to submit more information, which they did, and there I think is the reason we come before you today, because in the course of looking over this

evidence, we were unable to reach the same conclusion as the firm in regard to whether or not 1202 was a confirmatory trial. In face, we viewed 1202 -- and to this day do -- as a study which fails to confirm the results of Study 1200. That is the Division's view. The firm takes a different stance. They have been able to conduct analyses based not upon the initial described in the protocol, which convinced them that the trial at worst is not contradictory and at best is supportive.

That really is the issue before us today. We thought that it would be impossible for us, given the fact that we had spent several months with the firm going over the data, we were unable to reconcile our differences, we thought it was impossible to make a decision without sharing it in a public way with everyone here and gaining the opinion of experts who could look at this evidence in a disinterested way and decide whether or not it met the test.

That is really what your charge is today, to look at the evidence and to decide whether it is sufficient for its treatment use. The issue of the approvability of the NDA cannot technically be on the table, of course. It cannot be on the table at all because no NDA is pending before the agency. But one has to consider the evidence nonetheless in its entirety, what it can support and what is likely in the future.

Clearly, that is the intent of the regulation, and within that context, we hope you can struggle with the data, as we have, to see what it really means.

That concludes my opening remarks. One thing I would like to point out and ask the Chair's permission, we had prepared our presentation on the basis largely of the briefing materials supplied by the firm some time ago.

As late as yesterday, we were receiving revised presentations of arguments. In addition, there are other points made that would take so much time for us to discuss, in fact, we would as a practical matter have to present the firm's argument in order to explain what we find weak or deficient in it.

So accordingly, I would like to ask the Chair if it is possible, after the committee and the firm have made their presentation, for us to be able to explain our view on various arguments they are going to present for the first time today.

They have already seen what our presentations are, so they will be fairly and directly prepared to discuss any of them.

DR. GILMAN: That is perfectly acceptable. Any concern from the committee about that request?

Let's proceed in that fashion. Dr. Leber, let you ask you about substantial and sufficient. The way we

usually work in this committee is to see plural of trial, we wish to see at least two well-constructed, valid trials showing evidence, and we then conclude if the data are convincing that we have a substantial piece of evidence.

With the term "sufficient," would it be fair for this committee to assume that a single trial, if it is convincing, does in fact provide sufficient evidence and therefore would constitute enough evidence to approve an IND?

DR. LEBER: It is a little more complicated. Yes is the simple answer, but I suggest that it is a little more complicated than that, because sufficiency regards the evidence. It also regards the state of time the development of a drug where that judgment is made.

The evidence, if we had but a single trial, as we did in June of 1995, we thought the evidence was sufficient because all information bearing on the effectiveness of this drug and its safety was in our possession.

What becomes more complicated is when you have contradictory evidence, and then the standard may shift slightly. If you only had one study, and there was no other evidence, it is clear that one study would be sufficient, and has been in the past.

What the problem is now is that with the addition of conflicting evidence -- and you have to decide whether it

is truly conflicting, you may agree with the sponsor that it is not -- you may have to modify that view.

So again it may sound like I am trying to evade the response, but I think it is a conditional thing in the context of how much evidence you really have in your possession. If there was only one, it is enough, but it is than one, and it is not confirmatory, then, you have a different level of problem.

DR. GILMAN: I expect that if we had only one trial that were very convincing, you wouldn't need us here.

DR. LEBER: If we had only one trial, we probably would not have come. The minute we have two trials that do not appear to robustly confirm one another, there is always this question of what does the conflict mean, and I think that is why you are here.

DR. GILMAN: Thank you. Any other questions for Dr. Leber?

Thank you very much.

Let's proceed then. John Feeney, M.D., medical reviewer, Neurology Drug Group, will make the presentation on behalf of the FDA.

**PRESENTATION AND ANALYSIS OF THE DATA FROM STUDIES 1200 AND 1202 ON MYOTROPHIN'S USE IN ALS**

DR. JOHN FEENEY: Good morning. We are just going to get our slides together and get going in a few seconds

here.

[Slide.]

I have a few introductory slides here. Basically, Myotrophin is insulin-like growth factor 1 or somatomedin C. It is a 70-amino acid polypeptide that is produced in a yeast culture system. It share approximately 50 percent homology with insulin.

Circulating IGF-1 is produced almost entirely by the liver in response to human growth factor and it is believed to mediate the majority of effects of human growth hormone. IGF-1 can also be produced locally in a number of other tissues.

Cephalon undertook studies of Myotrophin in ALS after it was shown that Myotrophin promoted axonal sprouting in animal models of denervation and also prolonged neuronal survival in the chick embryo model of neuronal loss.

[Slide.]

INDs for IGF-1 existed in the Division of Endocrine and Metabolism prior to 1992, but in 1992, when Cephalon opened its IND for the use of Myotrophin in ALS, the IND was submitted to the Division of Neuropharmacological Drug Products.

By mid-1995, two clinical trials that you have heard of, 1200 and 1202, had been completed and you just heard that the treatment IND was submitted in October with

the results of 1200.

Then, on October 31st, the results of 1202 were made public by Cephalon.

[Slide.]

I am sorry, this is kind of hard to read. Basically, both of the trials, 1200 and 1202, are capably by design of demonstrating an effect of Myotrophin in ALS. They are both double-blind, randomized, placebo-controlled trials.

They are both parallel in design with nine-month treatment periods. Both of the trials include eight centers. 1200 was conducted in North America. 1202 was conducted in Europe.

The 266 patients in Study 1200 were equally divided among three treatment groups. The three treatment groups were placebo, low-dose Myotrophin, and high-dose Myotrophin. I will just tell you that the low dose was 0.05 mg/kg/day given as a single sub-Q injection with a matching placebo injection later in the day, and the high dose was 0.10 mg/kg/day divided into two equal injections.

The 183 patients in Study 1202 were divided with a 2 to 1 randomization between Myotrophin and placebo. The dose utilized in 1202 was 0.10 mg/kg/day, essentially the same as the high dose in Study 1200.

I will just mention at this point that that dose

of 0.05 mg/kg comes from early Phase I testing where it was determined that higher doses caused an excess of symptomatic hypoglycemia. So that 0.05 mg/kg represents the maximal single tolerated dose.

[Slide.]

Both of the trials relied heavily on the Appel Scale to grade patients' clinical status over time. The Appel Scale was developed at Baylor University in the early 1980s, and the experience with that was first published in an article by Appel, et al., in 1987.

The Appel Scale grades patients with a range of scores between 30, for best performance, and 164, for worst performance. It consists of five components, three of which are shown here: bulbar, respiratory, and muscle strength.

The bulbar score consists of equal representation for swallowing and speech. The swallowing is assessed by a patient's diet and the speech is assessed at the time of the examination.

The respiratory score is based on forced vital capacity, which is basically, as most of you know, the maximal amount of air that a patient can expire after a maximal inspiration. Basically, changes on forced vital capacity are mapped to six-point increments on the Appel Scale.

I should mention that each of the components, each

of the five components contributes approximately 30 to 36 points to the total Appel score.

Muscle strength is graded on the MRC zero to five scale, the Medical Research Council scale. Muscles are graded zero to 5, and then the sum of numerous muscles are mapped to a score on the Appel Scale.

[Slide.]

The other two components of the Appel score are upper extremity function and lower extremity function. Each of these consists of four timed items, such as time to walk 20 feet, time to cut some theraplast in occupational therapy, time to perform some activities with a peg board, and then there are two functional items based on historic ability to do things, let's say, with the arms and shoulders or to dress and feed yourself.

[Slide.]

In the 1987 publication, Appel, et al., compared their Appel scores to an independent five-point assessment of severity of ALS symptoms. In doing this, they found that patients who were independent, still living alone, basically doing very well, had an average score of about 52, and the range here was very tight.

Patients who were no longer independent, might need a walker and some assistance, had an average score of 75. Patients who could usually no longer work, required a

caretaker for a lot of things, had an average score of about 100. Patients who were at the point where they might require tracheostomy or a gastrostomy had an average score of 120, and patients who were very severely affected had a score of approximately 135.

[Slide.]

Appel, et al., found that if they looked at Appel scores over time for the 74 patients in their experience -- they followed these 74 patients for up to two years -- they found that there was a remarkable linearity and that a linear slope could be fit to the scores over time.

Basically, this means that about 80 percent of the variability of the Appel scores for an individual patient could be accounted by fitting the line.

This shows the distribution of Appel scores over time for 74 patients in that 1987 publication. I want to point out that the units here are represented in units per day. This is in keeping with the original 1200 study report. Unfortunately, you are going to have to deal with the fact that sometimes units you will see today will be expressed in units per month, and I don't think I have to tell you that the conversion factor is about 30 there.

So this is the distribution of slopes for the 74 patients. Let me tell you that for a slope of 0.14 units per day, basically, patients with this slope or greater will

experience approximately a 50-point or greater rise in their Appel score in the course of one year. So these patients are moving fairly quickly through their disease process.

Patients with a score of about 0.03 to 0.14 are going to move approximately 10 to 50 points in the course of a year, and about 50 percent of patients fall into that range.

Patients with scores of 0.03 and less are going to move 10 points or less in the course of a year, and they might be considered slow progressors.

In a 1995 publication, Appel tried to validate his scale by using these slopes to predict time-to-death for patients with ALS. Basically, what he found is that the higher the slope, the better the predictive value.

Especially for patients in the slow-moving group of 0.03 units per day or less, they found that the predictive value is very poor, and what you are going to see is that the inclusion/exclusion criteria of Studies 1200 and 1202 basically tended to exclude these patients who were slowly moving.

[Slide.]

These are the inclusion/exclusion criteria. They are essentially the same for Studies 1200 and 1202. Patients had to be greater than 20 years of age, and they had to be diagnosed with classical, non-familial ALS. There

was no operational definition of how to define classical ALS, but I would expect that most of the investigators were using what has become accepted as the AALS score criteria for diagnosing ALS. Note that patients with familial ALS were excluded.

Patients had to have a disease duration less than 36 months and a forced vital capacity greater than 50 percent, and they have to have a score of 40 to 80 at the time of screening on the Appel score.

All of these criteria basically were meant to incorporate patients with mild to moderate ALS into the trial.

There is also a requirement that patients, once they were screened, they had to progress at least 5 points on the Appel Scale during a two- to three-month mandatory run-in period.

[Slide.]

This is an outline of study events during both trials. At month zero, this is the baseline visit or the time of randomization, and you will that once randomized, patients could continue on treatment for up to nine months. This represents a nine-month completer here.

During the course of that nine months, if patients reached an Appel score of 115, they were allowed to be censored by protocol and basically leave the study. They

were considered to be failures at that point, too sick to possibly return to the clinic for visits.

Not shown here is that independent of your Appel score, you could also leave the trial, be censored early, or a forced vital capacity of less than 39 percent.

So we have those categories, forced vital capacity and Appel score. I should note that some people actually endpointed for both of them at the same time.

Now, over here, to the left of the zero point, you will see this patient has a two-month run-in. This patient has a three-month run-in. Basically, this patient had met the five-point criteria progression within two months, was randomized at that point.

This patient took a full three months to progress five points and was randomized at that point.

If a patient was screened, went three months, hadn't progressed five points, they would not be randomized. They would not be eligible for entering into the trial.

You can see on this slide basically the distribution of Appel scores that is collected over time with monthly Appel scores recorded for patients.

DR. GILMAN: May I ask a question here.

DR. FEENEY: Sure.

DR. GILMAN: As I read the protocol, as I understand it, patients with primary lateral sclerosis and

patients with progressive bulbar palsy were excluded from that trial.

DR. FEENEY: That is right.

DR. GILMAN: My question is whether the original Appel Scale also excluded those variants of ALS.

DR. FEENEY: I don't know the answer to that. I don't know if Dr. Appel is here today.

DR. GILMAN: Please go to the microphone, Dr. Appel.

DR. STAN APPEL: Patients with either of those have been included, but in our database can be separated out by those criteria and can be looked at separately.

DR. GILMAN: So they are included in the original 74, however, they are excluded in the trials of Myotrophin?

DR. APPEL: Excuse me. No, the original 74 were patients that we were looking at collectively that had to meet all the typical criteria, having all systems compromised, and by definition, they wouldn't fit, primary lateral sclerosis would not fit. Primary bulbar palsy with no other involvement would not fit. So they were excluded from the original 74.

My point is, in the whole database, we have them included and we have graded them, as well, but with respect to the 74, they are not included, and they are also excluded from the 1995 paper, because those criteria do not fit the

AALS criteria for classical ALS.

DR. GILMAN: The reason for that is, the question about whether the patients examined with Myotrophin and placebo are equivalent to the patients in the original database, because those comparisons are made with slopes. I think the answer is yes, they did.

DR. APPEL: The answer is yes.

DR. GILMAN: They do correspond well.

Another question. Those cases that progressed more rapidly than others, were they people who had substantial bulbar involvement in both the original 74 and also in the cases studied?

DR. APPEL: They may or may not. Bulbar is a component.

DR. GILMAN: I know.

DR. APPEL: The point is to get that much involvement and that rapid a progression, you usually have to have either bulbar and/or respiratory, or large respiratory component.

DR. GILMAN: So the answer is yes, they were more likely to have bulbar involvement than those who progressed more slowly.

DR. APPEL: Yes.

DR. GILMAN: Thank you.

Dr. Adams.

DR. ADAMS: I have a question in regard to the inclusion/exclusion criteria. It is stated that at screening the patient had to have a score of 40 to 80, and in the first two to three months, had to progress at least five points.

DR. FEENEY: Yes.

DR. ADAMS: Was there an exclusion for people that may have progressed 40 points, we will say, in the first two to three months, so that the very, very rapidly progressing patients at far extreme were excluded or included?

DR. FEENEY: No, I can tell you that I think in Study 1200, at baseline, the highest total Appel score for any patient was I think about 110. So there were some people who were moving pretty rapidly, not a lot, but there were some. You will actually see the distribution of total Appel scores later at baseline.

[Slide.]

You saw that Appel scores were collected monthly throughout the trial. What do you do with those Appel scores? Well, you can combine them into different outcome measures, and four of them are shown here.

The first two are last observation carried forward endpoints, where basically the last observed score for any patient during the course of the trial is carried forward for analysis purposes.

There are problems with LOCF analyses in studies of progressive illness because any score that you carry forward would be expected to be less than the patient's realized score had they been followed forward in time. So just keep that in the back of your mind whenever you are looking at an LOCF analysis in an degenerative condition, anytime you have patients censored early, you are going to have to think about your LOCF analysis.

The next are slopes analyses. These basically compute slopes for patients over time, and then I want you to note that these two, this one here and this one, are both related back to baseline pre-randomization levels of functioning for the patients. So this is kind of a change from baseline, and this is a change from pre-randomization here.

This one here, this slopes analysis, post-randomization minus pre-randomization slope, is the analysis that incorporates all of the Appel scores over time for an individual patient as they were collected in the trial.

Now, in Study 1200, the primary protocol-specified outcome measure were post-randomization slopes.

In Study 1202, the primary protocol-specified outcome measure was last Appel score minus baseline Appel score.

You might ask why, in two studies that are

essentially the same, why the primary outcome measure differed, and to be honest with you, it has never been totally clear to us, and when this was defined as the primary outcome measure in Study 1202, we in discussions with the sponsor let them know that we would be looking at other analyses that might incorporate more data on patients over time. Just a point worth remembering.

[Slide.]

What I want to do now, if we could back on the right there, to highlight the similarities and differences between Study 1200 and 1202. I would like to present some of the findings side by side here, so that you don't have to be thinking what happened in the other study on this particular measure.

[Slide.]

As mentioned earlier, both studies were capable by design of demonstrating an effect of Myotrophin in ALS. Both were randomized, placebo-controlled trials, three treatment groups in Study 1200, two treatment groups in Study 1202.

The randomization was unbalanced 2 to 1 here, and was balanced here. Not shown on the slides is that the randomization in Study 1200 was stratified based on the baseline Appel score. That is, patients with a score of 61 or greater were stratified, were considered in the upper

strata. Patients with baseline scores of 60 or less were considered in the lower strata.

The reason for the stratified randomization was simply to create a balance between the three treatment groups. It was never meant for analysis purposes. In Study 1202, the randomization was never stratified.

The primary outcome variable, we have already talked about, differed between the two trials, and the primary analysis, both of these studies by protocol had a covariate analysis. The method for selecting the covariates was basically to look at from a preselected list of covariates, to look at the results of the trial and examine which covariates had the most predictive value.

In retrospect, we had to think that this method of selecting covariates had the potential to increase the chance for a false positive result, so that we chose to create non-covariate analyses, which we consider better analyses, but we will present the results for both covariate and non-covariate analyses for both trials.

DR. GILMAN: Let me ask you a question about the primary outcome variables in the two studies. It was not clear to me from reading both materials why these two studies had difference primary outcome variables.

What was the rationale?

DR. FEENEY: Not having done it myself, I think we

would have to defer to the sponsor.

DR. GILMAN: Please identify yourself at the microphone.

DR. WILLIAM GRANEY: I am Dr. William Graney from Cephalon.

The change between the 1200 or North American trial, and the 1202, or European trial, was initiated at the request of the European investigators. The trial, as you can see, had a slightly smaller number of patients, and their concern was that the number of patients required for the slopes or the number of measurements in each patient required for the slopes, a minimum of three, would reduce the number of patients getting into the primary analysis.

They felt that the use of the changed score, where it is only necessary to have a baseline and one successive measurement to be able to calculate the score, brought them closer to an intent-to-treat approach.

That really was the genesis of it and it arose from the European investigators themselves who, as you will see in our presentation, had a fair amount of input into the design decisions made in the European trial.

DR. GILMAN: I am not sure I entirely understand that. You mean that they wanted to have only a single observation before they randomized?

DR. GRANEY: They were concerned that during the

course of the trial, the dropouts that occurred would result in a relatively small number of patients or a smaller number of patients who had three post-baseline evaluations. In other words who had an event or left the trial in months 1 or 2 would not have three post-baseline measurements to allow the calculation of a slope. It was specified in the protocol ahead of time. As you can imagine, to get a realistic slope or line, three points would be needed.

They were concerned, especially having a slightly smaller number of patients in the European trial than in the U.S., that the credibility and the acceptability of that measurement would be lessened if there were a substantial number of patients who did not qualify for the primary endpoint.

DR. GILMAN: Are you referring to the pre-randomization or post-randomization, or both?

DR. GRANEY: These are post-randomization measurements.

DR. GILMAN: Post.

DR. GRANEY: Yes, sir.

DR. GILMAN: Thank you.

Dr. Drachman.

DR. DRACHMAN: Would you clarify the way the slope was figured, was that done algebraically, was it a best-fit regression analysis, or how did they do that?

DR. FEENEY: From my understanding, it was best-fit linear regression.

DR. DRACHMAN: What did they do with the dropouts?

DR. FEENEY: As Dr. Graney was just alluding to, the slopes analysis in Study 1200 by protocol required that patients have at least three post-baseline Appel scores to make the slope. If somebody had fewer than three post-baseline slope points, Appel points, they would not be included in the analysis. They were just not included.

You will see later just how many patients that comprises. It was about one out of nine patients in each study did not have three post-baseline Appel scores, so they are not entered in the post-randomization slopes analysis.

DR. DRACHMAN: Was linearity an issue at all here?

DR. FEENEY: No. I guess I failed to mention that, like the Baylor group, we found the linearity was very good in about 80 percent of the variability was accounted for by these fitted lines in both Studies 1200 and 1202.

DR. GILMAN: Dr. Leber?

DR. LEBER: I just want to emphasize that what we are talking about is within-subject variance, having a very high accountability. The between-slope variance is quite large, as you saw.

DR. GILMAN: Please continue.

[Slide.]

DR. FEENEY: Both of the trials had some secondary outcome measures that I haven't mentioned yet. In both trials, clinical global impression was performed on a monthly basis.

Basically, this had two components. There was a seven-point change from previous month scale and a five-point change from baseline scale, and patients were graded on a monthly basis.

The sickness impact profile is a quality of life questionnaire that is comprised of about 136 questions that, for the most part, are yes/no type questions. These 136 questions can then be broken down into I think about 12 categories, which are then further broken down into domains, two or three big domains, such as physical impairment and psychosocial impairment.

For treatment IND purposes, we have not performed full analyses of these scales, and we have chosen to focus primarily on the Appel scores, but realize that these scales were utilized. I think the sponsor will talk about some of those results.

[Slide.]

Now, what about patient flow? I know you can't read this, but take my word for it, for each of the five treatment groups across Study 1200, or I should say all of the slides on the left will be Study 1200, all the slides on

the right will be Study 1202.

Approximately half of the patients in all of the treatment groups were non-completers, so about half of the patients completed a full nine months of treatment during these trials.

The reasons for leaving the trial were mentioned earlier. There could be an Appel endpoint, an FVC endpoint, patients could die. Patients could, like in any trial, leave for adverse events, administrative reasons, and whatnot.

If you look here, you can see in Study 1200 the number of people censored early because of an Appel endpoint of 115 or a forced vital capacity of less than 39. You can see that already you can tell that in the high-dose group here, there seems to be a benefit for the Myotrophin group compared to placebo over there.

It is hard in Study 1202. You have to take into account the 2 to 1 randomization, but I think you can see that if you take that into account, there does seem to be some benefit on time to Appel endpoint and for FVC endpoints here, but unfortunately in 1202, this trend in favor of drug is counterbalanced by an excess of deaths on drug.

[Slides.]

This just gets back to that point that if you are going to do a slopes analysis as per protocol, patients with

three post-randomization Appel scores, with less than three Appel scores after baseline are going to be excluded, and you can see that roughly 1 out of 9 patients in all of these treatment groups were excluded on that basis.

It is pretty well evened out among the three treatment groups in Study 1200. In 1202, remember 2 to 1 randomization, there is a slight excess of patients on Myotrophin who don't go into the slopes analysis, accounted for by some adverse events.

[Slides.]

The next three slides are going to talk just about baseline comparisons among the treatment groups, and you will see that all the way across, Study 1200, Study 1202, basically, the age, race, baseline weight, it is almost identical. The patients on average were about 55 to 57, and the weight all seem to be about 155 to 160.

[Slides.]

Baseline ALS history, you will see that again totally comparable across both studies. Time since first symptom basically about the same. Time since diagnosis basically about the same. When you look at first ALS symptom, I really don't know what to make of this scale, because it has some kind of idiosyncratic things like sensory symptoms, which I presume are cramps or whatnot.

It does appear that in Study 1202, maybe more

patients had weakness as a first symptom and maybe more trouble with speech in 1202. I don't know what to make of all that.

DR. GILMAN: Maybe we could ask the sponsor or the investigators to comment on that. Some people with ALS do, in fact, complain about certain sensory symptoms. I assume that that is what you were observing. Will the sponsor comment?

DR. GRANEY: Yes. In fact, that is correct. These were reports. No patient, however, entered who had only sensory symptoms. All of the patients had the classic symptoms. Some of the reported to their investigator that they had these sensory symptoms, as well, and those are the ones that are noted there.

DR. GILMAN: But it is to be emphasize that these were symptoms, and not signs. They did not have sensory loss as examined neurologically I assume.

DR. GRANEY: That is correct.

[Slides.]

DR. FEENEY: Now, here are the baseline Appel comparisons across all five treatment groups. You have got to be impressed here that the average total Appel score at baseline for all treatment groups essentially identical, 70, and you have got to be impressed, too, that the component scores are essentially identical across all three treatment

groups.

[Slides.]

Now. these slides illustrate distributions of the pre-randomization slopes for different treatment groups. Here, the high does Myotrophin group with the squares in the placebo group with the circles and Myotrophin versus placebo here. These are cumulative distributions which basically means that any point here on the curve will tell you the percentage of patients on the vertical axis that have a score on the horizontal axis down here or less than that score.

So let's say if we take the 50th percentile here, 50 percent of patients really in both treatment groups had baseline or screening slopes of approximately 0.12 or 0.13. That is what that is telling you.

Now, the advantage of looking at cumulative distribution functions is that visually, it is easy to compare groups. Basically, in this case, a shift to the left would represent a favorable shift, and a shift to the right of a curve would represent a change for the worse.

For instance, here, there does seem to be a slight shift to the left of Myotrophin screening slopes by about 0.01 units per day, a slight shift there.

[Slides.]

These are more familiar distribution that you are

used to looking at. These are the baseline Appel scores for the high dose Myotrophin group, placebo, in 1200; Myotrophin, placebo in 1202.

Again, we already saw the means for these distributions. There are 70 at baseline. You will notice that the distributions here are fairly comparable, especially at the high range here.

You have to focus in that in the high range down in 1200, for the placebo patients, there is a group of about 7 or 8 patients here that seems to be outliers at their baseline Appel scores. You don't see anybody really above, about 95 here. It is about 7 or 8 patients with scores above 95 over here.

Now, this may not affect a slopes analysis, but this is going to kick in for your any time-to-event analysis that incorporates an Appel endpoint of 115. You only have to look at this patient right here to tell that he is going to endpoint very soon, and in fact, all these patients were early endpointers. So just bear that in mind for the time-to-event analyses in Study 1200.

[Slides.]

Every protocol should have a specified outcome variable and analysis, and that is what we are looking at here. These are the protocol-specified analyses for Study 1200 and 1202.

In 1200, the protocol said that the pooled doses, the high dose and low dose would be pooled and compared to placebo. Again, the covariate analysis without covariates, the p values were 0.055, 0.05 for the pooled comparison.

The high dose comparison to placebo reached statistical significance with a p value of 0.027. It just reached statistical significance based on Dunnett's correction for multiple dose comparisons. The low dose did not meet statistical significance.

When you come over to 1202, again, this is an LOCF change from baseline analysis. You can see that whether you use a covariate analysis or a non-covariate analysis, the difference did not reach statistical significance with a p value of 0.34 and a p value of 0.22.

[Slides.]

This actually shows you the mean slopes. Now, we are looking at slopes here for both Studies 1200 and 1202. This is the mean slope for the placebo group, mean slope for the high dose Myotrophin group. This was the primary analysis in 1200, so you know that this difference between these two reached statistical significance, we just looked at that.

In Study 1202, this is the mean on-study slope for the placebo group and for the high dose group. This difference did not reach statistical significance. The p

value here was 0.40 with covariates that might have come down to 0.27 or so.

Also, note that the difference here, the on-study slopes differ by an amount really very comparable to the difference that was already present at baseline before treatment began.

[Slides.]

Again, let's look at some cumulative distributions of on-study Appel slopes in 1200 and 1202. You can see that a shift to the left for the high dose Myotrophin group has occurred in Study 1200 compared to the placebo group. The shift shows a beneficial trend of high dose Myotrophin compared to placebo.

When you look at the distributions here for 1202, you see that the curves superimpose except for this one small area where there is a minimal separation.

[Slides.]

Now, what about time-to-event analyses? The sponsor in their briefing document has presented some results of Kaplan-Meier curves with an endpoint defined as the Appel or FVC. If the reason for looking at Appel and FVC endpoints is because you consider these failures or very poor responses, I think it is only right to incorporate death into that equation.

So we have performed time-to-combined endpoint

analyses with death, Appel, and FVC. You can see in Study 1200, you get a separation of the curves with Myotrophin favored up here compared to placebo.

When you look at the same analysis in Study 1202, the curves basically superimpose.

[Slide.]

You have to consider those outliers on the baseline Appel scores in Study 1200 at some point, so as an exploratory analysis, we did repeat the time-to-endpoint analysis in 1200, excluding patients with baseline Appel scores greater than 90, and what happens is you can compress these curves fairly close together with a slight separation at the end.

[Slide.]

The sponsor also wanted to perform time-to-20-point change analyses. If you remember the correlation between the Appel scores and that 5-point scale in the 1987 publication, the five groups based on ALS severity, spread out by about 20 points or 25 points. So you might consider that a clinically relevant change in ALS status.

So this is time-to-20-point change analysis in Study 1200, and you can see that it favors Myotrophin here, high dose Myotrophin versus placebo. We don't have a slide showing the same curves in Study 1202, but the curves essentially would not separate on this analysis.

DR. DRACHMAN: In the 1200, weren't there inclusion criteria scores of 40 to 80?

DR. FEENEY: A very good question. Forty to 80 were the screening -- a patient came in, was screened, and they had to have a score of 40 to 80. They then were followed for two to three months, had to demonstrate at least a 5-point progression.

So that if you look at scores at baseline, there is no upper limit on what your baseline Appel score could be. I pointed ou there were some patients with baseline Appel scores in Study 1200 in the placebo group with scores up around 110.

DR. DRACHMAN: So were those individuals with under 80 to begin with?

DR. FEENEY: Yes, that screen, they had to be under 80. So those patients had progressed during the two t three months screening period.

[Slides.]

These are the extended survival analyses from both studies. I want to point out that the study was only 300 days in duration, so 300 would cut you off right about here, 300 would cut you off right about here.

What happened after day 300 is anybody's guess, because certainly patients after day 300 were not going to respect their treatment assignments. Any patient who was

originally assigned to the placebo group, I am sure is crossing over to other experimental drug therapies, maybe had crossed over to open label Myotrophin, whatever.

So it is very difficult to interpret anything that happened after 300 days in both of these.

Now, the placebo group is the slope on the bottom here, and it is the slope on the top here. You can see, at 300 days, there did seem to be a trend in favor of the Myotrophin groups in Study 1200, but at 300 days in Study 1202, the trend was reversed and was in favor of placebo.

[Slides.]

Now, we are aware that the sponsor has a couple of arguments to explain the discrepancies between the results of Study 1200 and 1202. One of them is that the placebo groups may have performed differently between the two trials, thereby diminishing any difference between Myotrophin and placebo in Study 1202.

We disagree. You know, the baseline Appel scores were 70 in both trials, and if you look at the distributions of on-study Appel slopes for the placebo groups, these are the placebo groups on-study slopes for Study 1200 and 1202, and you will see that the distributions of on-study slopes are exactly the same.

So if you have the same baseline scores and you have the same slopes, it is hard for us to imagine how the

placebo groups differ.

[Slide.]

Now, the other argument that the sponsor has made is they would like to focus in on the upper strata now. They want to focus in on patients who, at baseline, had Appel scores of 61 or greater.

Recall that in Study 1200, the randomization was stratified for this upper strata and lower strata. It was stratified simply for balance between the two treatment groups, not for analysis purposes.

Study 1202, the randomization was not stratified and certainly there are no analysis plans that incorporated strata into the analysis.

So basically, when you do an upper strata analysis, you are doing a post hoc analysis with data in hand, that is always problematic in any clinical trials.

Now, in trying to rationalize why we should look at the upper strata, one of the arguments that the sponsor would like to make is that people in the upper strata just have different slopes. They are progressing more rapidly.

To examine that question, what we did is we looked at the placebo patients in the lower stratum of Study 1200, in placebo patients in the upper stratum, Study 1200, and we did the same in 1202.

What you see is that the slopes really pretty much

-- the distributions overlap to a very great extent. Now, we acknowledge that there is a group of outliers over here with high slopes in the upper stratum. These are going to drive the means of the upper strata, the mean slope, a little bit higher, but if you look at the medians for these distributions, the median here, the median here, the median here, the median here, they are all going to be fairly comparable.

So if you look at the upper strata, at least based on the data from these two studies, don't think that slopes are the difference.

Now, this is going to be carried forward by the sponsor, I am sure, because what they have done is looked at the Baylor database, and they found, using certain techniques of analysis, such as time-to-20-point change, that you can differentiate upper strata and lower strata patients based on their rate of progression. It just doesn't happen in Study 1200 and 1202.

DR. GILMAN: Could you go back on the left screen just one slide. Is it the case that those curves also match the original 74 untreated patients? In the original Appel series of 74, do we have slopes like this that approximate this?

DR. FEENEY: Well, it is hard to compare because the distributions are done differently. I would have a

hard time saying. I mean it looks pretty comparable to me just eyeballing it.

DR. GILMAN: Thank you.

DR. FEENEY: You remember that most of the patients, in the 74 patients, 50 percent had slopes between 0.03 and 0.14, and I think that is pretty much true here.

So I just want to make the point that in 1200 and 1202, there is a big overlap in slopes between the upper strata and lower strata. It doesn't mean that there is not some other characteristic that differentiates the upper strata and lower strata, but it doesn't appear to be slopes.

[Slides.]

Now, if you look at the upper strata this is the mean on-study slope for the placebo group and for the high dose group. This is the slope for the placebo group and the Myotrophin group in 1202 here.

[Slides.]

Now, if you look at the distributions, this is taking it a step farther. We took the on-study slope for each patient and we looked at change in slope. We looked at the on-study slope minus their screening slope for each patient, and then we did distributions of these for high dose Myotrophin, placebo, and high dose Myotrophin and placebo here.

You will see that in 1200, performing this

maneuver in the upper stratum, you get a separation, but when you look in 1202, the curves superimpose, and again, this is the upper strata. So even if you do look at the upper strata, there are ways to look at it that just kind of take away from any apparent effect there.

[Slides.]

You can perform time-to-combined event analyses for the upper strata. Again, the combined event is death, Appel, FVC, and you will see that for the upper strata in 1200, the high dose Myotrophin group performed better than placebo, but for the upper strata in 1202, the curves are pretty much superimposable.

[Slides.]

Another big problem if you want to just focus on the upper strata in 1202 -- and again, you don't really need to focus on the upper strata in 1200 because the overall results seem to favor high dose Myotrophin over placebo -- but if you want to look in 1202 and focus on the upper stratum, you can see that the slopes favor Myotrophin here.

The problem is that when you look at the lower stratum, it goes in the other direction, and it goes in the other direction by an order of magnitude that is comparable to the effect up here.

So it is just another problem in focusing out a subgroup analysis in 1202.

[Slides.]

So take a step back and I think in our memo to the committee, you saw that we seem to favor these analyses where we take the on-study slope minus the screening slope and look at change in slope.

These are the distributions for those changes for both strata combined in Study 1200, and you can see that for change in slope, there was a beneficial effect of high dose Myotrophin versus placebo, but for the combined strata in 1202, the curves superimpose.

[Slide.]

So where are we with regards to the efficacy of Myotrophin? Our conclusion is that in Study 1200, a difference between high dose Myotrophin and placebo that favored the Myotrophin was demonstrated, but in Study 1202, when we looked for independent corroboration of the results of 1200, unfortunately, we didn't find them, and we didn't find them based -- remember, for primary analysis, the primary analysis reached statistical significance in 1200, did not in 1202. Post-randomization slopes analysis reached statistical significance, was a primary analysis in 1200, for 1202 did not reach statistical significance.

Change in slope, the trend on those cumulative distributions was in favor of Myotrophin in 1200, other direction was -- there is no separation in 1202. I don't

think I need to go on. You get the drift.

The only other thing I haven't covered is safety. At this point in time, at the level of the treatment IND, we really haven't examined all of the safety data in great detail. In fact, we don't have the full safety data from 1202 in-house yet.

I can tell you that in a review of all the deaths from both studies, there was nothing that would make us think that use of Myotrophin should be precluded. There were a lot of deaths, obviously. Most of them seemed to be in line with the disease process.

For Study 1200, a review of discontinuations for adverse events and whatnot didn't seem to raise any undue alarm on our part. I think the sponsor will probably present some of the more common adverse events. They can go into some detail on that if you want to hear more about that.

DR. GILMAN: Thanks, Dr. Feeney.

Let's take a couple of questions now. First, there is a commentary in the narrative on page 15 by the FDA about difficulty with blinding because of inflammation occurring at the site of injection.

I thought I had understood from the sponsor's statements that inflammation resulted from the vehicle, not from the primary agent, and therefore, I would assume

inflammation might have occurred on the skin in both placebo and active drug injections.

Can you comment on that or can the sponsor?

DR. FEENEY: I will just say from what I know, I think about 7 percent of patients in Study 1200 experienced what are called inflammation, redness, induration, whatnot, and for the Myotrophin groups I think it was about 35 to 40 percent of patients had that.

DR. GRANEY: If I could comment on that. In fact, there is a fair amount more of detail relating to injection site related reactions.

They were fairly numerous when you look across the whole possible classifications of them, which included bleeding, complaints of pain, swelling. We set up a collection of terms which we could put them. One of them was the one which we called "injection site inflammation."

That included, in general, terms which tended to involve redness or some swelling. However, it is really clear on looking at the data that the individual patients having these injection site reactions were quite complex. They had combinations of pain, bleeding on one occasion. They had swelling.

When the classifications were done, they were not exclusive. We have items like swelling occurring in a couple of the different classifications. We, in fact, took

a look at all of the patients who reported injection site reactions, and I can show you the slide later as part of y presentation or following it.

When we look at all injection site related complaints that bring these together, they are very evenly divided between the treatment groups at all of the individual sites, and I do have a slide I can show that.

DR. GILMAN: But what about the placebo cases?

DR. GRANEY: They are very similar. They are quite similar. In fact, as you will see when I present the overall safety, injection site pain was actually more common in placebo patients.

DR. GILMAN: Dr. Feeney mentioned that there is a very big difference in the number that experienced inflammation at the site of injection, in the placebo group much smaller, in the treatment group much higher, is that correct?

DR. GRANEY: I think that is correct. What I would like to do, if I could, a little later is point out the relative difficulty with that classification. It is post hoc, was done at the time of data entry, and I think really does not have the apparent strength that it might from the simple display of the data, and we have other data to show you.

DR. GILMAN: Also, for Dr. Feeney, we heard from

Dr. Leber earlier that there was some concern about the number of deaths in Study 1202. I don't remember exactly the numbers, 18 I think it was or something like that, a much higher number than in 1200.

Can you comment on that?

DR. GRANEY: Well, the first comment you always have to make in talking about the excess deaths in 1202 is that the 2 to 1 randomization, remember, you know, the 18 is just because of the 2 to 1 randomization it is not totally out of line.

There was an excess of deaths. It wasn't statistically significant. A review of the causes of death doesn't raise any obvious drug-induced mechanism. It was there, it trended in the opposite direction from what we saw in 1200. That is really where we are at.

DR. GILMAN: I did want to ask about that point also. Do you have a cause of death -- and will the sponsor show that -- do we have autopsy verification in the patients who died, both of the disease process, do we have neuropathological diagnosis in these cases?

DR. GRANEY: Yes, we don't really have extensive autopsy or neuropathological, but we are prepared to provide extensive clinical information on the individual deaths.

In my presentation, in the safety I have a basic discussion of it from an overview point of view and with an

analysis that we performed. Additionally, we can provide information to you on the individual deaths, and I think you will see, as Dr. Feeney, mentioned that the deaths really appear from the clinical point of view to be quite characteristic of the ALS deaths that we saw elsewhere.

DR. GILMAN: Do you also have neuropathological information on these cases?

DR. GRANEY: We do not.

DR. GILMAN: On any of them?

DR. GRANEY: I would have to check and find out. We certainly don't have it on the majority of them, and I will determine what we have.

DR. GILMAN: All right.

Dr. Leber first and then Dr. Temple.

DR. LEBER: Since I made the statement, I probably should put it in the appropriate context timewise. We received three days before we were about to take action on the basis of 1200, a description of Study 1202, which is brief.

It provides raw information about 18 deaths occurring among the patients who were assigned to the high dose, single dose of Myotrophin in Study 1202, and 5 or 4 deaths at the time, I don't remember exactly.

Even if you double that, that is an excess. Now, we weren't only concerned about the possibility, the study

is not powered to look at mortality in the time frame that that could be a signal of concern, but also the effects of when the deaths occurred.

If you look at the survival analysis presented for 1202, you will notice there was a period during the trial where there were a great number of survivors, and therefore earlier deaths occurring on Myotrophin.

So part of our concern was the biasing effect in potential analyses of having people leave early by virtue of dying, and therefore their scores being carried forward. So it was a mixture of things.

Now, what John is telling you, of course, is in retrospect, now six months later, after looking at all the data, we are not willing to say what we think those deaths mean although I want to correct something. In terms accrued incidence, the number of deaths on Myotrophin is always greater. That includes 1200. I don't think it is meaningful, but I believe the lowest number is 7 deaths occurred in the placebo arm and maybe 8 and 11 in the other doses, and if you come to the other study, it is 18 versus 5.

So there is this. It could be statistically significant if you ran the numbers up, and it is always possible that the drug may benefit some and harm others, but we are not able, given the amount of information, to make

that judgment.

DR. GILMAN: Thank you.

Dr. Temple.

DR. TEMPLE: Dr. Leber made my point.

DR. GILMAN: Ms. Phillips.

MS. PHILLIPS: Just a question about the deaths. Has there been an analysis of where the people were on the Appel score when they entered the study?

DR. FEENEY: When they entered the study?

MS. PHILLIPS: In other words, were they sicker when they entered the study and therefore they were dying at a --

DR. FEENEY: Let me just make one comment along those lines. To say that people on the Appel score only die with high scores would be incorrect. People die on the Appel score who have low Appel scores.

DR. GRANEY: I think you will find that we cover that topic in Dr. Gelinas' presentation, and we have additional information that we can make available for you.

DR. GILMAN: Thank you.

Dr. Zivin.

DR. ZIVIN: In the analysis of covariates, the order in which the covariates are considered is of some importance, and I didn't exactly understand how that order was selected.

Can you explain that to me a little bit better?

DR. FEENEY: I think Dr. Hoberman was the statistician in our division. He could probably explain it much better than me.

DR. HOBERMAN: The order was actually selected by the sponsor. The one document that we received that gives a hint is there were simply a list of covariates one after the other down the page.

This list was a list of covariates that presumably were entered into the model in that sequence by the sponsor at the time they did the analysis. Now, I tried to repeat an analysis, but I did not use the same order, and I got a different result, and that is what you found in the document.

The purpose of explaining that in the document was not so much to say that the statistical significance should be at tremendous jeopardy, but to explain that the method in the protocol was not a really well-defined method to give an unambiguous result from two aspects.

Number one, the result could depend on the order of the covariates as it did in the case when I did the analysis, but I think even more importantly, or at least as important, it is not a method which is known to control Type 1 error at 0.05.

Now, let me just say a little history. This plan

was in the protocol. At the time that I learned about it after taking over this project, I communicated with the sponsor and said that I did have an objection to this plan, and at least I think I learned about it for the purposes of 1202, and subsequently decided to do independent analyses.

As far as the substantiality of this issue for 1200, I don't believe it is a terribly substantial issue because of the independent analyses. For 1202, I don't think it is a really substantial issue because again if you do what was actually stated in the protocol, you don't get close to statistical significance.

DR. GILMAN: Can I just follow up with a question.

It is stated in the protocol to be a computer generated algorithm. Is that a fixed algorithm or did it vary?

DR. HOBERMAN: It all depended on entering. First, you enter a variable. Then, you see whether or not that is statistically significant. If that is statistically significant to some extent, it could be at the 0.05 level, it could be at the 0.10 level, whatever you dictate.

Then, the next variable is entered into the model. If that is statistically significant, that will be entered into the model. However, there is also a criteria, so that if the first one that you entered one now rises above a certain level and loses its statistical significance, it

could be kicked out of the model.

So what it is, is this algorithm of playing with the data and building up a series of covariates and ending when you have a whole bunch that do meet a criterion and along the way some are kicked out, some are brought in, and you can get kicked out at any time. It is like musical chairs.

DR. GILMAN: So it is a search for something that will turn up?

DR. HOE RMAN: Right, it is a search that depends on the data that was gathered.

DR. GILMAN: It is almost a post hoc analysis in a sense.

DR. GRANEY: If we could, we would like to make a comment about that.

DR. GILMAN: Please.

DR. TOM DOBBINS: Tom Dobbins, Cephalon.

I think that the order per se is not the issue. An analysis of covariates with the specified criteria should not be order-dependent in the variables, and the potential dependence of that order may be some other aspect that maybe we could answer that question separately, but I think that as far as the statistical method of stepwise selection in a regression procedure, that is completely determinable.

So it should not depend upon the order of the

variables entering or leaving the model. As a practical matter and I think as a scientific matter, there will be ordering in the list that we chose where the variables are most relevant to the disease.

So, for example, we would enter something like bulbar score as opposed to country of origin in the European study, for example.

DR. GILMAN: Dr. Leber first and then Dr. Gennings.

DR. LEBER: I want to emphasize what Dave said earlier, that this has no substantial effect on anything that is in dispute before us. Whether you use this analysis method or not, with all its well-known generic flaws, it does not affect the judgment on Study 1200, and if you use it on 1202, it doesn't affect the judgment from our view because it isn't statistically significant either way on the primary specification.

I will say for the record that the way the protocols were written the precise listing of covariates that would be entered are not identified, and as I believe Dr. Gilman points out, to some extent there is a flavor there for data conditioning because it depends upon the realized set of individuals randomized and what they display as personal attributes that will determine what order of entering you do.

You don't know on the next occasion that you repeat this experiment mythically that you would end up with the same set of covariates in the model, and I don't think you could know because they might have different distributions of attributes in the patients entered.

I think that is just the problem of this type of analysis.

DR. GILMAN: Dr. Gennings and then Dr. Temple.

DR. GENNINGS: I just wanted to emphasize that the algorithm is also going to be conditional on the selection criteria for what goes in and what goes out, and those numbers can change, and that could change the results.

DR. DOBBINS: That is true, and I think that that might be part of the issue with regard to the discrepancies.

DR. GENNINGS: And were those numbers specified to begin with?

DR. DOBBINS: Yes.

DR. GENNINGS: And what were they?

DR. DOBBINS: 0.1.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: I think what is being said is typical of many covariate analyses and it is one of the reasons that people get nervous when a finding of no significant difference becomes significant based on a covariate analysis. That doesn't happen very often, fortunately, so

we don't have to bear the burden of worrying what it means.

My feeling is it may help you get a better point estimate of something if you already have made it on the primary and adjusted analysis, but it is treacherous business, this is not an unusual problem.

DR. GILMAN: Dr. Adams.

DR. ADAMS: I would like to change the topic. I would like to go to Section D in your briefing, page 15.

DR. GILMAN: Which briefing, the FDA briefing?

DR. ADAMS: The FDA briefing, Section D, page 15.

DR. GILMAN: Tab?

DR. ADAMS: Tab D.

There is a discussion of 7 patients in the placebo arm who have a baseline score of 95 and greater, and I would like some more discussion from you and from the sponsor in regard to these 7 patients because 6 of these had endpoints, 1 death, 5 Appel endpoints. One of these apparently had an Appel score of 115 at time of randomization, and I would like some more discussion on those patients and how it affects the overall results of 1200.

DR. FEENEY: Let me tell you those patients affect the time-to-endpoint analysis, as I showed here, and they affect it greatly. It is an exploratory maneuver, but you have to think of it because there are outliers in the placebo group compared to the high dose Myotrophin group.

Now, an interesting phenomenon happens. The primary analysis is based on slopes, and as you heard, in order to enter the slopes analysis, you have to have three Appel scores during the treatment period.

If you look at those 7 outliers, at least a fair number of them aren't even in the slopes analysis because they were out so quickly that they did not have three on-study Appel scores.

So although if you start exploring the slopes analysis and the effect of those patients on them, you might whittle down the treatment difference a little bit, you do not seem to affect the overall statistical properties of this primary analysis.

DR. LEBER: On the fly, I don't want to disagree with you because I haven't thought about it all that carefully, but it dawns on me that you have a slope analysis, and the individuals who had high slopes, if in this case they were more rapidly progressing, and on the basis of arguments John has made, that someone to get to an Appel of 115, who had to enter with an Appel of no more than, what, 80 at screen, has to have a very high slope to get there over the time.

Accordingly, these individuals with high slope aren't included in the slope analysis, and if that is the case, it is biasing against the drug, because they are on

placebo, so it is the opposite effect of what you are suggesting.

But I think this is the treachery. If you now turn to a time-to-event analysis, you have a different bias arising from the same censoring process, and that is why I think the evaluation of trials becomes analysis-dependent.

You have to decide how it is operating, not in a general way, but specific to the analysis being examined, and here you can see it going in opposite directions. It just makes it so complex.

DR. GILMAN: Dr. Snead.

DR. SNEAD: I would like some clarification on a comment made on page 12 at Tab C of the agency handout regarding the placebo patients, in which it is stated that they are really not a valid statistical analysis of the population of the patients with ALS because they are samples of convenience, and not truly representative of the population.

What exactly does that mean?

DR. FEENEY: I will let Dr. Leber.

DR. LEBER: I wrote a good part of this document, and I think it is very important that I step back again, and I will go into the heuristic mode -- I apologize for needing to do this.

If you were going to forecast an election, what

would you do? You would make very certain that the individuals in your sample on which you are basing your poll reflect very much the public that is voting. If not, you run into the Dewey-Truman or Netanyahu-Peres type problems.

If you think what we do in clinical trials, we obtain patients that are available to us. They on face may look something like the population because we pick them on the basis of various attributes we find appealing, but in no way are they a true statistically random sample of the population.

That is one of the reasons why we always want to look within a study, because we don't really know about how representative the sample we capture for study is of the population as a whole.

So ergo, when you start looking between studies back to the Baylor database, which, in fact is a registry, you run into all sorts of kinds of problems, and I was really trying to make the case that the way we sample for our trials is for our convenience. It is not, in a statistical sense, a stratified random sample or a random sample of the population.

That is what that is all about. That makes it very difficult compare one study to another or one study to a registry, and that was the thrust of that argument.

DR. SNEAD: So that was a generic comment rather

than a specific one.

DR. LEBER: A generic comment, which I think you have got to worry about all the time.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: I am sure this is clear, but it is not a complaint about the study because all studies partake of this problem, it's a warning against crossing between studies.

DR. LEBER: Well, it is really a warning about explanations offered that turn on the idea that we really do have a random sample when in fact we don't.

DR. GILMAN: That is helpful. Any other questions from the committee?

If not, Dr. Feeney, thank you very much.

It is 10:15. Let's take a 15-minute break. We will convene at 10:30 sharp.

[Recess.]

DR. GILMAN: The meeting is about to begin again. Please take your seats.

This is time for the sponsor's presentation. Dr. William F. Graney will make the introductions for Cephalon.

**SPONSOR'S PRESENTATION**

**INTRODUCTION**

DR. GRANEY: Thank you. I would like to thank the committee and therapy agency for the opportunity to present

the Myotrophin clinical program today.

[Slide.]

Dr. Feeney did a very fine presentation of the protocol designs and the results, and before beginning our presentation, I would like to review the areas of agreement between Cephalon and the Division.

We agree that the AALS total score is an appropriate measure for the trials, that the North American trial was positive, and that safety is not an issue for us here today.

We are here today to discuss the two studies as sufficient evidence for the safety and efficacy of Myotrophin in the treatment of ALS. We maintain the European trial is supportive of the positive North American trial and that Myotrophin's effect is most evident in the majority of the patients who have rapidly progressing disease.

[Slide.]

Our speakers this morning will present the evidence for this position. Dr. Deborah Gelinas, of the California Pacific Medical Center, will review the Appel ALS Scale as a measure of the progress of disease and will discuss its application in the current trials. Dr. Gelinas will also review the variation of disease progression between patients.

I will then review the efficacy from both trials, and Dr. Thomas Dobbins, of Cephalon, will review related statistical points which require consideration.

Following a review of the safety of Myotrophin, and the body of evidence for its efficacy and safety in ALS, Dr. Robert Miller, of the California Pacific Medical Center and the University of California, will provide a clinical interpretation of the results of the program.

[Slide.]

As Dr. Feeney noted, Myotrophin is recombinant human insulin-like growth factor 1 or IGF-1, a 7 kilodalton, 70 amino acid protein. The preclinical studies that led to the clinical program for Myotrophin indicated multiple activities of the drug which could be of benefit in ALS.

Myotrophin promotes the survival of motor neurons in cell culture and ir animal models where motor neuron death can be quantified. Myotrophin is essential in the maintenance, growth, and myelination of nerve axons and is the primary contributor to nerve sprouting in response to various injurious or pathologic stimuli.

Myotrophin enhances functional recovery following nerve injury, promoting reinnervation and increasing muscle plate size.

Finally, Myotrophin has profound effects on muscle catabolism, increasing muscle mass, and decreasing muscle

atrophy.

These diverse activities in preclinical work led us to develop the clinical program for Myotrophin in ALS.

I will now ask Dr. Gelinas to discuss the use of the AALS Scale in that program and the features of ALS which affected the design of the clinical studies.

**CLINICAL STUDY DESIGN**

[Slide.]

DR. GELINAS: Good morning. I am a neurologist at the Forbes North MDA/ALS Center and I see many patients with ALS. I was also a principal investigator of the North American Myotrophin study.

[Slide.]

Amyotrophic lateral sclerosis is a progressive degenerative disorder of motor neurons in the motor cortex, spinal cord, and brainstem. It is characterized by muscle wasting, weakness, and spasticity. There are no significant sensory, bowel, bladder, or cognitive abnormalities in this disease.

[Slide.]

The diagnosis of ALS is a clinical one and it is confirmed by the concomitant presence of upper and lower motor neuron signs in two or more body regions. The diagnosis ultimately becomes evident by progression of symptoms.

[Slide.]

Initially, symptoms of ALS may be quite focal. A patient may present with a footdrop or a hand clumsiness or some slurring of speech. However, with time, there will be contiguous spread of disease to previously unaffected areas and ultimately, all patients with ALS with look clinically alike.

[Slide.]

The natural history of ALS is that there is a steady decline in strength and respiratory function, and that decline is linear throughout the majority of the course of disease. The rate of decline, however, varies greatly from patient to patient, and those of us who care for patients with ALS know that some patients go from the time of diagnosis to death within a year, and other patients are still ambulating more than five years out from diagnosis.

[Slide.]

Our objective as investigators in designing this study in ALS was to examine whether Myotrophin could slow the rate of disease progression in ALS. To demonstrate this, we chose to measure progression with a functional rating scale that could evaluate both upper motor neuron abnormalities with slowness and spasticity, and lower motor neuron abnormalities with its inherent weakness.

[Slide.]

The scale that was chosen was the Baylor AALS Scale, which was developed by Stan and Vickie Appel. This scale has been validated in over 1,200 patients with motor neuron disease over a 10-year period.

The AALS is a quantitative measure of clinical disease in ALS. It is a comprehensive disease-specific, objectively measured scale which provides a single total index of disability regardless of the site of onset of symptoms.

The rate of change of the AALS correlates with disease progression, and is an important co-predictor of patient survival along with the rate of change of pulmonary function and the age of a patient at the time of presentation of diagnosis.

[Slide.]

The AALS is compose of five separate scales: the bulbar, which evaluates the ability to swallow and to speak; respiratory, which evaluates forced vital capacity; muscle strength, which is composite of a manual muscle exam, as well as grip strength and pinch strength; upper extremity function, which are an accumulation of time-to-test which look at manual dexterity; and lower extremity function, which again are time-to-test which look at functional ability to walk, sit, climb stairs, and stand.

A normal person would have a score of 30 points.

A patient with maximal disability would have a score as high as 164 points.

[Slide.]

This table illustrates the correlation between the AALS score and disease severity. A patient who presents to an ALS clinic initially, typically has an AALS of between 40 and 80.

Let's take an example of one of these scores. A patient with a score of 75 would typically be eating a dental soft diet, would have some slurring of speech, would have a forced vital capacity that is slightly down, but probably would have no symptoms whatsoever, and would be walking with a walker or occasionally, for longer excursions, with a wheelchair. They would need some minimal caretaker assistance perhaps for bathing.

Some months later, when that same patient comes back to clinic, the score might be 99. At that point, the patient would be eating a pureed diet only. The speech would be quite slurred, and the forced vital capacity would be down, such that they might have difficulties with coughing and clearing the upper airway. The patient at this point would be spending most of the time in the wheelchair and would be fairly dependent on a caretaker for activities of daily living.

It is rare to see patients at these extremes in

the center because of the fact that the disability becomes so great that it becomes a coordinated family effort to the patients to get into clinic for evaluation.

However, at above 115, patients typically are drinking only a liquid diet or else they have a feeding gastrostomy. They not longer have useful speech. They are wheelchair-bound or, if they are not able to leave the home, bedridden, and they are always considering or facing major life issues of tracheostomy and dependence.

The thing that I wish to emphasize is that a particular AALS score is a snapshot in time of how a patient looks. However, the rate of change of score is a moving picture over time of how the disease progresses in one person's life.

To illustrate this, I would like to give two patient examples.

[Slide.]

This patient is a 39-year-old man whose symptoms of ALS began in 1991 with cramps and weakness in his left leg. He was first seen for evaluation at the ALS center in February of 1993.

He was found at that time to have mild weakness in the upper extremity, and in the lower extremity, fairly good strength proximally, but a great deal of weakness distally, such that he could not ambulate on his heels.

His reflexes were brisk, he had Babinski and clonus. He would walk, however, with the assistance of a walker. He was diagnosed as having ALS and has been followed since that time.

He has shown a very gradual progression of his difficulties, always more marked in the lower extremities, and he has been able to participate in a number of drug trials for ALS.

He continues to work, although part time, at home as an accountant, and he is working at home because the disability makes it so difficult for him to get out to his office.

His rate of change of his AALS score is linear, and the slope is 0.9 points per month. We would term him a moderate progressor.

[Slide.]

In contrast, this 56-year-old woman, who was first seen in November of '95 for evaluation of weakness in her right arm, had only symptoms that started July of that same year. She noted a gradual weakness, progressing however to the point where she could no longer brush her hair or feed herself or dress herself.

At the time she was first seen, she too had mild proximal weakness and some distal weakness in the upper extremities, as well as in the lower extremities. Her

reflexes also were brisk, she had crossed adductors and she had positive Babinski bilaterally. She too was able to ambulate on her own.

She had a borderline normal vital capacity at that time and had virtually no pulmonary symptoms. However, her progression has been extremely rapid, and she is currently wheelchair-bound and unable to ambulate.

Her AALS slope is 7.8 points her month, and we would term her a rapid progressor.

[Slide.

The Baylor Natural History database has been validated in more than 1,200 patients with motor neuron disease for over 10 years. 831 of those patients have been diagnosed as having classical sporadic ALS.

This cohort provides a longitudinal scale on the relationship between disease progression and AALS score and slope. The database offers a pool of patients from which to reference and match the patients who were enrolled in our study.

A review of this database revealed 181 patients who were matched both in terms of clinical presentation and inclusion and exclusion criteria to the patients who were enrolled in the Myotrophin studies.

These patients were further subdivided into moderate progressors, those with an AALS of less than or

equal to 60, and rapid progressors, those with an AALS score of greater than 60.

DR. GILMAN: Dr. Gelinas, I wonder if you could tell us how many or what percentage of these patients who expired have come to autopsy examination of the Baylor database.

DR. GELINAS: I cannot answer that. Perhaps Dr. Appel can answer that.

DR. APPEL: In approximately five years ago, when we had a database of about 500 patients at that time, Dr. Gilman, we were running an autopsy rate of about 60 percent. Since that time, it has dropped considerably even though we are making every effort to keep it up, so that the number is less than that for now 1,500 patients.

DR. GILMAN: Are you able to verify classical ALS in those autopsies that you had performed?

DR. APPEL: Absolutely.

DR. GILMAN: And no other modifying features, no dementia, no parkinsonism, on cerebellar degenerations in those cases?

DR. APPEL: In a rare number of cases, less than 5 percent, we have made the diagnosis of neuropathological Alzheimer's with no verification that they truly with Alzheimer's by clinical criteria because we had not studied it extensively. This is in a very, very small number of

such cases.

The remaining 95 percent are free of those changes.

DR. GILMAN: Thank you.

[Slide.]

DR. GELINAS: In this review of the database, two-third fell into the rapid progression category, one-third fell into the moderate progression category. Symptoms which identified moderate progression were a greater bulbar involvement and a greater pulmonary involvement, as well as an older age.

DR. DRACHMAN: Was the gender difference significant?

DR. GELINAS: I cannot answer if it was -- you mean statistically significant?

DR. DRACHMAN: Yes.

DR. GELINAS: I don't know. It looks like it would statistically significant, but I don't know that that was run, that analysis.

DR. GILMAN: We heard from the sponsor that the answer is no.

DR. GELINAS: In the North American study, we stratified patients a priori to ensure proper distribution of both moderate and rapid progressors, and we stratified according to the AALS score. In the European study, this

stratification scheme was adopted post hoc.

Trial design in ALS necessitates that one look at rate of progression of disease and that one evaluate patients who are progressing in order to detect a change in the short study, such as a nine-month study.

DR. ADAMS: Dr. Gelinas, would you explain to me how the score of 60 was used to determine moderate versus rapid progressors?

DR. GELINAS: Initially, that score was rather empirically chosen, and based on the Baylor database and the characteristics of a great deal of variability, also based on the fact that initial presentation to ALS center was between 40 and 80, and so 60 was the middle point.

DR. ADAMS: Well, the question is that some people that got to the centers may have had symptoms for nine months, when they came in at 60, and others may have had symptoms for two months when they arrived at 60.

To me, 60 -- and I am learning here -- 60 seems to be a score of severity, and really not a score of progression.

DR. GELINAS: You are absolutely right, and a much better way to have done it would have been to divide them into two cohorts based on rate of progression, but we weren't that knowledgeable at the time of design of this study.

DR. GILMAN: Dr. Khachaturian has a question.

DR. KHACHATURIAN: Is the rate of change linear over time on the two groups? Do they change at any time, that is, a slow progressor would become rapid, and vice versa? Is there any data on that?

DR. GELINAS: That is actually a rather hot debate. There are those who say that maybe at the very far edges of disease, at the terminal phases of disease, that there is a more precipitous drop-off and a more rapid slope. However, during the phase of illness that most physicians are able to evaluate and study the patients, the rate of progression is linear.

DR. DOBBINS: We are going to address directly the stratification in terms of disease severity versus disease progression in our remarks in a few moments.

DR. GILMAN: Dr. Katz did you have a question or comment?

DR. KATZ: I was just going to say given the acknowledgment that ALS score above or below 60 isn't necessarily the same thing as moderate and progressive patients with regard to slope.

It is not really accurate to equate the two, and to speak about moderate and rapid progressors as if that is the same thing as categorization by above or below 60.

DR. LEBER: I have another I think technical point

here. When you talk about slope, there is pre-slope and there is post-randomization slopes, and there probably is a relationship between the attained baseline score which is related to the rate you progress during screening, and there is a correlation there, but there is a much lesser correlation between what your baseline attained score is and your post-randomization slope, and we are prepared to discuss this because I think you have got to be very careful, once again, of what you are talking about when you say things predict other things.

But I guess we take the point that baseline score, which everyone passes through eventually, is a poor predictor of rate of progression, a very important point.

DR. GILMAN: Dr. Zivin.

DR. ZIVIN: Can you or Dr. Appel please tell me how the items for the scale were chosen, and more important, how the weightings were chosen?

DR. GELINAS: Perhaps with the initial development of the scale, Dr. Appel can answer that better than I. I can tell you that the weightings, each of the five categories, would be given a potential of 6 points per category.

DR. ZIVIN: But the question is how were those points chosen, why is swallowing more important than stair climbing, and by what factor.

DR. GILMAN: Dr. Appel.

DR. APPEL: The tests were administered to 30 patients prior to our establishing the weighting. Based on those 30 patients, we established a weighting, such that no individual component would override the scale and such that the total score would be an accurate reflect.

In fact, we had to change the weighting slightly as we went on before it was actually adopted, so that we were assessing clinical parameters, how the patient walks, how they talk, how they communicate, how they breathe, and, in essence, give relevant information of clinical importance that would be reflected in the score and the rate of change of the score.

DR. ZIVIN: But the question is by what process were the weightings selected.

DR. APPEL: They were first selected arbitrarily to be somewhat unequal and then they were weighted, such that one could have a total score that monitored the rate of progression of the patients and the rate of clinical change. This was done in 1981, 1982, and 1983, before we even adopted this based on the fact that, in ALS, you need to monitor what is happening in terms of function in upper and lower extremities, strength in upper and lower extremities, distal musculature, as well as proximal musculature, speech, swallowing, and breathing.

DR. ZIVIN: How did you decide how to change the weightings from your initial arbitrary decisions?

DR. APPEL: Well, what happened is we didn't have a linear scale initially when we started before we established this, and so what we did is, by playing with this -- and we are not statisticians -- but by playing with this and doing the weightings slightly differently, we found that by giving relatively equivalent weightings to important clinical parameters, the most important of which is respiration, less of importance going down the scale, being speech and swallowing, because these are things that get these patients into trouble, and then going down from that to upper and lower extremities, strength and function, we came out with a balanced approach.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: Would you look back at your mild patient and that slide several back?

DR. GELINAS: Would you like us to go back to it?

DR. DRACHMAN: Could you please, yes.

DR. GELINAS: Go back to the mild patient, please, or the moderate progressor, the patient picture with the man.

[Slide.]

DR. DRACHMAN: When you look at the curve, I would think that you might pick various 3-point intervals and get

very different slopes. How do you deal with that? I mean if you look at the first three points, that would be very different from the three points at 35 to 40, very different from those from 45 to 50. How do you deal with those aspect of slope?

DR. GELINAS: First, let me state that I am not a statistician, but secondly, let me state that what I have gleaned from statisticians is that the more points you have, the more accuracy you have in predicting a slope, and then we did a best-fi ed regression analysis.

DR. DRACHMAN: Yes, but in the study, you are willing to use three points to determine -- or at least three -- but somewhere no more than.

DR. GELINAS: Some completed the study, so we were able to have a better fit of slope.

DR. GILMAN: Dr. Dobbins wants to comment.

DR. DOBBINS: Yes. This is a very important point here. When you look at this graph, you are looking at the disease in months over a 60-month period versus a 9-month window in our studies.

In the course of that 9-month window, the Appel Scale score is highly linear, and that was evident from the slide that Dr. Feeney showed earlier of two types of patients, a more rapidly progressing patient, if you recall, and a less rapidly progressing patient.

So within the 9-month window, in particular, of the North American and European studies, the Appel Scale score is highly linear. I would like to address that point even further with regard to the remark made regarding pre-slope scores versus post-slope scores.

A particular patient within pre-study score is highly predictive of his post-baseline score precisely because of this linearity.

DR. GILMAN: Dr. Leber.

DR. LEBER: I actually had a question of Dr. Appel, which I just wonder for clarification if you have changed the weightings over time in the scale. Has there been a period where the published results of this scale represented different, or has, since its publication, been stable? That is for historical purposes.

DR. APPEL: The scale was never changed from the time that we adopted it, and all publications are the same in 1984 as they are at the present time. I was addressing Dr. Zivin's question, which was how did we start in the beginning and how did we come with the idea of weighting it.

From 1984, and all publications since that time, this is exactly the same scale that we have today.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: It is perfectly true that if you only have three points, and they are all fairly close together,

there is going to be some imprecision in what the person's rate of change is. Probably the further apart they are, the longer the experience, the better. But that is just where the variance comes from, there is an error rate in these slopes, and the presumption is that you have the same problem in both placebo and treatment group, and that is why you need relatively large numbers, because it is not a very precise measurement if you only have three points and if they are taken fairly close together. So it is true, but that is what you deal with. That is the nature of the data.

DR. GILMAN: I think Dr. Dobbins wanted to respond.

DR. DOBBINS: Two points at the moment with regard to that. Among the patients with at least three post-baseline scores, the majority of the patients overwhelmingly had much more than three point post-baseline.

In fact, in both the North American and European studies, 60 percent of the patients in that group had at least eight or nine observations, in fact, the entire study. About the percentage of patients with only three observations in the analysis in both studies, it is less than 10 percent, it is about 5 percent and evenly balanced between the treatment groups.

In fact, in both studies, patients excluded from the three-point slope analysis, were balanced among the

treatment groups, and we can show that specifically.

DR. GILMAN: Could you comment on why you established more in some cases than in others before randomization and treatment?

DR. DOBBINS: More?

DR. GILMAN: Oh, you are talking about post-randomization, I am sorry.

DR. DOBBINS: I was talking about post-randomization, yes, because that is a key point with regard to the amount of data that we have on patients. The thought may be that if we require three post post-baseline, that there are a lot of patients in the sample who only had three points, and we want to be very clear in that matter that the majority of patients had large numbers of points, again 60 percent with at least eight.

DR. GILMAN: Yes. All right. Please continue.

[Slide.]

DR. GELINAS: There are other important study design elements which are mandated by the disease ALS, based again on the Baylor historic database, it was observed that patients with scores, AALS scores above 115, often were not able to get into clinic. When they got to clinic, they were too tired or too weak to be able to complete the entire AALS assortment, and that slopes, which would be derived at this late stage of disease, were no longer linear.

Due to this, we decided to address this issue directly and we defined protocol-specified termination points, such that patients would be able to complete as much as possible a reliable AALS score, and we terminated patients who had an AALS score of greater than 115 or a forced vital capacity of less than 39 percent or predicted.

[Slide.]

Because ALS is a uniformly fatal disease, it was anticipated that some patients would die during the course of the study. This graph from the Baylor database shows us that the total AALS score per se does not predict patient death and that, in reality, death is not infrequent at any point along the time one is diagnosed with ALS, but especially is not infrequent with an AALS score of greater than 80.

DR. DRACHMAN: That table gives the number of deaths, but it does not give the percent by score. Are you saying that the percentage of deaths for those under 80 and those at 100, and so on, are equivalent, or how would you view that?

DR. GELINAS: I can view this only by the patients evaluated in this database, and actually I would defer for the statistics to Dr. Dobbins.

DR. DRACHMAN: There is no denominator there, so I don't know what to make of those numbers.

DR. DOBBINS: The figure is only meant to illustrate that within two months proximal to death, the Appel score can vary greatly over the range. So, for example, a patient, if you look at one month prior to death, based on that chart, patients are relatively equally likely to have an Appel ALS score as low as 80 and as high as 120.

DR. DRACHMAN: How likely?

DR. GELINAS: The denominator is 34.

DR. GILMAN: Let's halt there. Dr. Leber is next, then, Dr. Temple.

DR. LEBER: I think what we are struggling with, and which Dr. Drachman is picking up, is the issue of conditioning upon who was available to suffer the event given a score of a certain size.

It is very much like a survival analysis. You can't look the accrued rate because you really want to look at the hazard, that is, the likelihood of suffering the event having survived to a point in time where you have a given score.

Now, what will happen, that there will probably be many, many fewer people available who have a score that is very high compared to a score that is very low. So when you do the rate of death, instantaneous, conditioned upon an attained score, that would be a different display than this one, which doesn't provide the denominator and doesn't

condition the proportion on how far along you have gone in the disease.

So it fundamentally doesn't provide the answer that you want.

DR. GILMAN: Dr. Appel.

DR. APPEL: I just wanted to concur with Dr. Leber's point, that the point here is that the reason you have fewer people -- and I think this is what caught Dr. Drachman's eye -- appearing in the 121 to 130, 131 to 140, is these patients were not coming back, were not able to be assessed, and therefore, could not be included.

We are talking about an n of 181 that matched things, and in fact, the sole point of this slide is to show that patients can die at 80, they can die at 85, they can die at 95, and you can't do the kind of analysis Dr. Drachman would like because of what Dr. Leber said, and you can see it in the graph here, fewer patients are coming back.

DR. GILMAN: You could input those scores, though, surely.

Dr. Leber.

DR. LEBER: I think I agree entirely with what Dr. Appel is saying. It is not that you can't do it. That is not the issue here. The issue is that this is presented to imply that one has information that one does not, and I

think that is what we were responding to, and what Dr. Drachman was responding to.

You can't tell from this what proportion of individuals would die had they had that score. All you can say is this is what they saw, but it is not a complete accounting of everyone in the race, and I think that is the problem.

DR. DRACHMAN: The fundamental issue is whether death is a surrogate measure for the degree of severity of the illness, and whether the Appel Scale is comparable in that way. One would ordinarily guess with very mild ALS, they will not die of the disease, whereas, with very severe ALS measured by the Appel Scale or any other means, they would be more likely to die, so that death is not an independent factor. That is the point that I am addressing.

DR. APPEL: May I make the point, I wish Dr. Drachman's statement were true, that with a mild rate of progression, the patient would not die of this disease. Unfortunately, it is not true. Even with a mild rate of progression, patients will die with ALS.

DR. DRACHMAN: Not rate, but severity, not rate, severity.

DR. APPEL: And will progress to a severe score which cannot be monitored because we don't have the information here.

DR. GILMAN: Dr. Temple and then Dr. Leber.

DR. TEMPLE: That still isn't the question that I think is being raised. The question is what sort of scores should you attribute to someone who turns up dead when you haven't seen them for a few months.

It must be true that between a score that is not associated with dying, it is very early, and a score that is very high where people die. There must be some increase in risk with score. It is just, unfortunately, not very precise and you can't make the observations to really pin it down, but it is inconceivable that there isn't a rising risk with score.

At some point there has got to be a steep curve, because you have got to go from zero to a risk, and you have got to get there by going through some numbers. It is just that, as you said, you can't quite pin it down because they are not coming to clinic.

DR. GILMAN: Dr. Appel.

DR. APPEL: Let me try and get my point across. I guess I am not succeeding here, but I really do want to succeed.

The point here is that one cannot impute a score of 130 or 140 based on this information. The fact that when we looked in our database, it was random, means that you cannot take a fixed score and say the patients will die at

that point.

DR. GILMAN: Well, the cause of death is another factor in here, and the frequency of autopsy examination is an important factor, so that one can establish the cause of death if possible.

For example, some of these people may have had acute pulmonary emboli and thereby expired with a score that is very low as one example.

Dr. Leber.

DR. LEBER: I think this is the usual confusion between reverse and direct probabilities. We are interested in assigning score for people who died that is representative of their condition at the time of their death.

The LOCF analysis, which is based upon a score they attained earlier than the time of death, may somewhat predict what they are likely, if a long time elapsed, we expect them to deteriorate. Whether they deteriorate along the slope they had prior to that time or they accelerate is an open question. I don't think we have enough information.

The trouble is that the representative score for a person that is dying is not available from this. What you really want probably is to start out and say, having survived to a given score on the Appel score, what is the probability that you will die in some forward interval of

time having attained that score.

I would argue logically that I would expect it to be higher having attained a higher score than if you only had a score of, say, 50 or so. I mean that just stands to reason.

DR. GILMAN: Given probability, however, the patient may have an acute myocardial infarction or pulmonary embolus or pneumonia.

Dr. Temple, then Dr. Dobbins.

DR. TEMPLE: I guess, Dr. Appel, I don't understand why the questior that is being raised can't be answered. There must be a denominator for the population less than 80, the population 81 to 90, 91 to 100. You could at the bottom of that put the number of people.

It is censored, but you can say of the people who achieved this number, how many then died in the subsequent one or two months. That is an available number. Everybody's guess is that the number for less than 80 is a lot larger than all the other numbers, so the percentage of people who died in the next one or two months is smaller. I mean that seems almost inevitable.

So if that were true, then, there would be a relationship between what your score is and the probability of dying. It seems almost inconceivable that there is no relationship. I mean it has almost got to be.

DR. GILMAN: Dr. Dobbins, do you want to respond to that?

DR. DOBBINS: Yes. I think we are overlooking a very important point, and it was brought forth in the 1995 Brain paper by Havercamp and Appel, and that shows that the survival is directly related to the rate of disease progression, and not disease severity at a particular point. That is a very fundamental point. As measured by the Appel score slope.

DR. GILMAN: Dr. Leber.

DR. LEBER: John made this point earlier in his presentation that the predictive value of time-to-death is much better when you are progressing more rapidly, and in fact you are shooting at a much closer target, to use a bad metaphor.

If, in fact, you have a very slow slope, the opportunity for slight deflections in error to predict the time five years hence is going to be off, so the quality of prediction is terrible, the precision of prediction. If you are just about on death's door, and you are very rapidly progressing toward it, obviously, your prediction will be off by less. This is question of shooting at the moon versus shooting at Uranus.

I think the problem for us, however, is not that.

[Laughter.]

DR. LEBER: Well, perhaps you would like the galaxy. I mean I think this is going beyond the evidence to such a point. Neptune? You pick your planet, you pick your star.

I guess what we wanted to do, all of us, is to be able to fairly provide an estimate for the state of patients who were censored. All of this is an attempt to get at the question of what is the fair comparison when you have missing data, and I think that neither of us, the firm or the agency, have found a way to do it.

However, we tried one way based upon what we thought were basically in Dr. Appel's paper, a description of what the typical patient -- I use his words, I think, or their words -- would be like at about the time you begin to discuss tracheostomy and you are really far advanced. I think that number was about 130 to 135, wasn't it? I think that is described in your paper.

DR. APPEL: Absolutely.

DR. GILMAN: Dr. Appel, maybe you should respond directly to that.

DR. APPEL: What Dr. Leber is saying is true. In the paper, we used 140 to predict that, but let me read the last part of the sentence that was in the legend to that paper. The first part is just what Dr. Leber is saying, the score of 140 used here in predicting survival is based on

clinical experience. Use of a different score would not alter the nature of the relationship between predicted and actual survival, and in fact, we have run it all the way from about 100 all the way up, and it is the same. So you get the same prediction, and that is one of the reasons that I don't think it is valid to use 140 per se.

DR. GILMAN: Dr. Dobbins and then Dr. Temple.

DR. DOBBINS: I would just like to follow that from the statistical standpoint, and the other, I think sentence in that article that we have referred to -- and I will quote from it because I think it is very instructive -- says, "When patients have reached a total ALS score of 120, they are usually incapacitated and returning to the clinic for scoring is difficult."

That is related to our clinical trials where the patients are terminating the study at 115. So it is representative of late stage disease, and not necessarily end stage disease.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: Obviously, there is going to be a relationship between how rapidly you progress and how rapidly you die. That doesn't mean the basis for that relationship isn't that you achieve a score associated with death more rapidly. That is perfectly possible. The two are not inconsistent.

I guess I still don't understand why there can't be a presentation something like what you had there with some denominators in it, so that you could say, of 100 people whose score is 80, here is the fraction that will die in two months, of a fraction of people with a score of 100, here is the fraction who will die within the two months, et cetera. You can do that.

DR. LEBER: Because the denominator you use there, on the ones you have in your hand, it doesn't take into account the numbers that have been lost along the way.

Say we change metaphors. We are looking at who finishes the marathon in New York City, and you stand at the finish line and you count the number who ran and the number who finish that cross that point. You get a different proportion than if you looked at the numbers who started at Verazano Bridge and across that point.

DR. TEMPLE: That is just the censoring problem.

DR. LEBER: Well, the censoring is enormous here because those patients aren't coming back, so you have no idea who is at risk in the interval. Let's not think of it in time, think of it in scores. Of those who achieve a score of 120, how many of those who achieve that score can be accounted for in the next interval, how many who achieve the score of 130, the interval now in progression of ALS, and I think there is high censoring, so you don't know those

numbers.

But, frankly, this is all irrelevant because none of us are contending the imputation business right now.

DR. GILMAN: Dr. Hoberman.

DR. HOBERMAN: Dr. Leber just basically made my point. The purpose of the imputation was a sensitivity analysis on results that we already regarded as negative. So therefore, it is essentially saying that if you see something on these screens and something reported by the sponsor, we found that this kind of imputation further weakens the case.

But as far as what Dr. Appel said, I think the issue is not the issue of prediction of death for rate. Remember, the endpoint for which the imputation was made was change from baseline, not for slope.

So when we used 140 in the paper, it was simply a stand-in for the worst score that you regarded clinically when you are on a respirator. It was simply substituting something for death.

Now, as I wrote in my review, if you impute all the deaths as 115, you don't get anything different from the regular LOCF. The point is that if you impute anything between 115 and 140, you get a worse result, but again, this is not a statistically relevant issue as far as formal statistics is concerned. It is simply an issue about trying

to see whether if there is some difference between treatments, in what trending direction would it go if you try to account for deaths on study.

DR. GILMAN: We have ground to a halt here over a point that is not particularly directly relevant to our decision. So I would like arbitrarily to say that last slide demonstrated that people with a score of 80 can die, and let's move on.

Please continue.

DR. GELINAS: The point that I actually wanted to make was that although the AALS score per se is not predictive, how fast you get there is predictive.

If you look here at two different patient populations, based on the rate of change, with a slope of 3.3 or less, they are in the moderate progression category, and above 3.3 points per month, they are in the rapid progression category.

The median benefit, the median increased survival between these two is about two years.

[Slide.]

The AALS, because of its clinical relevance and its ability to measure deterioration in function in a linear fashion in ALS, lends itself to several analyses to assess the effect of Myotrophin on ALS.

Dr. Graney will show you slopes which indicate the

rate of disease progression, as well as total change in AALS scores.

Because early termination events were specified a priori in the North American trial, Dr. Graney will be able to review time-to-event analysis and to show the difference between groups until severe final impairment.

In summary, the AALS is an objective physician-based assessment of illness and a single index of disease severity and progression that is of clinical relevance. Therefore, these analyses and any therapeutic benefit derived from them are of direct clinical importance.

The SIP, the Sickness Impact Profile, in contrast, is a patient-based assessment of disease.

[Slide.]

The SIP was an independent assessment composed of 136 questions which related to daily activities of living, such as the ability to walk, to talk, and to go out and enjoy yourself.

The SIP survey was conducted by independent consultants who had no other relationship to the Myotrophin ALS study. Dr. Graney will also review these important results which demonstrate that for the first time in the clinical research study in ALS, a slower decline in health-related quality of life was demonstrated.

[Slide.]

In conclusion, ALS is a relentlessly progressive neurodegenerative disease which is uniformly fatal. Loss of function over time is the hallmark of ALS and it is the reality for patients, week by week, month by month.

The AALS is a valid measurement of this disease progression, and for the purpose of design of clinical trials in ALS, the partitioning of patients into moderate and rapid progression is clinically meaningful and prognostically important.

Of greatest importance, there is currently no therapy which halts the disability in ALS.

Drs. Graney and Dobbins will present data to demonstrate that Myotrophin does delay disability.

DR. GILMAN: Thank you, Dr. Gelinas.

Can I ask you why or how the team decided to use nine months as the interval that people would be studied here?

DR. GELINAS: There is a lot of debate among leaders in ALS as to what is the right study length. The RPR people did a study which was much longer. They were looking for survival, so they needed to be powered with a much longer study in order to detect a change.

As a rule, in functional studies, you can get by with a shorter study, and when you look at times shorter than six months, you don't have a chance to really detect a

change. So nine months is probably the shortest that you can run a study and hope to detect a change.

From a patient perspective, when you go to a study that is longer than nine months, it is a very desperate time because patients feel that this may be their last chance, so that the shortest study that you can offer a patient is really the most attractive to them, because then they have hopes that if this one doesn't show it, maybe they will be in another one that will.

DR. GI[illegible]AN: Dr. Coyle.

DR. COYLE: Just as a point of clarification, why was forced vital capacity used as a termination factor in addition to the score?

DR. GELINAS: At forced vital capacities of less than 39 percent, it has been shown by many different experienced clinicians in ALS that death becomes likely. At forced vital capacities of less than 39 percent of predicted, a patient can no longer blow their nose, they can no longer cough, they can't clear their airway. They get definitely a dyspnea on exertion. They are often lost to follow-up at that point, and they often don't have the strength and the reserve to be able to comply with a set of examinations.

DR. COYLE: Right, and you would have a fair proportion of them that would have a score below the 115

cutoff, but might have that lower forced vital capacity?

DR. GELINAS: No, the majority of patients who would have a very low FVC would also have a high AALS.

DR. COYLE: I see.

DR. GILMAN: Any other questions from the committee?

If not, thank you very much.

Dr. Graney.

**MYOTROPHIN DATA**

DR. GRANEY: Thank you for that presentation, Dr. Gelinas.

[Slide.]

By agreement with the Division, our presentation today will focus on analyses using base statistical models except for the protocol specified primary analyses as we review the data on the efficacy of Myotrophin in the two clinical trials.

[Slide.]

We believe that both clinical studies provide evidence that Myotrophin is effective in slowing the progression of disease in ALS. Three findings support this position.

First, the study endpoints derived from the AALS total score, the measure of functional impairment are positive and directionally consistent between the two

studies.

Second, the time until the occurrence of one of the protocol-specified termination criteria indicating advanced disability is increased in both studies.

Third, in both studies, the therapeutic effect is most evident in the rapidly progressing patients, and the size of the effect in these patients is similar between the two studies.

As Dr. Gelinas noted, the AALS total score is our primary measure of disease progression. Our presentation will examine the rate of change of that score or slope, as well as the actual change in the score from baseline to endpoint.

We will also examine the occurrence of the events defined prospectively as mandating termination. An AALS score of 115 or more or an FVC of 39 percent or less of predicted.

Throughout the presentation today, in our slides, the results for placebo will be indicated by the yellow, for the low dose Myotrophin by the orange, and the high dose by the pink.

[Slide.]

In the North American study, the slope or the rate of change of the score shows a dose-response relationship, with the high dose producing a 21 percent reduction in the

slope.

The protocol-specified analysis comparing the combined Myotrophin groups with the placebo-treated group yielded a p value of 0.055. A pairwise comparison of the high dose group with the placebo group was statistically significant with a p value of 0.009.

As you can see, the treatment groups are equally represented in this analysis which, as I noted, requires at least three evaluations. You will see that about 10 patients in each of the groups did not have a sufficient number of points to qualify for this three-point slope.

[Slide.]

As in Dr. Feeney's presentation, we were also interested in whether Myotrophin altered patient slopes from the pre-treatment or screening period to the treatment period.

We examined this within-group effect by looking at the slopes for each of the treatments before and after randomization, and we display here the difference. A negative value for the difference indicates a favorable treatment effect.

In the North American trial, there was a favorable effect in both of the treatment groups, and this was absent in the placebo group.

DR. GILMAN: Dr. Graney, could you go back two

slides, please. I wanted to ask you how you established the dose. Why did you double the dose? You used 0.05 and 0.10.

DR. GRANEY: Yes. The dose is based upon blood levels that were seen in preclinical models as giving effects, showing a response of the nervous system to Myotrophin in some standard mouse models of injury.

When we looked at our Phase I studies and at the mouse levels, the dose in man that produced blood levels equivalent to the effect of animal levels was 0.10 mg/kg. As Dr. Feeney noted, from our Phase I studies also, it was noted that this dose does produce hypoglycemia or it does produce episodes of hypoglycemia in a limited number of the volunteers. Only 8 or 10 patients got it, I think 25 percent had evidence of hypoglycemia. So we decided that that, as a dose, was not workable. The decision was then made to go ahead and split that dose into two during the day. The 0.5 was chosen as a logical intermediate between the placebo and those dose.

DR. GILMAN: Oh, the idea was that you wanted three arms. I don't understand why you didn't just go ahead with 0.1 in divided does.

DR. GRANEY: I think part of the concern -- and there were many factors that went into it -- was even at the beginning of the study, an underlying concern that the 0.1 dose in these debilitated patients, where there might be

some problems with nutrition, would give problems in hypoglycemia and cause problems with the progress of the trial. The 0.5 dose would provide some cover for that.

Exactly your point came up and was brought up the by European investigators, and that is one of the reasons that the 0.1 was used alone. At the time that the European trial was being designed and fleshed out, there was enough experience, although double-blinded still, from the American trial, to indicate that the 0.1 must be well tolerated. In effect, the change that was then made in the European study was to just take both of the groups that would have gotten the two different doses of Myotrophin and assign them both to the 0.10, effectively giving us the 2 to 1 randomization we see in Europe.

DR. GILMAN: Also, did you test the difference between placebo and 0.05?

DR. GRANEY: Yes, and it was not significant.

[Slide.]

We see here the change in the AALS total score from baseline. This analysis, although you will hear more discussion of the LOCF by Dr. Dobbins, does include virtually all of the patients by virtue of the activity of this analysis.

In the LOCF, patient scores are carried forward beyond the point where they have ended the trial as if they

continued in the trial, so a patient that ends at an early point will be carried forward in the analysis, and effectively, all of the patients are represented in all of the months.

I think the significant finding here is that there is a dose-related effect of Myotrophin, that it emerges as early as the first month, and that at baseline, we have about a 24 percent reduction in the change of the score from baseline in the high dose as compared to the placebo-treated group.

[Slide.]

Myotrophin increased the time until the development of advanced disability as indicated by the occurrence of one of the protocol-specified termination criteria, and we have certainly talked about this at length at several points in the discussion today, but we are looking here at a display of basically the surviving patients who have not reached 115 of an FVC of less than 39 percent.

The effect is significant in the high dose group and dose related. The difference between the high dose group and the placebo begins to emerge relatively early in the study.

A Cox proportional hazards analysis of this data shows that the risk of an event in the high dose group as

compared with the placebo is reduced by 44 percent.

[Slide.]

Now, we will go to the Sickness Impact Profile, an alternate means of evaluation that Dr. Gelinas described to you. I think the important point here is that this profile is independent of the effect on the AALS total score, and yet it is confirmatory.

Remember we are looking now to determine the effect of the drug on the patients' quality of life as perceived and reported by the patient. The overall SIP, which includes 12 items, showed a dose-related effect with significance in the high dose.

We also saw a dose-related effect in the physical and the psychosocial domains that you saw described earlier.

[Slide.]

In summary, in the North American trial, Myotrophin produced dose-related slowing of the progress of disease. The magnitude of the effect was about a 20 to 25 percent reduction from the values seen in the placebo-treated groups.

We saw these effects in the reductions of the rate of change of the AALS score or slope, and in the change of the score from baseline. Further, we saw a change in the time to the development of the pre-specified events.

The Sickness Impact Profile does give us another

measure. I would point out that this is an independently administered evaluation. Interviewers contact the patients by phone, and so were not subject to getting information from the investigator sites on other elements of the patient's well-being, and again, what we saw was a dose-related effect significant in the high dose compared to placebo.

[Slide.]

The effects of Myotrophin on disease progression were also seen in the second multicenter trial. As Dr. Feeney pointed out --

DR. GILMAN: Can I interrupt you there to ask, you also administered the Clinicians' Global Assessment?

DR. GRANEY: Yes, we did.

DR. GILMAN: And what were the results of that?

DR. GRANEY: We have scattered elements of significance over time, and I can show you the data later if you would like. After the start of the study, it was recognized that the CGI was probably not well suited to ALS.

If you will recall, on the CGI, basically, half of the extent of the scale is used to record improvement, and I think, as our clinicians would tell you, there really is no prospect even with therapy of ALS patients having a measurable degree of improvement or reporting improvement in their well-being.

With the becoming clear, the CGI was actually removed as one of the primary endpoints before the end of the study. We do have data. There was some scattered evidence of effect, but we don't believe that it was a particularly good tool for this protocol.

DR. GILMAN: Was that a prospectively determined tool?

DR. GRANEY: Yes. The CGI was included in the protocol at the time it was put together.

DR. GILMAN: Dr. Kawas.

DR. KAWAS: Just a clarification. On the Sickness Impact Profile, the 20 percent of patients that aren't in those results, who are they?

DR. GRANEY: In the Sickness Impact Profile, the studies were conducted at months 3, 6, and 9, so that we don't have as many measures as we had in the Appel Scale. Patients who ended the trial without having had a Sickness Impact Profile after baseline simply don't have a score available.

DR. KAWAS: So that 20 percent of people who didn't make it to three months, is that --

DR. GRANEY: I will have to look at that specific analysis. Yes, that is the case.

DR. KAWAS: Thank you.

DR. GILMAN: Dr. Adams.

DR. ADAMS: In regard to the Sickness Impact Profile again, you said there were three assessments, at 3, 6, and 9 months, and the change in score from baseline reflects which of those assessments, or is that an aggregate value?

DR. GRANEY: I am almost certain that is an endpoint that we are looking at.

DR. ADAMS: So that is at 9 months.

DR. GRANEY: Yes. Just a second, let me ask Dr. Dobbins on that.

DR. GILMAN: Please identify yourself.

MR. MICHAEL MURPHY: Michael Murphy, Senior Vice President, Cephalon. I wanted to address the CGI measure and then I can also comment on the SIP. Perhaps it would be of interest.

In both protocols, two different measures of global improvement were employed. One was identified as a clinical global impression of change from a previous visit. The second was identified as a clinical global impression of therapeutic response which was from baseline.

In the North American trial, both of those measures yield fairly consistent results through time and/or at endpoint, and we obviously can show you the data.

In the European study, only one of the measures is significant at endpoint.

On the Sickness Impact Profile, the results which Bill showed were endpoint analyses which only requires that a patient have a baseline in at least one post-baseline evaluation. So it is the maximum sample size permitted by the analysis, and the missing patients simply reflect those who do not have either a baseline or a post-baseline measure.

DR. GILMAN: Dr. Zivin.

DR. ZIVIN: I am not sure that the question I had was answered or not, which is in the Sickness Impact Profile, was the analysis done with the last observation carried forward?

DR. DOBBINS: Yes.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: In the AALS scale, then, would one be accurate to say that there is roughly a two- to three-month advantage for those on full dose versus placebo, is that the way you read that?

DR. GRANEY: It is somewhat difficult to convert the slope exactly to time and event, but --

DR. DRACHMAN: Not slope, but the score.

DR. DOBBINS: Yes. Within the context of the nine months, the hypothesis being that it would be greater going beyond the nine months. In the window in which we captured the differential progression, that would be correct.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: I didn't understand that last part. most of the differences that were seen did not continue to get larger with time, differences on slope, and things like that, did they? So why would one expect that it would grow with time?

DR. DOBBINS: The slope would not change with time, but a one-point change in the slope over time is 10 points at 10 months, 20 points at 20 months, and so on.

DR. GILMAN: Thank you. Please continue, Dr. Graney.

DR. GRANEY: Thank you.

[Slide.]

We will talk now about our European trial, contrasting it with the North American. Again, the overall design was similar with several differences that I would like to note. Only a single dose of Myotrophin, the 0.1 mg/kg/day was studied and I briefly revealed the reasons for that. The European investigators also preferred a trial that treated a larger number of patients with the high dose.

At randomization, as a result of the compression of groups that we just talked about, two patients were assigned to the single Myotrophin dose for each patient assigned to placebo.

The protocol-specified endpoint for the European

trial was the change in the ALS score from baseline, and as I mentioned in answering one of the earlier questions, this analysis does include a larger percentage of patients than the slopes analysis chosen for the U.S. study, because of course you can't generate a three-point slope without three post-baseline slopes.

However, in order to provide a more extensive comparison of the trials, I will also present the slopes analysis and the times-to-event for the European trial as I did for the North American.

[Slide.]

In looking at the change in the score from baseline, as compared to placebo, Myotrophin produced a decrease in the change of the AALS score from baseline at endpoint of 3.3 points or 13.1 percent at endpoint. This compares to a reduction of 5.9 points or 24 percent in the North American trial.

You will see that this pattern of a drug effect, which although statistically significant is in the same direction as the North American trial with a lesser magnitude as seen across the AALS-related measures.

[Slide.]

Again, because of the interest that we had in slopes, as well as the Division, we did calculate slopes for the European trial, and I will turn first to the slope that

we calculated with three observations.

Myotrophin produced a reduction of 0.6 points per month or 16 percent, about 50 or 60 percent of the change we saw in the U.S. trial. The p value on this was 0.063. You can see here that we had about 85 percent of the patients involved.

We did go ahead in this study to do a two-point slope, recognizing the limitations of that. When we did that analysis, we had basically the same magnitude, but we did get a p value of 0.047.

The difference between the two analyses in terms of the patients included is 168 patients with the two-point slope as compared to 155 for the three-point. I think it is notable that the magnitude of change is really the same between the two even when we include more patients.

DR. GILMAN: Could you go back one slide, please. It looks as if you are not getting much difference if one just looks at the difference until six months from the first observations, whereas, with the slopes in the North American trial, there was a change from the very beginning.

DR. GRANEY: Yes.

DR. GILMAN: Could you comment on that?

DR. GRANEY: We have looked at it extensively in our effort to try to determine the difference between the two studies, and I really don't have a specific answer for

the delay that we see.

DR. DOBBINS: Just to add a little to that.

DR. GILMAN: Dr. Dobbins.

DR. DOBBINS: We do note in the North American study, although significance begins earlier, that the break actually begins to magnify at around five to six months. So the same phenomenon to some extent is observed in the North American study.

DR. GILMAN: Dr. Leber.

DR. LEBER: It is not just that the statistical significance changes, but the directionality shifts here, which is the kind of thing you often see because of dropouts, but I am not going to argue that that is the explanation.

I would also like to point out something that I think important as you hear it presented. The slopes analysis the firm is presenting has p values that are nominally in the range of statistical significance or statistically significant.

The slopes analysis done by the FDA on the same data has p values of what, around 0.22 to 0.4. I would like to call everyone's attention to that because it suggests very strongly that the differences are analysis-dependent, and it might be useful, while the firm is here, to explain how that came about, where these models they are using came

from before they just present it as, in fact, the result of the slope analysis.

DR. GILMAN: Can you respond, Dr. Dobbins?

DR. DOBBINS: Yes, we would be perfectly happy to do that at the appropriate time.

DR. GILMAN: Well, why not now?

[Laughter.]

DR. DOBBINS: Dr. Gilman, may I suggest that I include those remarks in my discussion with the efficacy issues that is part of my discussion. The short answer to the question is that we used a more sensitive method, and actually the best method for analyzing longitudinal data in a clinical trial, which although unfortunately was not a method that was chosen at the time prior to the studies being analyzed, in the end is the most efficient method.

And this method I refer to is a repeated measures analysis of variance.

DR. GILMAN: I think we need a little discussion on that. Dr. Leber.

DR. LEBER: Well, I don't challenge the idea that it is a different method. I just wonder by what criteria you say it is the best method.

DR. DOBBINS: It is the statistically most efficient method for this kind of problem.

DR. LEBER: Does that mean it is the most valid

method or the most efficient method? Are the two the same?

DR. DOBBINS: Yes, I think it is. I think it is most efficient and most valid.

DR. LEBER: I would suggest this battle is on the biometric plane and we need to bring out biometrician champion.

DR. GILMAN: Dr. Hoberman.

DR. HOBERMAN: When I saw this slide presented, I was disturbed because I have the impression that the sponsor was presenting this as a primary analysis, that is, the results of getting the data in, unlocking the data set, and then doing something that was in a protocol. That is not true.

This analysis was done quite recently, and it is a technical issue, and the last thing I want to do is turn this into dueling statisticians, but it is going to educate nobody.

The issue here is that the sponsor, after many, many covariate analyses in all kinds of models that have been unspecified, some of which have been submitted, decided to do an analysis which accounts for more information about what happens from time point to time point, then simply fitting straight lines to each individual and then doing an analysis of variance to decide whether the averages of those slopes are different.

That is basically what was in the protocol for both studies in terms of analyzing slopes.

Now, what the sponsor did was take into account the degree to which if a person was above a mean at one time, above the group mean at one time, that they tended to be above the group mean at the next time.

In this way, when Dr. Dobbins measures efficiency, what he means is that it tends to cut down on the estimate of noise in the data, and all a statistic is, is a ratio of signal to noise. You try to find a signal. Then, we have to relate that to a measure of noise, and the larger the signal is compared to the noise, the more we say this couldn't have happened by chance, it is not noise.

So what this model tries to do is incorporate information which decreases the amount of noise in the problem. It is a sensible thing to do.

Now, when I found that they had done this rather late in the game, I went back and I did another analysis. Now, the analysis that the sponsor did prescribes a certain pattern of this correlation that I spoke about over time.

You simply say to the computer find me a correlation, do a goodness-of-fit test, then, use that one in order to get the efficient analysis.

Now, we are not God, neither is the computer God, and we don't really know what the correct one is, but what

the sponsor did was use the data in order to estimate this pattern of correlation over time.

Now, that was all done by the computer. What I did was use a slightly different method which has been extensively used in the literature, reported on the literature, and I don't want to give you the name because it is just going to make you mad, and what it does is account for any misspecification of this correlation structure.

So, in other words, it uses more of the data to get an arguably more accurate estimate of the noise. When I did that, the p value for the same analysis, the same data set, was 0.16 using the same correlation structure that they hypothesized only I used more information to correct for the degree to which that was incorrect.

It went up to 0.16. If I used another correlation structure, it went up to 0.21. If I used another one, it went up to 0.23.

There is another issue. The other issue is the estimate of the signal. Now, there are many ways to get statistically valid, unbiased estimates of the signal. Now, it turns out that the sponsor's measurement of the signal, when using this result that they got with the 0.06, was minus 0.58.

However, if you do other analyses, this can go down to 0.5 and in fact, I did an analysis where it went

back down to minus 0.46.

The upshot of all of this is that when the sponsor shows you p values at or near 0.05, I want you to be aware that this not a robust result, and by "robust," when I was a kid, robustness had something to do with coffee. Now I am a statistician it has to do with the degree to which you can slightly perturb the problem, ask a slightly different question, do a slightly different analysis, and come up with a conclusion that is congruent with the one that you have done initially.

In this case, there is no robust analysis of a p value less than 0.05 no matter what analysis you do. Now, the 0.047 is a late entry, late entry within the last 24 hours. So I haven't been able to look at that one, but my comment is precisely the same, you can always perturb the data in a way to get a better result -- and obviously the sponsor is doing that -- and you can do other analyses that make the case much less compelling.

DR. GILMAN: Dr. Dobbins.

DR. DOBBINS: Yes, I would like to respond to that. We take great issue with the implication that somehow we picked a particular correlation structure which best suited our needs.

In fact, and before I respond to that, I think a little mixing in the beginning with some kind of

sophistication and that this method is not well known or well established in the literature, repeated measures analysis of variance has been around a long time and is widely regarded as the most efficient method for this.

Secondly, if I may, Dr. Hoberman, you have had your comments, I would like to respond. With regard to his statement with the use of covariates the models that we used for repeated measures include no covariates. They included simply the design parameters of study site and treatment. So it is a very simple model which exploits the information within a patient over time, that correlation.

Our analysis showed, an analysis very similar to what Dr. Hoberman which we are prepared to present today, showed that we had robust results. We are not talking in everything less than a 0.05, but what we saw was in the range of actually 0.001 to about 0.14 assuming several different kinds of variability structures for the data, the essential point being is when you use a more efficient method which better distinguishes the signal from the noise, treatment effect is more apparent.

Secondly, the treatment effects that we observed, the treatment estimates that we observed, as Dr. Hoberman pointed, one being around 0.4 or 0.5, we would argue that the range 0.4 or 0.5 to about 0.7 that we saw is a very tight range, and in fact, the optimal models, the optimal

correlation structure we saw had essentially identical treatment estimate to the simple linear method, what is called the naive linear regression, which is the ordinary least squares.

We can discuss the issue of the robustness of the results. We are simply saying that we used a better statistical method, and I don't think we can be faulted for using the best method available even if we didn't specify it pre-hoc. If we are taking an x-ray of a tumor and we have a CT scan available, I don't think because the protocol said that we have an x-ray, that we should continue to use the x-ray, and that is effectively what we have done with this analysis and this method.

DR. GILMAN: First, Dr. Hoberman, then Dr. Temple, then Dr. Leber, then Dr. Drachman, and please be brief.

DR. HOBERMAN: I think Dr. Dobbins has misunderstood my criticism. First of all, when I was talking about your using the pattern that was most advantageous, I thought, and I am sorry if I didn't make it clear, that the computer chose that with the goodness-of-fit criteria. I have the printout.

DR. DOBBINS: Yes, that is correct, but it wasn't arbitrarily chosen by --

DR. GILMAN: Dr. Dobbins, please wait until he is finished.

DR. HOBERMAN: So it was not a prespecified structure, it was determined by the computer, and I thought I had said that.

The second thing is I did not mean to imply that the model had covariates in it. I was referring to the panoply of covariate models that have been submitted and that I know have been done aside from the repeated measures.

Third, I was not referring to the repeated measures model in the literature, I was referring to, pardon the expression, GEE, so there is no issue about repeated measures, it is older than time. So that is not the issue.

I also concur that, yes, if you have a more efficient method, do it, fine, and you did it, but you yourself have stated that there is a wide range of values that you can get from this analysis, and I think that minus 0.4 to 0.7, I am not exactly sure why you say it is tight, because if you apply those to all the different standard errors, you are going to have an incredible range of p values.

So the idea that somehow there is a p value of 0.06 or 0.04 that you are stating is the result of this trial in slopes, I don't think it gives a full picture, and I simply wanted to point out that this is not a robust result in the sense that you can take these results and say wow, this study was statistically significant.

DR. GILMAN: Dr. Dobbins, would you respond? I see from your body language you would like to do that.

DR. DOBBINS: I think I can simply say that we agree to disagree on that point. We believe that the results are robust and that the p values and the level of significance are substantially reduced with this method based on what we saw for the ordinary least-squares method in the European study.

We do have a slide where we could show the range of values, the results that we had from these various correlation structures, but I guess the simple point being is that where we disagree is that Dr. Hoberman, and I presume the agency, feel that that is a relatively wide range.

We don't feel that it is such a wide range. In the application of this method, we had significance levels ranging between 0.01 and about 0.14 in our analysis of the robustness of various structures.

With regard to the treatment effect in the range of about 0.45 to 0.7, given that the results in this study is about 0.58 based on the naive method, we don't consider that to be a large variation in the range.

The key point is the variability was reduced, not the treatment estimate. The method reduces the variability and therefore makes the signal, which is arguably weaker in

the European study, more clear, and that is what the method does.

DR. GILMAN: Would you define robust?

DR. DOBBINS: In the sense of values, significance levels in the range of about 0.001 to 0.14. We would expect, if the method was not actually taking more information from the data, then, we would expect that significant levels to vary much more widely.

DR. GILMAN: Are you saying that robust in your mind is a significance level of 0.001?

DR. DOBBINS: Yes, that relatively tight range.

DR. GILMAN: But that is not what we are seeing.

DR. DOBBINS: This particular analysis being at 0.06, our optimal analysis, yes.

DR. GILMAN: Dr. Temple first, then, Dr. Leber, then, Dr. Drachman.

DR. TEMPLE: Not burdened with any comprehension of the specifics of this, I don't have to worry about the intimate details.

What I think the message that David is presenting is that the result is analysis-dependent and is after the fact. If the obviously correct analysis to have done is the one that was finally done, it would have been specified. Now, maybe people learn more and then get better at it, but if it was always the right thing to do the repeated measures

analysis, then, everybody would do it, but actually things don't always work out that that is the most favorable. Sometimes something else is more favorable. So people make a judgment about what overall the best analysis is.

No one would say that any given analysis or the one that was done is obviously wrong, foolish, unprecedented, or anything like that. The point is that it is one of a variety of analyses that are plausible, and once the data are in hand, it gets very hard to say how exactly one makes the judgment about which one to choose.

I don't think it is an insult to a company to say that they like the analyses better that make the drug look better. I mean how could it be any other way?

The point is that once you have the data in hand, it becomes very hard to say which analysis is self-evidently the most logistical, which one is the best, et cetera. That is why you specify the analysis beforehand. I don't see David is saying anything more than that, and illustrating that fact by saying he could some fairly plausible analyses, too, and they don't look as good, which just shows that there is judgment involved, and when there is judgment involved, it is a difficult question to say what your true p value or alpha level is.

I think that is what everybody is saying.

DR. GILMAN: Good. Thank you.

Dr. Leber.

DR. LEBER: Basically, the points that Dr. Temple just made. I brought all this up because I wanted to call attention to the analysis dependency of the p value here, and very frankly, once you start modeling something -- and these are all models whether we like it or not, some of it is the evidence, but some of it is also the model we apply, and by changing models you can often get different numbers.

I just wanted to point that out because we think we guard against that usually by specifying in protocols what we intend to do, and no more intended. I didn't want to insult anybody either. I just wanted to call attention to the numbers, you know, flashing before your eyes changing and why.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: I was just a little bit puzzled because earlier on, when I asked Dr. Gelinas about how many points make a slope, the reply that I got, not from Dr. Gelinas but from Dr. Dobbins, was, well, we had many more than three points.

Here, however, I see that there are two observations that are being used to determine the slope also -- or maybe used -- also, in a group of people in whom baseline slopes were not known, so we have no idea whether this was a change of slope or what.

Could you comment on that?

DR. GRANEY: Yes, I can, thank you. Part of the problem may arise from my not repeating clearly enough how Dr. Gelinas' description does indeed echo in here. When I say three-point slopes, these were all the patients who had at least three post-baseline slopes.

The two simply gave us additional numbers and added a total of about 15 patients because it did include those patients who had only two. The same thing still holds. The majority of the patients in both of these analyses have a much larger number of points going into their slopes. All points available were used in the slope.

DR. DRACHMAN: Would you regard the two as being reliable? I mean is that a reasonable way of determining slope?

DR. GRANEY: Just to give you a brief answer, I will tell you that it really comes down to a question of the statistical mechanism used. The tools that were used with the two-point slope were felt to draw enough in terms of the internal consistency of patients' behavior or patients' slopes behavior that it was a good basis to draw a line on the basis of just two points.

Maybe Dr. Dobbins can comment a little further.

DR. DOBBINS: It is a minor point with regard to it was just intended to include as many patients as possible

in the analysis. We believed that at least three-point post-baseline observations is the better analysis from the standpoint that it captures more of a patient's information, and I just elaborate or reiterate a point I mentioned before is that for the difference between the two analyses is the addition of about 11 patients, I think, who had two points post-baseline, but the overwhelming majority of patients again had much greater than three points post-baseline.

So there really is not much difference in any regard between the two analyses although we prefer, as the literature has shown, at least three points post-baseline.

DR. GILMAN: Dr. Leber.

DR. LEBER: This is a point I think Dr. Drachman started to bring up, and I would like to pursue it a moment.

It is conceivable that all these differences exist on a post-measure, that is, post-randomization slope, that they actually existed on pe-slope and account for the differences seen between the groups.

One of the reasons we have looked at the difference between groups on pre-slope minus post-slope, or vice versa, was to see whether or not you could correct for the fact that patients might differ by chance a little bit in terms of how well they were doing when they began, because clearly, these differences could pre-exist the assignment of treatment.

So one of the things these are not adjusted for is what these patients were like at baseline, and that is something I would like to find out, if you have done this on a change from slope measure, that is, pre-slope versus post-slope.

DR. GILMAN: Dr. Dobbins, can you answer that?

DR. GRANEY: I am not it answers exactly your question, Dr. Leber, but our next slide does give the difference between the pre-slope and the on-treatment slope for the two groups in this study.

[Slide.]

Here, we have the total number of patients contributed 155. We are looking at the high dose and the placebo. We are looking at the treatment slope, the post-slope minus the pre-treatment slope, and we see the negative value as we did with the treatment groups in the North American trial.

We thought that it was certainly interesting that we get a negative value, as well, for the placebo group. This is in contrast with the number that you saw in North America and does suggest to us that there is some difference in the populations that could contribute to the difference that we saw between the trials.

We would certainly hesitate to try to quantitate that over, say, what portion is based on that.

DR. GILMAN: Dr. Leber.

DR. LEBER: Do you have a p value for this?

DR. DOBBINS: The p value between treatments is simple analysis of variance, is non-significant, and as you can see, largely because the difference between the European study and the North American study was, as you see in the placebo group in the European study, you have a change of minus 0.31 per month. In the North American study, that change was plus 0.16 per month, with the treatment effect changes being about the same between the two studies.

So I think this is an indication of the placebo response in the European study.

DR. LEBER: Actually, you made the point that I was hoping you would make, that this is a not statistically significant, and when you take into account pre-slope, that is, prior to randomization how these patients were doing, you find a difference.

You offered an explanation for it which might be true, but we have no guarantee that it is, in fact, the true explanation. In fact, we displayed very similar data. If you will remember that when John Feeney was making his presentation, he showed you the cumulative distribution of pre-slope minus post-slope or vice versa, but the difference, and you saw that those ogives -- that is what that sigmoidal curve is called -- is pretty much

superimposable, which is why this mean difference is so small.

DR. DOBBINS: Not to belabor this point, but to clarify, this is again the ordinary simple analysis. The method applied was to the post-slope analysis and it takes into account all the total scores post-baseline.

DR. GILMAN: Dr. Hoberman, did you want to continue?

DR. HOBERMAN: I just have a minor appendix to what Dr. Leber said. The real issue I think here is the difference in the visual display that Dr. Feeney showed makes it quite clear that these are indistinguishable and that any variation he sees of noise.

The problem with the way the sponsor has presented this, I think, is to present what in numbers, actually quantifying the noise and saying, gee, there is a trend going on here, and when there is nothing even close to a statistical significance.

The third thing is I think that, also as Dr. Feeney pointed out, it is very treacherous to compare the placebo groups in these two trials and say that something happened in placebo group of one trial, it happened in this trial, and that is an explanation for why anything happened. I don't think there is any merit in there.

DR. GILMAN: Do you want to respond, Dr. Dobbins?

DR. DOBBINS: Yes. The figures shown this morning are not analyses. The ogives, as it is called, is a presentation of the raw data. This was a designed experiment. In a designed experiment, you take into account the effects of site and treatment, and when you do that, and you look at the difference in terms of averages, what we are the difference in terms of averages, and we believe that that represents a meaningful effect.

DR. GILMAN: Dr. Gennings wanted to ask a question.

DR. GENNINGS: I just wanted a clarification about the repeated measures analysis. Are you actually fitting the linear relationship within patients?

DR. DOBBINS: The repeated measures fits the group. It fits actually a slope for the treated group and a mean slope for the treated group, a mean slope for the placebo group, and then compares on an average basis.

DR. GENNINGS: So your model is that it is linear, not just letting the means go.

DR. DOBBINS: I am sorry?

DR. GENNINGS: You are not just fitting means, you are forcing a linear fit.

DR. DOBBINS: Yes, and it is very key point because, as we have seen earlier, this data is extraordinarily suited to this kind of method because within

a patient, how highly linear the Appel Scale is. That is a fundamental point. The data are very correlated within a patient and very suited to capturing that kind of correlation with this method.

DR. GILMAN: Well, we have successfully ground down to a halt again.

Dr. Temple.

DR. TEMPLE: I just wondered whether there was a way of doing the repeated measures analysis that could take into account baseline slope. It seems to be one of the critical points here. I mean yours didn't, but it could be done, couldn't it?

DR. GILMAN: Dr. Dobbins.

DR. DOBBINS: I think from a simple standpoint, the average difference in the pre-study slopes between treatments was not significant.

DR. TEMPLE: I don't think that is a full answer. It could still be different enough to affect the analysis.

DR. DOBBINS: That would seem to be borne out in a noncomparability at baseline.

DR. TEMPLE: I am sorry, I didn't understand that.

DR. DOBBINS: I think to the extent that that was true would be seen in the noncomparability of the pre-slopes at baseline in terms of their averages. In other words, there would have to be a pretty large deviation on average

at baseline for it to be meaningful enough the influence the post-study slopes, and we did not see that.

DR. TEMPLE: I don't think that is necessarily so, but I don't want to get into that.

DR. GILMAN: In the interests of moving on, let me try to summarize this little point in the duel of the statisticians here.

I am taking away from this the following. The prospective analysis was nonsignificant in the European trial. Post hoc analyses showed different results than the results of the prospective analysis, and we can take away, each committee member, how we want to interpret that, but at least for me, this is not a robust finding.

So I will simply state that and let's proceed.

DR. GRANEY: May I have the next slide, please.

[Slide.]

The colors may not be optimal here, but in a look at the time to the occurrence of an event until a protocol-specified event in Europe, there is a separation although it is not statistically significant.

A Cox proportional hazards analysis shows a 36 percent reduction although I would hasten to point out that the confidence intervals on that 36 percent does include one going along with the fact that the difference, although the magnitude was correct, was not statistically significantly

different.

DR. ADAMS: Mr. Chairman, can we go back to the slide, the last one.

Now, this is proportion without termination.

DR. GRANEY: Yes.

DR. ADAMS: So the N below there, on months, would vary between active and treated patients because there is a fair number of patients that prematurely terminate for death or adverse experience or something. These are only patients that are on active treatment?

DR. GRANEY: The patients are counted as they move along, so all patients really count in this, because they either move to the portion of discontinued or they stay with the group that are in the population. That is why it basically says that 100 percent of each group are included here, because we are basically just counting them one way or the other as the analysis moves along.

DR. ADAMS: So what does the heading mean? I thought this was the number of patients that reached either a score of 115 or an FVC under 39 percent.

DR. GRANEY: Yes, this is the patients who -- basically, the fraction we see here are the percent who have not terminated, one at the beginning, heading down to somewhere between 0.6 and 0.7 at the end.

DR. ADAMS: I am still confused. This is the

number that reached one of those endpoints.

DR. GRANEY: It is the number of patients who have not reached one of those endpoints. It is the proportion without termination, which basically means the patients who are represented by the 60 percent or 70 percent figure here are the patients who have not yet reached the total score of 115 or an FVC of 39. The proportion of patients represented above the line are those who have had an event.

DR. GILMAN: The label is misleading here.

DR. LEBER: Put another way, is this a smooth Kaplan-Meier plot? In other words, instead of showing the jumps, have you just smoothed out a Kaplan-Meier, is this just a survival function?

DR. DOBBINS: Yes.

DR. GRANEY: I think you have got a sense of the discussion that Dr. Feeney had relative to whether patients who die should be included in here. I think you heard from our earlier discussion where Dr. Gelinas and Dr. Appel commented. It is our feeling, and the feeling of our consultants after we reviewed the data, that death occurs independent of the progress of the disease, and our feeling on this was that the AALS total score of 115 and the FVC of 39 represented events that were clearly tied to the progress of disease as measurable by the Appel, which was the overall goal of the study.

We did not include death because death occurs sort of independent of that progress, as you saw -- although I can't give you the fraction of patients who have an event based upon their score -- it does occur along all of the scores. That is the reason for which we have not included death in this analysis either in this protocol or in the North American one.

There are differences of opinion on that.

DR. GILMAN: First, Dr. Leber, Dr. Zivin, Dr. Temple.

DR. LEBER: The reason I asked about this being a Kaplan-Meier plot is I was trying to clarify, I believe, Dr. Adams' point, and that is that you reach a given month. How many patients are at risk at the beginning of that interval compared to earlier ones, because that probability of suffering the event, that is, either having a total score exceed 115 or having a forced vital capacity go below 39 percent, is a function of how many remained at risk for that.

If you are having censoring or deaths going on in this time, the numbers at seven months are quite different, are they not, than those at one month, because of the nature of the censoring process or death. What are they actually would be the question.

DR. GRANEY: I will ask Dr. Dobbins to comment on

that.

DR. DOBBINS: Yes, that is essentially a correct statement, but the month-to-month withdrawal in both studies for all reasons was generally uniform.

DR. LEBER: But the issue would be if you would look at the conditional probability of having an event in any subsequent month, having reached that month without having an endpoint, the confidence limits are going to blow up because they are going to be fewer at risk. The hazard may go up, but your confidence limits around that hazard differ, so there is great imprecision at the end of those two months, the point in this plot that you are emphasizing. So I mean you have more error there.

DR. GRANEY: We are not necessarily emphasizing it, I would say.

DR. LEBER: Huh?

DR. GRANEY: We are not necessarily emphasizing it.

DR. LEBER: I understand that.

DR. GILMAN: Dr. Zivin.

DR. ZIVIN: My question was answered.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: If people who leave because of death aren't included, how does it turn out that the groups are 100 percent? Those people aren't in that analysis anymore,

they must be censored, right? Am I misunderstanding?

DR. LEBER: At the beginning of this analysis, everybody is in it. You start with 100 percent. Everyone is thrown into it, but all Kaplan-Meier product limit survivals are based on the idea that either you have the event or you are censored and then you reach the end, and everybody is right censored.

During the time, the way it is constructed, is you reach a point in time -- it is almost like an actuarial life table -- and you say how many are still at risk, and you say in the successive interval how many will fail adjusting for the losses over that interval, and you multiply these together to get the number surviving.

DR. TEMPLE: But in this case you die, so to speak, and have an event only if your AALS total score gets above 115 or your FVC goes below 39 percent. Hang on. You don't die if you die. That is not counted.

DR. GILMAN: You are dropped, yes.

DR. TEMPLE: I guess my question is -- you may or may no believe that progression is correlated with death, although as I have said before, it is difficult to believe that there is no relationship -- do you have the same analysis for the other events that get you out of the study, as well, in addition to these two?

DR. GRANEY: I think we can give you a display of

the events. I am not sure whether we have it over time.

DR. DOBBINS: Maybe we can have a short answer to that. An analysis was performed in both the North American study and the European study including death, and the results in the North American study are essentially the same with a little less significance.

The European study is nonsignificant, and the results did not change with the inclusion of death.

DR. TEMPLE: These results don't change with the inclusion of deaths?

DR. DOBBINS: Yes.

DR. TEMPLE: The p doesn't get worse?

DR. DOBBINS: No. I mean not worse than that, no. That p value is actually favoring treatment, so the p value goes up.

DR. TEMPLE: Yes, that is what I meant.

DR. DOBBINS: Yes, in that sense it gets worse, yes.

DR. TEMPLE: I am not surprised.

DR. GILMAN: We resolved that one.

Please continue.

DR. GRANEY: Thank you. May I have the next slide.

[Slide.]

We are looking here at the results of the Sickness

Impact Profile study in the European trial, and I think you will agree as we found there were no significant differences. There is very slight magnitude differences in the overall end physical, but we would not make much of those, and of course, it is reversed in the psychosocial.

I think we have to comment on this, that this was the first time that the SIP had been attempted in a multi-language, multi-cultural environment, and I think, prospectively, we did not pick up that there were likely to be problems in the interpretation and indeed in the application of the study. But in any event, we did not reach statistical significance in the SIP in Europe.

[Slide.]

I would like to turn now to the area that Dr. Feeney indicated we would be spending a fair amount of time on, which is the discussion of the patient by strata, and it is a complex area. Dr. Dobbins will actually discuss quite a number of the statistical and the fine points involved with why we believe strata is an appropriate way to look at the rapid progressing patients that Dr. Gelinas mentioned exist in this disease.

The sequence in which we turn to do this analysis is that after the initial analysis was done in the North American trial, and an effect was seen by strata, it was, as you will see, fairly marked and really we would have been

remiss had we not looked at the European trial where again the effect in strata is strong.

I think as we were looking at those data, we saw that strata is not a perfect way to pick up the rate of progress of patients, and Dr. Dobbins will talk about that at some length.

So I would ask you to just keep those caveats in mind when I show you the data from our look at the strata, and I will ask Dr. Katz' forbearance because we do call them rapid and moderat progressors, and I can't change the slides now.

[Slide.]

The consistency between the trials in terms of the responses in these rapidly progressing patients is seen most clearly in the rapid progressors when we look at slopes and the change scores.

In the North American study, we found, if you recall the values that we had previously, that really the effect, both for slopes and change score were largely concentrated in the rapid progressors.

In the European study, that was true, as well. I think a notable finding for this, two-thirds of patients now who are represented in this strata, is that across the two trials, the magnitudes are very, very close, and they are the same for the change score.

Granted that this was not a prespecified analysis. The fact that it does represent two-thirds of the patients, that fortuitously, the European trial had a distribution of rapid and slow progressors across the treatment groups and across the sites that was almost the same as the U.S. does lend some weight to this along with the actual numbers.

Now, there is another side to this, and we will look at the moderate progressors next, and Dr. Feeney pointed out one of the concerns for you in the European trial.

[Slide.]

If we look at the North American trial, we basically find the effect is squeezed out of the North American trial when we look at the one-third of patients who are these moderate progressors, the lower strata, if you will, and a problem for us, as well as for the agency when we are looking at this, is do we just have a seesaw effect, are we getting a positive effect in the high strata and we are getting positive values here, which I have told you are not favorable, and in fact, we have to keep in mind that we are looking at one-third of the patients, and especially in the placebo group, where this comparison is made between the placebo and treatment, obviously, we are talking about relatively small numbers here.

But there is another point that several of the

questioners, as well as the speakers, have brought up. The initial stratification that we did, this cut by 40 to 60, 60 to 80, really is imperfect. It is a snapshot in time. What Dr. Dobbins will show you when he presents his data is that if we look a little further and do this analysis on the basis of pre-slope, trying to sharpen our stratification, we find that this really resolves, and yet the effect is maintained in the upper stratum.

Dr. Dobbins did that analysis and will present it for you. Again, my comment is we freely admit these were not prespecified analyses. Stratification in the first trial really was done to balance patients, but the findings, especially in the high group and in both groups, when we look at the strata another way, really are compelling.

DR. ADAMS: A clarification. For the North American studies, the N's reflect both the patients and the active treatment, both the 0.15 and the 0.1 -- is that right?

DR. GRANEY: I am sorry. The stratification study here is done for the 0.10 dose groups only in both trials. So the intermediate dose is not included.

DR. ADAMS: Thank you.

[Slide.]

DR. GRANEY: Again, we want to extend this look further, and if we take a look at the strata for the SIP,

what we find is again a prominence of the effect with the dose relatedness in the North American trial, sort of localizing it into the rapid progressors, and we find in Europe, although we don't get the significance, we do see that the difference between them becomes more apparent.

So the effect carries over even into the SIP, which was administered by a different group of testers.

[Slide.]

To summarize the data that I have shown you, I think it is clear that the North American study demonstrates Myotrophin's effectiveness in ALS.

The European study is supportive. You have heard the arguments back and forth as questioners and speakers have discussed it today, but I think we have to note that the values are in the correct direction.

The therapeutic effect remarkably really is most evident in the rapidly progressing patients in both trials, whether we are looking at the AALS or the SIP. I think together the North American and European studies provide sufficient evidence of the efficacy to support the treatment use of Myotrophin in patients with ALS.

This has been a complex presentation, and you have heard the intensity and the length of discussions that have gone on. I think there are a couple of points that we would like Dr. Dobbins to address specifically for you.

DR. GILMAN: Thank you, Dr. Graney.

Questions for him? Dr. Zivin.

DR. ZIVIN: I would like to get away a little bit from the statistical complexities and ask a simpler question, which is to the best of my information, this drug does not get into the central nervous system, and the question is what is this drug doing about the upper motor neuron disease.

DR. GRANEY: I think we don't really have from this clinical trial, information that addresses itself to that, and we have to turn to the preclinical environment to look at that, where there are a range of models.

I will ask Dr. Jeffrey Vaught from Cephalon to address that issue of what is the relative effect likely to be on upper as opposed to lower motor neurons.

DR. JEFFREY VAUGHT: There is no data to suggest that we have an effect on upper motor neuron preclinically. However, there is one report that IGF may cross the blood-brain barrier although in small amounts.

However, I think it is important to point out that for the disease parameters that are being measured, and also from the preclinical animal models, it is not necessary for IGF to cross the blood-brain barrier, and that signals to the central nervous system due to the peripheral projections of the lower motor neuron can be manifest by systemic

administration of IGF.

So the simple answer is that for upper motor neuron and cortical involvement, we have no data to support or refute any effect there.

DR. GILMAN: Another way of asking that question is whether the substance will pass across the synaptic cleft going from the motor neuron to interneurons, and thereafter to the terminals of cortical spinal track fibers.

Is there any evidence for that?

DR. VAUGHT: There is evidence that Myotrophin or recombinant human IGF-1 or IGF-1 can be retrogradely transported by peripheral axons, and actually appear proximal in the motor neuron. There is also evidence that in fact retrograde signal can signal to the motor neuron.

Now, as far as crossing the synaptic cleft and actually going through a variety of events, there is no data that would indicate that.

DR. GILMAN: Thank you. Any other questions?

Dr. Graney, thank you.

Dr. Dobbins, before you begin, can I ask the length of your progressor approximately without questions?

DR. DOBBINS: Less than 10 minutes.

DR. GILMAN: I suggest that we hear Dr. Dobbins. Please go ahead, and we hope to break for lunch by about 1:00.

DR. THOMAS W. DOBBINS: Thank you, Dr. Graney.

[Slide.]

At this time we would like to address two key points regarding the results presented by Dr. Graney and respond to points addressed by the agency earlier. We want to briefly review patient withdrawal in the North American and European studies and stratification.

We will examine patient withdrawals in the North American and European studies and show that patient withdrawal did not influence conclusions in either study.

[Slide.]

This table shows the patient disposition in the North American study. Terminations fall into two categories, protocol-specified termination, patient withdrawal including death, adverse experience, all other.

Protocol-specified terminations are expected to be imbalanced if the treatment is effective. Also, ALS scores in these categories are reflective of late stage disease. Protocol-specified terminations were dose related, 17 percent in the 0.1 mg/kg group, 26 percent in the 0.05 mg/kg group, 33 percent in the placebo group.

Patient withdrawals, on the other hand, should be unrelated to treatment effect and therefore are not expected to be imbalanced. Patients withdrawals in the North American study were balanced between the Myotrophin groups

and the placebo group and total discontinuations were balanced among the Myotrophin groups and slightly higher in the placebo group.

[Slide.]

The next table shows patient disposition in the European study. Again, protocol-specified terminations clearly demonstrate treatment effect, 20 percent in the Myotrophin 0.1 group, 34 percent in the placebo group.

Total discontinuations were balanced among the treatment groups, 48 percent in the Myotrophin 0.1 group, 47 percent in the placebo group. However, an imbalance was observed in the patient withdrawals.

To determine if this imbalance influenced results, in particular with regard to the LOCF analysis that we discussed earlier, we performed an analysis of the robustness of that result focusing on the rapid progressors. We focused on rapid progression for two reasons. First, the majority of withdrawals were in the rapid progressing patients, actually in both studies, but in particular in the European study were greater than 90 percent in the upper stratum.

As we have observed and the point we are making is that rapid progression is where the treatment effect was observed in the European study. So to address this, we performed two simple analyses. First, simply removing

deaths from the analysis, and secondly, removing all withdrawals, essentially, an analysis of terminations versus completions. If an imbalance is influencing results, we would expect the results to be dependent on these analyses.

[Slide.]

This table shows the results of the analysis of the AALS total score change from baseline in rapid progressors. The analysis including all patients is the analysis presented by Dr. Graney earlier. The results showed a significant treatment difference favoring Myotrophin at minus point 7.8 points.

When analyses were performed first removing deaths and then removing all withdrawals, the results were essentially unchanged. The analysis removing deaths, minus 8.6 points, the analysis removing all withdrawals, minus 7.9 points. This indicated that the results were not dependent on patient withdrawals.

[Slide.]

Therefore, we conclude that patient withdrawal did not influence the conclusions from either study.

DR. DRACHMAN: What score did you use in the all patients for those who died?

DR. DOBBINS: Well, to address the question simply, we simply removed them from the analysis. In the all patients analysis, it was the score at their last visit

prior to death. The average score for the patients in the treated group was 92.

DR. GILMAN: Dr. Katz.

DR. KATZ: A couple points. First of all, you call these analyses Last Observation Carried Forward, which ordinarily is usually used to apply for an intent-to-treat analysis, in other words, an analysis that takes into account all patients.

These analyses do exactly the opposite, they remove patients. So that is one thing. It is sort of counterintuitive to what we ordinarily think of as an LOCF analysis.

Beyond that, these analyses don't correct for the bias that both Dr. Feeney and Dr Leber talked about earlier this morning, which is that in a degenerative disease, a monotonically, if you will, degenerative disease, early dropouts will tend to bias -- the treatment with early dropouts will be positively biased, I think we actually even have an overhead of that, the point being that you are going to be carrying forward scores that are better than they would have been had they stayed in the trial.

So the analyses that you have done in which you dropped those patients actually doesn't get at the bias that we had mentioned earlier.

DR. DOBBINS: It simply assumes that it didn't

influence it.

DR. GILMAN: Well, but it may have.

DR. DOBBINS: I think it makes that point pretty clearly.

DR. LEBER: Point taken.

DR. GILMAN: Other questions? Please.

[Slide.]

DR. DOBBINS: Next, we would like to review stratification on baseline AALS score in the North American and European studies. We would like to make the important point here. We will show that stratification is related to disease progression, and in particular, stratification based on AALS score at baseline did delineate rapid progressors.

[Slide.]

This figure illustrates the correlation between baseline AALS score and AALS pre-study slope among the evaluable patient population in the North American and European studies.

The vertical axis shows baseline AALS score, the horizontal axis shows AALS pre-slope in points per month. The horizontal line in the figure represents the stratification based on baseline AALS score of 60.

The figure illustrates several essential important points about these clinical trials. First, there is a clear correlation between the baseline AALS score and disease

progression as measured by the pre-study AALS slope.

Secondly, rapid progressing patients based on the AALS slope are overwhelmingly represented in the upper stratum, as we see rapid progression based on AALS pre-study slope in the range 6, 8, 10, 12 points in the month entirely captured by the upper stratum in these studies.

However, equally important, patients in the upper stratum are not necessarily rapidly progressing as exhibited by the group of patients in the upper stratum with low AALS pre-slope scores. That is this group in particular here, and that group effectively represents the overlap noted by Dr. Feeney earlier.

Alternatively, the majority of lower stratum patients are moderate progressors by AALS slope, this group in here.

Therefore, although not a perfect surrogate for disease progression, stratification based on the AALS score at baseline was clearly capturing rapid progression. Based on these observations, we considered stratification based directly on disease progression as measured by the AALS slope.

To determine an appropriate cut point, we consulted the literature.

[Slide.]

This figure, as you have seen earlier, is adapted

from the important paper by Havercamp and Appel, Brain 1995. The figure shows a clear relationship between survival and rate of disease progression based on a cut point of AALS slope of 3.3 points per month using, as you see, the upper, less than or equal to 3.3 points per month, greater than 3.3 points per month.

As Dr. Gelinas pointed out, based on this cut point, there was a greater than two year advantage in median survival for moderate progressors.

Therefore, using the cut point of 3.3 points per month to define strata, we performed an analysis of the AALs slopes in the North American and European studies. We will present the results of this analysis first for moderate progression, then for rapid progression.

[Slide.]

This table compares the results of the AALS slope analysis for moderate progression defined by AALS pre-slope less than or equal to 3.3 points, an AALS score at baseline less than or equal to 60.

As you can see on the right-hand side are the results for the lower stratum Dr. Graney presented earlier. On the left-hand side are the results for the AALS pre-slope stratification less than or equal to 3.3 points per month.

The results were consistent whether patients were stratified by AALS pre-slope or baseline AALS score.

[Slide.]

The next table compares the same results for the AALS slopes analysis for moderate progression in the European study. Note the nonsignificant positive difference observed for AALS score than or equal to 60 resolved when patients were stratified directly by disease progression.

Note also in this figure that the sample sizes virtually remained unchanged in the two definitions of moderate progression.

[Slide.]

Next, we consider rapid progression and we ask ourselves the question did the change in the stratification based directly on disease progression change the results in the upper stratum in the rapid progressing patients.

This table compares the results of the AALS slope for rapid progression for the North American study. Again, therapeutic effect is evident whether patients were stratified by pre-slope or the baseline AALS score.

[Slide.]

This next table compares the results for the European study. Again, the therapeutic effect is evident whether patients were stratified by pre-slope or baseline AALS score.

[Slide.]

So our conclusion then, and a very important point

that we want to make today, is that stratification based on the AALS score at baseline delineates rapid progressors in these studies.

Thank you.

At this time, I would like to turn the presentation back to Dr. Graney, who will present the safety of Myotrophin.

DR. GILMAN: Dr. Leber.

DR. LEBER: Actually, I think it would, if I can suggest, be important for the committee to understand why we don't necessarily agree that pre-slope in any way tells you what it should, and believe it is confounded with the entry criteria and almost auto-correlates in the sense that you will have a more rapid progression if you have a higher baseline slope.

We would like to explain it. It comes about that if you wanted to use -- well, I don't want to explain what Dave is going to do, but basically, it says this. If you have two patients who have the same AALS score at pre-slope, say, at entry of this study, the patient with the higher slope is going to achieve a baseline score by the time they are randomized.

The one with the higher slope is going to be higher systematically than the one with the lower slope. This is on pre-slope. So there will be sort of an auto-

correlation. What you really want to know is given a baseline score, does it predict the post-slope after randomization, and it has a little bit of predictive power, but not very much.

So this whole thing is very complicated and not so easy to understand, and I think it would be useful for you to understand the rebuttal to the arguments that have just been presented before too much time goes by.

DR. DOBBINS: I think that I would like to address that comment directly.

DR. GILMAN: Please.

DR. DOBBINS: I think this is a fundamentally very simple analysis, and the pre-slope is completely predictive of the post-slope within a patient. If this analysis were performed -- and it was directly on post-slope although we don't have that information here -- it would show exactly the same results.

It is simply not true that the pre-slope value within a patient does not predict that patient's post-slope progression. These slope scores within a patient are highly linear. The agency's own presentation this morning, in which two patients were shown, the linearity, the progression made that quite evident.

They were very illustrative of the type of patients that are in both of these studies. Irrespective of

whether we consider pre-slope or post-slope, the implication of this analysis is that the stratification captured rapid progression in these studies. It wasn't perfect, but it delineated rapid progression, and progression of this disease, the optimal stratification for future studies should be based directly on disease progression, as the Havercamp and Appel paper point out, I think very clearly and very profoundly.

Thank you.

DR. GILMAN: Dr. Leber and then Dr. Drachman.

DR. LEBER: I think Dave should be given a chance to respond. I don't want to argue about this. Actually, this morning, very early, I was able to take Studies 1200 and 1202 using data provided by the firm and actually show the relationship between pre-slope as a predictor of post-slope, which does shown an r-square of somewhere around 0.4 or so. It explains about 40 percent of the variance.

But if you actually look at pre-slope predicting baseline and actually baseline predicting post-slope, you get correlations, r-squares that are very small, relatively small, around 10 percent, 20 percent of the variance, which is not something you would normally say is a robust predictor.

I don't have overheads of this. I will pass these around as self-explanatory. In the meantime, Dave can take

a look at them. Again, I haven't had a chance to verify it. We just got some of these arguments presented last night, and I was doing this early in the morning. They could be in error, but I think, since I was using a cam stat program, they are unlikely to be.

DR. GILMAN: Go ahead.

DR. HOBERMAN: Again, Dr. Leber has done my work for me. Thank you.

I want to make a very simple point, and as I listened to the discussion, I get a little confused. I hear about pre-slopes, I hear about baseline values, I hear about strata. I am here only to illustrate what Dr. Leber said about baseline values and slope, and respond to an analysis the sponsor did. I just want to talk about something very simple.

I want to reiterate what Dr. Leber said about a primary flaw in the sponsor's analysis. The sponsor may be correct. All I am doing is I am saying that they did not choose the best way to make the argument, and if you use other data that I think is more appropriate, the argument becomes a little weaker.

Because of the entrance criteria, as Dr. Leber mentioned, there is a potential -- and we certainly didn't have time to investigate this tremendous detail -- that because a person in order to get into the trial because of

the selection criterion was likely to have a higher slope just to get into the trial, there is a possibility that there was some selection bias, whereas, you get a self-fulfilling prophecy.

The self-fulfilling prophecy is that you are not going to be surprised if you wind up having higher baseline Appels associated with higher pre-slopes.

So what we did is simply look at the alternative way of looking at the data, which is to look at the post-slopes.

[Slide.]

Now, this is what the sponsor produced in their document showing the scatterplot of pre-slope and baseline score. I like to think of it the other way around, but that's all right.

[Slide.]

What we did very recently is simply produce a scatterplot in 1202 that has unfortunately baseline on the horizontal and post-slope on the vertical. Now, this is only partial data and what I did was I took both placebo groups in Trials 1200 and 1202, and pooled them.

I asked a very simple question: What is the relationship between baseline Appel score and the placebo slope on study?

The answer to that was rather than getting a r-

square in this case which would be around 0.36 or 4, in other words, roughly 40 percent of the variation being explained by the relationship between baseline and on-study slope, it turned out to be about 10 percent.

Now, 10 percent variation, it is statistically significant, but it is important to realize that there is a difference between something that is real and something that has any predictive value.

So what we are merely doing is questioning the strength of evidence that baseline Appel really does relate to the slope on study, no more, no less.

DR. GILMAN: Thank you.

I think we should break for lunch. It is now seven minutes of 1:00. We will back here starting at seven minutes of 2:00.

[Whereupon, at 12:53 p.m., the proceedings were recessed, to be resumed at 1:53 p.m.]

AFTERNOON SESSION

[2:00 p.m.]

DR. GILMAN: Take your seats, please. This session is about to begin.

I thank the patients who are here for your patience. We do need to hear additional information from Dr. Graney and Dr. Miller. Then, the committee will discuss the information they have heard, and then we will hear from you. Appreciate your patience.

Dr. Graney, would you please continue.

DR. GRANEY: Yes. Thank you, Dr. Gilman.

[Slide.]

We will open this afternoon with a brief discussion of the safety of Myotrophin. Myotrophin was very well tolerated in both studies. As you saw, there were few discontinuations for adverse experiences and drug-related events, as you will see, are largely those anticipated from previous experience with IGF-1 or from the disease. There was neither clinical nor laboratory evidence of hypoglycemia in our trials.

[Slide.]

The pattern of adverse experiences was similar across both clinical trials and this slide, which may be difficult to read, so I will point some things out, shows the 10 most frequently reported adverse experiences across

both studies. Also, the data on each study is included in the briefing book.

It shows that disease-related findings, such as weakness and dyspnea and coordination abnormality were, as we expected, common. The most frequent drug-related event was pain at the site of injection. As you can see, it occurred quite frequently, and in fact, the overall total for all injection site events was quite high and occurred the most frequently in the placebo-treated group.

Dr. Gilman, you had a question relative to the potential of this for unblinding, and if you would like, I can show a transparency about it now or come back to it later.

DR. GILMAN: Did you say that correctly, did you say that injection site pain was most frequent?

DR. GRANEY: It was most frequent in the placebo. The percentage is given, yes.

DR. GILMAN: I see, yes.

DR. GRANEY: In any event, actually, the differences are not very large between the groups.

DR. GILMAN: The patients that received 0.05 had even fewer in percentage anyway than placebo.

DR. GRANEY: Yes, that's right, and I would remind you that the placebo, as well as the drug, were all in the same vehicle with a pH of 4.0.

DR. GILMAN: That is probably the reason for the pain, yes?

DR. GRANEY: Yes, we believe so. In any event, to just basically tell you what we would show on the transparency -- and we would be happy to -- when we looked across all of the injection-related events and the number of patients who had events, they distribute at all of the sites quite evenly in total across the various treatments.

That, in fact, ties in with the fact that many patients had not just an event that might be described as pain, but they also had bleeding, they had some redness. So, in fact, it was a fairly complex constellation that presented in the clinic of reactions at the injection site.

DR. GILMAN: Can we conclude from this that pain at the injection site would not be a way that patients could be unblinded?

DR. GRANEY: That is correct. That is our impression.

DR. GILMAN: Dr. Adams.

DR. ADAMS: I think I know the answer, but for the record, were there any adverse experiences attributed to the study drug that were serious, that resulted in death, admission to the hospital, or some compensatory therapy?

DR. GRANEY: We actually had a very simple clinical profile. I will ask Dr. Richard Civil about any

that may have, other than the disease related ones, that might have been translated or described as serious by the regulations.

DR. RICHARD CIVIL: Rich Civil, Cephalon.

In tabulations of serious adverse events by regulatory requirements, one quickly finds that the tabulations encompass a litany of the most common and expected adverse events encountered in progressive ALS.

For example, the most common serious adverse event -- and by this I mean adverse event requiring a hospitalization -- was percutaneous gastrostomy placement or PEG. This was the number one serious adverse event occurring in the trials.

DR. GRANEY: Perhaps I could just go further and say we did not see a pattern of serious adverse events that appeared to be related to IGF-1, unrelated to the disease.

DR. GILMAN: Including the deaths in the European trial?

DR. GRANEY: I will talk about those at some length. We believe that those were ALS-related.

[Slide.]

Although the clinical program was not intended to examine survival, we obviously reviewed the mortality experience from the point of view of safety.

In the North American study, this study displays

mortality experience. ON the left we have the North American study with its three treatment groups; on the right, the European study.

The first row of data displays the deaths of patients during the double-blind treatment and because patients had a variable length of time in the double-blind treatment, we also went out to 300 days, which is close to the amount of experience that we would see if all of the patients did continue through the full possible nine months.

As we look at the North American trial, we find that in the placebo there were 7.8 percent of deaths, in the 0.5, 12.4 percent, and in the 0.10, 9.2 percent of deaths.

We will go over to the European trial, and as regard to numbers, I will remind you again there was a 2 to 1 ratio. So we look and we find that the placebo-treated patients had 8.5 percent deaths and the high dose drug had 14.5 percent deaths, and this was the origin of some concern at which we wanted to look further.

When we did go out to the 300 days, as I mentioned, which would be about the experience we would expect -- and we have to keep in mind that many patients here had entered open-label, which was open to virtually all patients who ended or discontinued from the double-blind trial -- we find that the numbers really do smooth out.

In the North American trial, the placebo has 24

percent, the low dose 22 percent, the 0.1, 19.5 percent. Placebo here is 22 percent, and 29 percent in the European trial.

It is important to note, as I believe was noted this morning, the differences in the deaths between groups nowhere in this presentation reached statistical significance.

We did want to look further, and there is always a clinical interest in the nature of these deaths. One of the items that drew our attention was the early death within the first 30 days of five patients in the 0.1 mg/kg. These were examined very carefully and were in fact typical ALS deaths with no apparent factors that separated them from the other ALS-related deaths within the study.

[Slide.]

We looked in a broader sense beyond looking just at these particular patients, and we found that there were factors identifiable in our group, in our clinical program, also identified in the literature that are associated with a greater likelihood of death, and those are greater age, a lower vital capacity, and the greater rate of change of AALS total score during screening.

When we looked at these factors, we found that they were evenly distributed across the patient groups in the North American trials, but in the European trial there

was a predominance at baseline of these factors, suggesting that the randomization which succeeded in the U.S. in distributing the risk factors for deaths through the treatment groups, did not succeed in doing that in the European trial.

Again, in light of the extensive discussions of analyses that went on this morning, we should point out that this, like some of the others, was a post-hoc analysis, but it is interesting that the three factors that we found had indeed been identified within the literature.

[Slide.]

We then took a further step and again these are post-hoc analyses, but we did a Cox proportional hazards regression model, and I know this has only been completed within the past few days, and I apologize to the agency for that.

The analysis that we did when considering these factors basically shows that the experience of the two groups is very close all the way through the end of the trial. I offer that analysis as one we believe has been done in good faith and one which is congruent with the other things that we found with this group of patients.

[Slide.]

In summary, I think you saw other than what we believe are the well-explained mortality experiences in the

European trial, a fairly straightforward Myotrophin safety experience. The drug was well tolerated and certainly has an acceptable safety profile for the treatment of patients in ALS.

DR. GILMAN: I would just like one bit of clarification. You said that the patients in the European trial who died, died of typical ALS complications or words to that effect.

Can you explain what you mean, what did they specifically die from?

DR. GRANEY: Yes, in fact, I was again ask Dr. Civil to come to the microphone. He was the safety officer who reviewed the data extensively in both the North American and European trial, really looked at all of these in great detail, compared them across studies, and I will ask Rich to talk about that.

DR. CIVIL: Thank you. In a review of all of the deaths, it was very clear that the vast majority of deaths that occurred in the course of both the North American and the European trial had directly contributing factors identified by the treating physician of two types: one, respiratory insufficiency either alone or respiratory insufficiency in combination with a pulmonary infection.

That probably accounted for 90-plus percent of all deaths as attributed by the investigators, and based on

medical review it seemed to be very clear that that was the predominant cause. These patients had clear evidence of disease progression with declining respiratory function both symptomatically and on forced vital capacity measurements, as well as other clear indices of disease progression, namely, increasing swallowing difficulties often leading to PEG placement.

So based on these clusters of progressive deficits leading to both respiratory insufficiency and swallowing difficulties often associated with the requirement for PEG placement, investigators and I regarded these as really being quite prototypic of the expected outcome in ALS patients.

DR. GILMAN: Again, I believe we heard that there were no autopsies performed on any of the patients who died. Is that accurate?

DR. CIVIL: No, that is an inaccuracy. I am aware of perhaps 10 to 12 autopsies. I had actually just been informed that, unknown to me previously, that the majority actually came from Dr. Appel's site, not surprisingly given the database being accumulated there and the interest in obtaining autopsy results.

In reviewing the autopsies personally, I found no patient who had an autopsy who did not have a diagnosis, an autopsy-confirmed diagnosis of amyotrophic lateral

sclerosis.

Oftentimes the attendant ante mortem or agonal associates of respiratory insufficiency and/or overwhelming sepsis and pneumonia were present, as well, but in all instances, patients with autopsies in our clinical trial were pathologically confirmed amyotrophic lateral sclerosis.

DR. GILMAN: That is reassuring.

Dr. Leber wanted to comment and Dr. Hoberman.

DR. LEBER: Again, we can probably unfortunately spend a lot of time since neither the agency and the firm have had a chance to join each other and look at the same data and the same analyses because there has been iteration of arguments as the days pass, but I want to make a distinction between the issue of an analysis done in good faith and a valid analysis.

We could easily challenge the validity of analysis even if we think it were done in good faith. I bring that up because I believe the method of correcting the deaths probably is flawed as to the extent we understand it, and therefore I just don't want it to stand unrebutted as though it is explained, and if we find it necessary, Dave can explain why.

I would also like to bring up the point that only on the unstudy period can you fairly compare the deaths as to causal attribution because of the mixture of treatments

assigned to patients after the end of the double-blind period, and even then the failure to detect statistical significance is a bit bogus because the studies are not powered to detect it.

What you have is a difference which is different as much as anything else, but you can't determine whether it is due to chance or not. You just can't say for certain that it is not or that it is. It is just not the kind of study that was done.

So we just leave these things out as they are without reaching a firm conclusion. Nobody is saying the drug kills anyone, but I want one last point to make. Not too many months ago or time ago, this committee voted to approve a drug to prolong survival in which there was no clear basis for how that drug acted to do so.

We took an empirical look at the distribution. So that the idea that you can explain the mechanism of death by examining cases and saying they are the same kind of deaths that patients had, had they had ALS and nothing else, doesn't really say that the drug could not have had a causal role.

I just throw that out as a logical argument, because it, in fact, could change slopes, it could change how you handle secretions, you would never know it. The way we look at this is empirical, what are the rates, and I

think that would be our position.

We don't know, but we don't say you can discard it simply because you come up with an argument.

DR. GILMAN: Dr. Dobbins, do you want to reply

DR. DOBBINS: No.

DR. GILMAN: Dr. Hoberman was next. Dr. Hoberman, did you want to comment?

DR. HOBERMAN: I would like to make this optional for the committee. The sponsor has stated that there was an imbalance at baseline in risk factors in 1202, suggesting that that is why there were an apparent excess of deaths.

I don't agree with that analysis. I don't know whether the committee wants to hear my explanation of how they came to that conclusion because they didn't explain how they came to that conclusion, or else they are satisfied that mortality in these trials is not an issue, so that you don't need to spend time on it.

DR. GILMAN: I think you should explain further to us what you have in mind.

DR. HOBERMAN: I will need the overhead projector.

DR. GILMAN: Please, go ahead.

Dr. Adams, in the meantime, do you want to comment?

DR. ADAMS: Maybe I am misunderstanding something again. The slide that shows the overall data from the North

American and European studies had the number of deaths during double-blind treatment, when the patient was taking study drug, is that right?

DR. GRANEY: Yes.

DR. ADAMS: And then there were a number to day 300, which is approximately 10 months, and the numbers obviously increase because of the nature of the illness. Now, I think you said it, I think Dr. Leber said it, were patients in this period -- there are a number of patients that drop out of the trial --

DR. GRANEY: Tes,

DR. ADAMS: And are they getting active drug during that time?

DR. GRANEY: Yes, that is correct.

DR. ADAMS: So they would meet at endpoint, for example, it would be 115 by that Appel Scale.

DR. GRANEY: Yes.

DR. ADAMS: And then would be stopped as far as the study and be given active drug thereafter?

DR. GRANEY: That is correct.

DR. ADAMS: That is kind of on an individual patient and investigator decision?

DR. GRANEY: That is correct, although the majority of patients, I believe the number approached 70 percent in most of the groups, went on to open label after

either completing the nine months or reaching an endpoint.

DR. GILMAN: Dr. Leber and then Dr. Temple.

DR. LEBER: This is just a technical clarification. The answer to your question is it depends when in the time course of the trial, the real secular time, whether or not someone could go on to open label treatment. I believe there was a period of time when there wasn't enough drug available to put everybody on, and then later on there was.

So not consistently did everyone immediately go from double-blind to drug. Isn't that correct?

DR. GRANEY: That is correct. There was a period for some patients, that is correct.

DR. GILMAN: Dr. Temple.

DR. TEMPLE: If the period on study shows one thing and then people on the placebo group who were doing slightly better, at least in one study, at least in 1202, while on placebo cross over, and the numbers get closer, what do you think that means?

DR. GRANEY: Well, I think I can come to a conclusion of what you are implying. I think the concern, as has been expressed other times, is the fact that the rates come together due to a possible adverse effect on Myotrophin when it is first administered to patients, and I think one of the important points to bring out is that we

did not see this in the North American trial where we started a very significant number of patients, and there was no evidence of a sorting out or a significant increase in the deaths there. That is really all the data that we have available.

DR. GILMAN: Dr. Hoberman, would you please proceed.

DR. HOBERMAN: First, I would like to acknowledge an error that I made in one of my earliest remarks of the day. Dr. Carl Yoshizawa of Chiron pointed out to me that in stepwise regression, the selection is based on the maximum F statistic, and thereby implying that order would not be a factor in the selection of the covariates.

I apologize to the committee for that error, and I thank Dr. Yoshizawa for the correction, but at any rate, I expect it is something that one UNC grad would do for another anyway.

Ultimately, as I said before, the conclusions are totally unaffected by that issue.

Now, getting to the question of the baseline factors, the sponsor has submitted to the FDA a couple of analyses regarding this issue, and I just want to explain why I think that the logic isn't -- it certainly isn't quite clear to me.

What they, in fact, did was to go into the

database in 1202 and they looked at the subgroup of uncensored. Uncensored people are people who die and censored people who are alive at the end of the study.

Now, what they did in again as simple terms as possible is construct for each patient their own personal score that would predict death, so the higher the risk score, the higher probability of death on study.

Now once you have all of these risk scores, then, you can ask the question what is the distribution of these risk scores at baseline between the two treatment groups. Now, when the sponsor first submitted this analysis, what they did was they concluded that since among the people who died, there was a slightly higher mean risk score at baseline than the people -- I am sorry -- the mean of the risk scores in the treatment group, but only among people who died, was greater than the baseline risk average among placebo patients, again among people who died.

Now, at the time, they stated that this implied that there was a 27 percent higher risk of death just based on baseline factors alone. I question this logic because the answer to the question -- and the question is very important -- the question is: Was there a maldistribution of risk of death at baseline in the entire randomized cohort?

By going into and only looking at the people who

died, you are looking at a subgroup.

[Slide.]

Now, if you look at the distribution of risk scores at baseline, using -- we just got another later version of the model -- first, it had a muscle function score and all of a sudden it doesn't -- but I had to use this, and this does include a muscle function score in order to predict death.

This is actually the representation of the answer to the question you are really interested in. You don't have to go into a subgroup of people who died in order to infer back to what was correct about the distributions of patients you were really interested in.

So if you want to say, well, it is true that there was a slightly greater mean in the risk factors of the people who died on the study in the treatment group, that is all well and fine, but you can't make any inference from that about the predisposition of people when the started the race and what would befall them during the trial.

DR. GILMAN: Dr. Leber.

DR. LEBER: David, I still have a couple of questions about what you are actually displaying. You didn't put the slide on the projector in a way that would show us what the key was. What are you actually plotting in terms of is this combined across the groups and what are the

plots?

DR. HOBERMAN: No. I am sorry.

DR. LEBER: Okay. Treatment group of pluses. So when this lies to the right, is that a benefit?

DR. HOBERMAN: No. The higher the risk, the greater the number. The pluses is the treatment group. So if you want to make any case at all that there was any kind of imbalance at baseline, you might as well point up there and say, gee, aha, I see some pluses that happen to be to the right of the squares.

But that is not the analysis that the sponsor did, and I would say that if somebody really wants to answer this question, as to whether the patients who died or in some sense there was some collective excess of risk at baseline, it is going to take a considerable more analysis or at least if you want to try to explain why there was an excess of deaths in the drug group, it is going to take considerably more work than the sponsor had yet done.

DR. LEBER: This one last clarifying question. The scores that you are actually plotting that go across on your ogive, they represent a function that is applied to every patient or his covariates. They get a score that supposedly predicts death, and you are just plotting that score from that function.

DR. HOBERMAN: Yes.

DR. LEBER: Where does the function come from, Dave?

DR. HOBERMAN: I was trying to avoid that. The function comes from using a logistic regression model where you simply compute the coefficients that, when multiplied by each person's covariate, each person's baseline characteristic, and you add all those up, B1X1 + B2X2 + B3X3.

Then, you get coefficients from that model that you are going to apply to each individual patient. Then, you take each individual patient's scores and you construct a score for each individual patient.

The scale on the horizontal axis is completely arbitrary. It has no clinical meaning. However, it is a perfectly valid scale to show the range of risk scores that you get and the fraction of people who get those risk scores or less.

So this is the background of what the sponsor did, but the difference between what they did and what I did is take scores. They took scores and applied them to the subgroup of people who died, and I am maintaining that this is an improper way to make a statistical inference back to the original baseline population.

DR. GILMAN: Any further questions?

Dr. Graney.

DR. GRANEY: No, we are fine, thanks. What I would like to do, then, is just if I can have my last slide, I will close the clinical data presentation.

[Slide.]

The North American trial demonstrates Myotrophin's effectiveness as measured by the AALS total score and the sickness impact profile, and the results are statistically significant.

This morning you heard a great deal of discussion about complex statistical arguments on the European trial, but we believe that at the end of it, the effect of Myotrophin in this study in Europe, although not statistically significant, is directionally correct and is supportive of the North American study.

A review of the findings in the two-thirds of patients who progress rapidly, whether selected by original score or by pre-slope, demonstrates the mutually supportive findings of the two trials.

In summary, the body of evidence indicates that Myotrophin is well tolerated and reduces disease progression.

In closing the presentation of the clinical trial results, it is necessary to take a moment to express appreciation to the consultants and investigators who participated in the design and implementation of the

clinical program and to the patients and their families.

Their efforts made the clinical evaluation of Myotrophin in ALS possible.

With that, I will now ask Dr. Miller to present a clinical interpretation of the findings of the Myotrophin program.

**CLINICAL INTERPRETATION**

DR. ROBERT G. MILLER: Thank you.

Dr. Gilman, ladies and gentlemen, I am grateful for the opportuni y to provide a clinician's perspective to the information that you have heard this morning, shifting gears a little bit from such an intense discussion of so many methodological and statistical issues to look at this from the perspective of a clinician.

I was not involved in this study, and yet I am very involved in the care of patients with this disease and also in clinical research in ALS.

[Slide.]

So I want to remind you about the disease itself. This patient who has a tracheostomy and a feeding tube, feeding gastrostomy, is completely paralyzed in his arms and in his legs. He has a motorized wheelchair that can be driven by head movements and by a puff and sip mechanism.

He has full time attendant care and still has considerable quality in his life, but he illustrates the

extraordinary burden that this disease ALS places upon persons who suffer from it.

[Slide.]

We really are still in the unfortunate position of being able to treat only the symptoms of the disease, and we have gotten better and better at helping to relieve some of the suffering of the symptoms of ALS.

We can control the spasticity to some degree, and cramps, and excessive saliva, and the disturbed sleep that so many patients with ALS suffer from, and we have really developed a lot of methods to help with mobility and with nutrition, and even with modern methods of helping with ventilation, and these symptomatic therapies are helpful, but we have nothing that stops or reverses the progress of ALS, and I want to provide you with a perspective on the past several decades in attempting to find a treatment for this terrible disease.

[Slide.]

There is a large body of literature documenting scores of negative clinical trials in ALS including all manner of immunosuppressive drugs, calcium channel blocking agents, branch chain amino acids, and even, more recently, some studies using other neurotrophic factors, and these studies have been uniformly negative. There has been no drug until now where the progressive, relentless decline in

function and quality of life for ALS patients has been altered in a beneficial way.

[Slide.]

As a clinician, I would like to reiterate a few points that have been made today, and I must say that this is the first time I have heard a public peer review discussion of these data, and I am grateful to Dr. Leber and his team, and to the penetrating questions of the committee, because a lot of information has come out that is important about the methodological considerations in the trial and about the very complex statistical issues in the trial.

But having said all of that, I believe that the evidence from these studies does demonstrate that the progressive decline in function of patients with ALS is slowed with Myotrophin, and that in patients who are progressing rapidly, these effects are particularly clearly seen.

I am grateful also for these discussions about safety because we participated recently in a trial of CNTF where patients were made quite sick by this neurotrophic factor, and the increased death rate was very troubling, but patients were made so sick and the adverse events were so obvious that it was easy to understand that there were safety concerns, and I personally feel satisfied on the basis of the discussions that we have heard today that there

consistency is seen across each of the scales in the European trial.

The point that I would particularly like to underscore as a clinician is that strength and upper extremity function, these two categories which are so critical in terms of a person's function as they attempt to manage this disease were beneficially effective and no other drug had shown this kind of beneficial effect upon strength.

DR. GILMAN: Excuse me. Strength where? Where is that measured?

DR. MILLER: This is manual muscle testing.

DR. GILMAN: Arms or legs or both?

DR. MILLER: Both upper and lower extremities, a composite measure.

DR. GILMAN: Yet, there was no change in lower limb function.

DR. MILLER: Yes. Dr. Gelinas, do you want to comment about that?

DR. GELINAS: If I could address that. Muscle strength was assessed with the manual muscle examination, and it did examine upper and lower extremities across joints. However, the lower extremity functional testing are time-to-test, so that they involve much more than just strength, but they involve also assessments of strength through the spine and the ability to right yourself when you

are about to fall, how quickly you can walk, your timing, so a lot more attention to upper motor neuron problems and spasticity problems with regard to function.

[Slide.]

DR. MILLER: Comparable data are shown here for the roughly two-thirds of patients in each of the two studies, the North American and the European trials, who were considered rapid progressors or upper strata patients.

I would just point out again the consistency across every measure of the Baylor Scale in the North American study, where the results are, I believe, robust, to use a word that has already been used today, and in the European trial, where the directional consistency is observed in each of the scales and where there appears to be supportive evidence about drug effectiveness.

[Slide.]

I would just make a comment about the European trial, and that is that the investigators figured prominently in the design of the European trial, and because the company worked closely with the investigators and respected their preferences, there were a number of issues that made the European study different from the American study, and as you have heard, one of them was the 2 to 1 assignment which changed the power of the trial.

Another point is that when this study was

designed, a larger effect size was anticipated than was observed, and therefore, this study, the European trial, was underpowered for the observed effect, something that we recently experienced in a trial of gavapentin.

This is particularly true for patients who are changing very slowly, where a much larger sample size is needed to observe an alteration in the slope.

[Slide.]

Quality of life for patients with ALS is a critical issue, and here you see the scales which were beneficially impacted by Myotrophin in the study where the Sickness Impact Profile was used to measure quality of life related to such important issues as ambulation and mobility, social interaction, improved communication, management in the home, and finally, the ability to enjoy recreation again showing tendency toward both a dose-response and a favorable drug effect upon the preservation of quality of life.

[Slide.]

Our group, separate from these studies, carried out an analysis of the Sickness Impact Profile in comparison with declining isometric muscle strength in a large group of patients with ALS, and found a very high correlation between the changes that occur in muscular strength and the changes that occur in the Sickness Impact Profile as a measure of life, again underscoring the value of this measure in

declining quality of life in patients with ALS.

[Slide.]

To sum up, then, this is a study that in many ways has grown out of the neurobiology laboratory where anticipated preclinical effects of this compound have now come to fruition in a clinical trial and where I think we have seen evidence of efficacy using a valid and reliable and disease-specific measure, the AALS Scale.

We have seen a robust effect in the North American trial and I believe we have seen a supportive effect in the European trial, and it is true that when patients are rapidly changing, there is more likely to be an effect than in patients who are moderately changing, and that was observed in the patients who were rapidly progressing.

I would make the point again that this is the first clinical trial in ALS demonstrating a slowing of a decline in quality of life, that is, patient ratings of their own quality of life, a very important element in the trial.

Finally, I would say that I believe that we are seeing here a drug that shows minimal risk.

[Slide.]

I would just like to comment about the therapeutic effect. In neurology, we don't have a lot of experience with therapeutic effects, particularly for neurodegenerative

diseases.

I would just like to make the parallel with the Guillain-Barre syndrome and the treatment plasmapheresis where a large North American trial demonstrated a beneficial impact on the slope of recovery for patients with Guillain-Barre syndrome. The size of the effect was about 25 percent, that is, patients who were treated with plasmapheresis improved with a slope that was about 25 percent faster than patients who did not receive the treatment.

This was not an effect that patients could see, it was not an effect that clinicians could see, but it was confirmed in a number of studies and quickly became adopted as the gold standard for therapy for patients with this disease.

In Duchenne's muscular dystrophy, another desperate progressive disease in children, prednisone has shown a very modest clinical effect, but it is sometimes apparent to both patients and physicians even though the improvement in strength is very modest.

The drug riluzole, which is the only drug that has been approved for ALS, has an impact on mortality, and the size of the improvement in mortality range between 4 and 18 percent, and with Myotrophin we are talking about an impact in the slope that ranges between 20 and 25 percent. It is

not clinically apparent. It doesn't stabilize the disease. It does not improve life for patients, but it slows the decline in a fashion that compares favorably with these other accepted therapies.

[Slide.]

So I believe that the one drug that is approved at the present time impacting on survival, but not function, and now we have a drug that slows the loss of function and delays the loss of quality of life, and I think we are in a position that in many ways is analogous to the early days of cancer therapy and the treatment of AIDS.

[Slide.]

This is a drug that patients want and that clinicians want, and it is really the reason that we are all here today, because ALS is, after all, the Grim Reaper of neurologic disease, and people like Jane here struggle courageously to cope with the disease, but the burden is too great for any patient, any family, and for the society.

As a clinical investigator in ALS, I am convinced by the data. Myotrophin has a beneficial impact on the disease both in terms of the loss of function and the erosion of quality of life.

As a clinician caring for patients with ALS, I urge you to approve this treatment IND for Myotrophin.

Thank you.

DR. GILMAN: Thank you, Dr. Miller.

Dr. Copple, you had a question.

DR. COPPLE: Yes. On the slide that you showed on the Sickness Impact Profile, there was substantial effect on social interaction and recreation, and I wonder if you have any thoughts as a clinician as to the mechanism of that or the rationale, since there was not that much improvement in strength and muscle function. There was certainly some, but --

DR. MILLER: The question is about Sickness Impact Profile and about the mechanism of improvement, and I should be clear that -- I think probably everyone understood, but just to be doubly sure -- we are not talking about people improving, we are talking about slowing the decline in function and slowing the loss of these various important motilities of quality of life.

I think what you saw is that every functional scale on the AALS Scale showed a response, a dose-response, albeit not always statistically significant, and I think it is very hard to say why each one of these very important factors was preserved, if you will, for patients. I don't have a specific mechanism, but I think it correlates with the slowing of the loss of function.

DR. GILMAN: Dr. Gelinas, did you want to respond?

DR. GELINAS: I have been very interested in the

impact on the quality of life of Myotrophin, and in looking at the separate categories that are endorsed under Recreation, they encompass such items as I am able to spend much time with my family members, I am going out almost as often as I did before my illness, and they really have functions that have a lot to do with fatigue in life, and if you can combat the fatigue, then, you have the energy to do those things on those outings. I think that is really where it hits in terms of fatigue.

DR. COPPLE: Thank you.

DR. GILMAN: Dr. Hoberman.

DR. HOBERMAN: Dr. Miller, I have a copy of the paper that you referred to, and it is true that you found a p value of $10^{-4}$, but in your talk you stated there was a very high correlation. That is not the same thing as a highly statistically significant result.

In one of the tables it states that the correlation between the TQNE and the change in overall SIP has an adjusted r-squared of 0.08. Now, that is not a very high correlation. That is almost of no predictive benefit.

In one of the concluding paragraphs in the paper, it states, "In its present form, the SIP is insufficiently sensitive for monitoring disease progression at the level of the individual ALS patient."

Now, I don't see how those statements in your

paper hang together with simply stating that there is a -- what you stated -- a high correlation between the TQNE and the SIP.

The second thing I would like to say is that stating that you didn't get an anticipated treatment effect and therefore less power is sort of tautological and is the excuse of a lot of failed trials, in this case, it is possible -- and we have produced and Dr. Feeney showed -- an analysis of the difference in the progression post-baseline to pre-baseline, in which the issue of power doesn't even arise because the effect is null, the distribution is superimposed. There isn't a statistical method on earth that could pull those curves apart and set one to the left of the other.

The last thing is you referred to a treatment effect. This may seem like a technical point, but my understanding is that we are not in a position to state that there is an actual documented treatment benefit that any patient can expect.

That would probably take further study, and just because there was a number like 25 percent that did come out in the North American study, it is not clear that people should walk away thinking that this in fact is an expectation that a patient should entertain.

DR. GILMAN: Dr. Miller.

DR. MILLER: Well, with respect to the first -- and those were all very good questions, Dr. Hoberman, in fact, I had a dream that you would ask me that question -- because the first question that you asked really reflects the difference between the way a clinician looks at a comparison of two different measures, the TQNE and the Sickness Impact Profile, and the way, with all due respect, you would look at these data as a person who is much more knowledgeable than I about the statistics.

I felt satisfied, as did our group, that the decline of the Sickness Impact Profile measuring quality of life, and the decline in muscular strength fall in parallel, and that the relationship between these two measures was highly significant, and if I overstated the correlation, I apologize about that.

The point that you made that the Sickness Impact Profile is not an adequate way to follow an individual patient is a good one. We don't use it to follow individual patients, but we do think that it has great value to follow groups of patients and to make comparison about quality of life.

The truth is we do not have an excellent quality of life measuring instrument, but the Sickness Impact Profile is about as good as they get now in my view, and this is a start. This is a first step, and we are now

measuring the best way we can quality of life, and we are seeing a change that appears positive and congruent with the changes measured in the functional scale by clinicians.

The issue about power is a very important one. You quite rightly say that if there is no therapeutic benefit, you can't talk about power, but I would say that since one-third of the patients were progressing at a very slow rate, and two-thirds were progressing at a rapid rate, and when you look at those patients who are progressing at a more rapid rate or are more serially affected, or both, you see changes that, to me, looked directionally consistent and not as robust as the changes in the North American study, but all in the same direction. To me, that is a therapeutic benefit, and if we had larger numbers, I believe that we would have had more of a statistically significant effect.

The final point about the treatment effect that people can infer from the changes in slope is a very important one. It is very hard for us to measure the impact of any treatment upon this disease. We cannot quantitate what people really want to know, which is how much longer will I live, how much longer will I be able to do the things that I want to be able to do, but we can quantitate the rate of decline of our best measure of quality of life and the rate of decline of function measured in a way that has been validated and where there is a lot of experience in ALS.

When we see a slowing of that rate of decline, and when the difference is about 20 or 25 percent, then, I think we can explain it that way to patients, and for the reasons that I explained here, I think that is meaningful.

DR. GILMAN: Any further questions from the committee for Dr. Miller, Dr. Graney? Any further statements from the sponsor?

SPONSOR: No, sir, that concludes our presentation.

DR. GILMAN: Thank you.

Any further comments from Dr. Leber, Dr. Temple?

All right. Then, it is time for the committee to do its due deliberations.

**COMMITTEE DISCUSSION**

DR. GILMAN: Let me start by reminding all of us that the reason we are here today is to respond to the question as to whether we agree that there are two seemingly adequate and well-controlled clinical investigations of the effects of Myotrophin in patients with ALS and whether we have sufficient data to support a treatment IND.

That is all we are being asked to do, do we think there is enough evidence to support a treatment IND.

To initiate the discussion, I think I would prefer to be provocative at this point and just tell you what I think at this point having heard the material today and

having read the material that we were provided.

Yes, Dr. Leber?

DR. LEBER: One critical point and I hate to interrupt you at this particular moment.

DR. GILMAN: That's all right.

DR. LEBER: We want to make certain that it is understood that the committee is not going to reach a final view until it has had a chance to hear from the open session testimony.

DR. GILMAN: That's right.

DR. LEBER: Right now I just want to emphasize this again for people who wouldn't have understood, that we hope this would focus on the evidence adduced in the two trials, and the final question about how to use that evidence, and what purposes it may serve, will be addressed after.

Is that a clarification that helps a little?

DR. GILMAN: Absolutely right. Yes, thank you for that.

Yes, we are here at this moment to discuss our views of the information we have had presented before us, so that we can share those views. Then, we will hear from the patients and other advocates, and then will have further discussion prior to voting.

So, to continue, it strikes me on having evaluated

the evidence, that we have convincing evidence from the North American trial, the 1200 trial, that there is efficacy. It was a prospectively designed and executed study with the data showing improvement at least as compared with placebo in the Myotrophin-treated group.

Personally, I was not convinced that there are sufficient data to be convincing, that the European study had data that convinced me that there are sufficient reasons to agree that it is an effective agent.

I think I would like to hold the issue of safety for a moment and see what others say about efficacy at this point.

So, committee?

DR. KAWAS: Can I ask a more procedural question about the comment you started the discussion with?

DR. GILMAN: Yes.

DR. KAWAS: Is the question we are trying to answer whether there are two studies, and is it two studies that are necessary for a treatment IND?

DR. GILMAN: No. We are trying to determine whether there is sufficient evidence for us to recommend a treatment IND. The "sufficient" will be our judgment. In order to provoke the discussion, I thought it would be best to reflect my own thoughts, which are that there is one study that to me provides sufficient evidence, another study

that does not provide sufficient evidence.

I think we need to talk about that first and then we can determine whether the combination of the two studies, with whatever you think about their results, provide you in your mind with sufficient evidence to grant a treatment IND.

Dr. Zivin, Dr. Snead, and then Dr. Drachman.

DR. ZIVIN: I have a question that I would like to ask first, which is, from both the FDA and from the sponsor, what are the practical implications of either approval or disapproval?

DR. GILMAN: Dr. Temple, do you want to respond to that?

DR. TEMPLE: Let me dance around it a little and just say a few things. It relates to the question, I can assure you of that. You will see it happen eventually.

We have obviously spend some time thinking about these data and discussing them with Cephalon, and are coming to you because we have to make a decision about a treatment IND request that seems somewhat complicated. This was all laid out well by Paul, so I won't try to replicate it.

There is one study, and you can tell we have few reservations about the 1200 study. We can argue about this and that, but on the whole, the primary endpoints were met and it all kind of leans the right way. So we don't have reservations about that, and as you can obviously tell, we

have substantial reservations about 1202, and we wanted to be sure you knew what those were.

To state the obvious, those reservations certainly don't mean that we think we know Myotrophin doesn't work, but in the face of a study that looked pretty clean and neat, one of the questions we wanted to ask was what are the implications of a study that is of very similar design, but not supportive.

As you have heard, Cephalon clearly knows that that study is not a clear winner, but they have a lot of reasons and they have offered them to think that you shouldn't be as discouraged as it might first seem, because there are reasonable explanations for why the study wasn't so robust.

Now, at the back of all this is, while we are asking you about a treatment IND, a marketing application based on those same studies would obviously have to make the same kinds of arguments. This is not a secret, everybody knows that. Cephalon has said that that is what they think the data are.

Now, the criteria for a treatment IND that are pertinent are two. There are really only two that are relevant here, one of which we have asked you an explicit question about, and that is, that there needs to be sufficient evidence of safety and effectiveness to support a

treatment IND.

Sufficient is not further defined in the law except to say that it is clearly less than the substantial evidence of effectiveness needed to market a drug. So you don't need the same level of evidence. If you did, then, you would market the drug, you wouldn't have a treatment IND.

So, even if you think that there is sufficient evidence for a treatment IND after a full discussion here, you don't need to think that you are then telling us what the answer to the NDA application would be, because it is a different standard and a different thing, and we would look at the data more, and so on, and there would be more discussions.

There is a second requirement for granting a treatment IND, however, and that is that the company be actively pursuing marketing approval with due diligence. In the regulation, that means generally that the trials that might support a marketing application are completed or that they are ongoing.

That question becomes at least potentially slightly tricky here, because it is no secret that Cephalon thinks that the current data would support a submission, and we have told them -- this has been publicly announced, so I am not telling anybody anything they don't know -- that we

would file such an application for review, we wouldn't say it is clearly not acceptable, and incidently, that it would get priority review. We have said those two things, and those are not secrets.

So you could say, well, the question is moot. Obviously, that sort of means that there is due diligence going on. But, in fact, you could tell us things that would shed light on that question. I am not offering them in any particular order.

If, for example, you felt really strongly, but admittedly before there has been a total review of the data, that 1202 is just really weak, you might want to say that because it conceivably could affect Cephalon's view and our view about what ought to happen.

I am not trying to predict exactly how it would do that, that is a complicated question, but you might in that case urge the sponsor to look very closely at any other ongoing studies or at least think about initiating further study early, whatever we might choose to do with the NDA.

On the other hand, if you found the kinds of arguments that have been made about 1202 reasonably persuasive under the circumstances, you know, one strong study and one study with a good excuse for not being as strong, you might tell us that, and that might affect our decision eventually and Cephalon.

So some of what you might say as you look at these studies and as you contemplate what you have talked about, could have implications. I am dodging what the exact implications are because we really haven't come to grips with the studies in the way we would at the time of an NDA, and it is too soon to be precise on this. So I am just trying to give some flavor.

Does that remotely come to answer what you were asking about?

DR. ZIVIN: Remote.

DR. GILMAN: Let me paraphrase. If we do not believe that there is sufficient evidence, then, the sponsor would have to initiate another study, I assume, or start again. If we do find there is sufficient evidence, we will make that recommendation to the FDA, and they will make that on up the scale. It is then up to the company as to whether it will or will not pursue an NDA, a new drug application, with the current data or whether they will decide to initiate a new trial. I think that is what Dr. Temple was saying.

Dr. Leber.

DR. LEBER: Bob, unfortunately, did not come early enough to hear what I said to you, which I think is a slightly different pitch on the same problem. I said -- and I was asked this question before -- what is sufficient

evidence. We all agree it is less than substantial by definition, but it is a term of art.

We don't know precisely what it means, but it isn't just the evidence alone. It is the context in which the evidence is used. You could say that we are anticipating the submission of an NDA, and if you say that you expect that the evidence that will be forthcoming will be enough to approve -- make a decision, definitive decision on the NDA, then, certainly the conditions of a treatment IND historically would be met, because you would have the evidence you need, and you want to accelerate the pace at which patients can gain access to the drug.

You could also approve a treatment IND under conditions in which you say, look, we think there is sufficient evidence for treatment use, but we don't think the evidence is sufficient to support an application's approval, and therefore we urge you at this point to consider the conduct of additional studies to decide the question in a definitive manner. That is another outcome.

Finally, of course, I won't preclude the possibility that you could look at this evidence and say I don't care, that 1200 is positive, the treatment effect is not large enough or important for us to say treatment use is necessary. So you have a full range.

But it isn't just the evidence alone. It is the

evidence and the path it leads to. Treatment use is intended not to allow a limbo system in which you have this unapproved new drug forever being circulated. You want to reach a final conclusion. So you have to factor that in.

But as a suggestion right now for this discussion, you really have two trials before you, and I would suggest the possibility, if the Chair agree, that you might want to parse this out until deciding what you think these two trials show. That would be step one. And from there, you can move forward.

I don't know even know what the sense of the committee about them is.

DR. GILMAN: I felt there was convincing evidence about efficacy in 1200, and not in 1202, to be concise.

Did you want to comment? Please identify yourself.

DR. MONROE KLEIN: Monroe Klein, Cephalon. I am going to make two comments, the first about the pursuit of marketing approval. When you look at the intent of the regulation, as indicated in the preamble which was published, the intent was to not unduly prolong clinical investigation, and clearly, neither Cephalon nor Chiron intend to unduly prolong clinical investigation. In fact, we intend to submit a treatment IND this summer -- NDA -- NDA this summer, and as Dr. Temple said, that is an

application that would be fileable.

Also germane to that, the purpose of this requirement of actively pursuing marketing approval was focused in on companies that were charging for a treatment IND, for the drug in a treatment IND. I wanted to clearly state that that is not our intent. We intend to provide the drug free of charge to patients if we are granted a treatment IND.

I would like to now respond to considerations of whether another study should be done. It is our opinion that the clinical studies conducted to date have established that Myotrophin is safe and effective.

We think there is additional work that should be done with Myotrophin, but we see that being done in a post-approval environment. One must consider the ethics of doing another placebo-controlled trial at this time.

Based on the epidemiology of this disease, the sponsor cannot justify spending additional resources to conduct another study pre-approval. We would like to do another study post-approval. We are committed to doing that if given the opportunity.

We think the appropriate study to advance this field is a combination study to see whether a combination of riluzole and Myotrophin have more benefit to patients than either drug individually.

We have discussed study designs for such combination studies with the World Federation of Neurology. We have submitted a proposal to the agency. I just ask you to bear in mind that for this serious disease, we think that a post-approval study, a Phase IV study or a Phase IV commitment might be something for your consideration.

Thank you.

DR. GILMAN: Dr. Snead, I think you were next.

DR. SNEAD: I had the same question.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: The issue that I see is that when you do one study, that should give you all the clues or most of the clues you need to design another study that is going to be more positive. Whatever you learn from the first one, you may apply.

If there is a subgroup that you believe is going to help more, if you believe there is a dose level, if you believe there is a duration, all of those may be used to give you a better second study.

Here, we see sort of the reverse. This is a little worrisome to me, that is, one study was carried out and worked. Based on the findings partly from that study, the dose of the treatment in the second study was the one that was believed to be more effective in the first.

But lo and behold, given this, things did not work

out quite that way. This is one of the issues that I regard as very troublesome. Were there a third trial, what would be done that would be different from the first two?

Well, it might be that only those with the most rapid progression would be entered, but I have no definite way of knowing, and I sort of wonder whether that would, in fact, alter the way the trial goes.

It seems to me -- and I am troubled by the excuses that are raised regarding why the second trial failed to reach significance. There were many of them, as you know. The control group really didn't match, there wasn't enough power, too many of the patients received drug, and not enough were in the placebo group. All of these were factors that should have been thought about and clearly would have been thought about in designing study number two.

One of the things that always worries me is if someone flips a coin 100 times and finds that tosses number 53 to 62 had a preponderance of heads, then, to say this is a subgroup of tossing a fair coin that is really different, so I am going to do another study, another trial of coin tossing in which I will ignore all the tosses until that point.

The issue then is whether these are random events or random concatenation of events, such that you see a lot more heads than you would have, but it is, in fact, by

chance, and not the result of what actually happened during the coin toss.

These are some of the issues that I find troubling, that is, that the redesigned study with the insights from the first one was less efficacious.

DR. GILMAN: Thank you.

Dr. Temple.

DR. TEMPLE: Just a factual matter. It wasn't my impression that the European study was actually designed to follow on the first. They were ongoing more or less concomitantly. You know, it is a fact of life that attempts to replicate studies don't always work, and it is also a fact of life that every time you chase one subset, you find out you were probably wrong.

So whether one can, in some way, by being smarter actually do better on those things is what we all dream about, but rarely achieve.

I just want to say that this is not a case where they tried to single out -- as far as we can tell -- single out particularly characteristics and then failed to get them. It just seems like a case where the second study was not nearly as robust, or not robust at all, if you like.

DR. GILMAN: I think Dr. Drachman was referring to the multiple post-hoc analyses in which they looked a whole bunch of factors, and by chance, one of those is likely to

be positive.

DR. TEMPLE: As you know, we are concerned about that, too.

DR. GILMAN: Dr. Leber.

DR. LEBER: I think it is fair to say that both studies more or less overlapped. There was a slight offset, so that the European study started slightly later. It is conceivable that data from that study might -- and this is what we have to ask the firm -- have influenced the late decision to change the outcome variable, but I can't tell that. It may have occurred totally independently, but it was not a leak of data from one study to the next, but rather a strategy for maximizing something.

But it is true, this is not an iterative development program where you do one result, look at it. It is typical of modern drug development. People know you need two studies. They try to do them simultaneous virtually and you sometimes get conflicting results.

One thing that Bob said, that you find a result and you try to confirm it. That is why we were ready to go ahead with the treatment IND without question when all we had in hand was 1200. The problem is when you have two studies and no clear means to decide which one is a better estimate of the truth.

Now, you have heard the firm's arguments of why a

treatment effect is, in fact, the way to interpret the two studies, and a lot of this has to do with personal judgments about how you get there with evidence, and I guess we want to hear yours. How do you see the evidence in these trials?

DR. DRACHMAN: The question that then would arise is what is the stage of the Japanese study that is ongoing and when might one expect those results.

DR. GILMAN: I would be glad to get an answer to that, but is that relevant?

DR. DRACHMAN: In a way I think it is. If we are sort of uncertain about what we would do, we might say we need a third look, and knowing when that would be or whether that would be might be helpful in thinking about how we would decide.

DR. GILMAN: Well, it seems to me we are here being asked to evaluate the evidence that is at hand, is it sufficient for us to recommend a treatment IND.

Dr. Temple.

DR. TEMPLE: The reason I was dancing is that we don't want you to review the NDA now. We don't have the NDA now. So we are not asking you that. I think we agreed ahead of time that that was not really the question.

At the same time, some of the things you think about these two studies could have implications for what everybody does, and we did think it was worthwhile to find

out how you thought about that.

I would agree with Paul. We would very much like to hear what your assessments of the two studies are and what they mean, and as I tried to say, your assessments have something to do with what Cephalon is going to take back and what we are going to take back, but we are not asking you to decide on the NDA. We don't have it. You don't have it. It has not been submitted. And that would not be fair or right.

DR. GILMAN: I would like to focus us on the question about whether there is sufficient evidence at this time from what we have seen -- again, I would very much like to hear from the committee their thoughts about 1200 and 1202.

Dr. Khachaturian.

DR. KHACHATURIAN: I am not quite clear about procedurally what we should do. I get the sense that we have been given quite a bit of lemons and being asked to make lemonade, and the question is I am not sure what is the best way to go about doing it.

We are being told there are two studies, and the question is whether an IND should be granted, and if an IND is granted, then, we also hear that they would be coming with an NDA, and if they come with the NDA, given the likelihood is it might not get approved. So the question is

what is the best strategy that we could use to solve a major problem, health problem that people are facing, what is the most expeditious way to proceed through where we could fulfill the requirements of the law for the IND.

My understanding is that there needs to be just sufficient evidence, and the question is do we have enough of that, at the same time, looking at the whole long-range implication of what is the best approach to take, so that this disease can be -- at least a treatment could come for this disease.

DR. TEMPLE: We think your first job is to tell us whether you think the evidence, those two studies looked at together, support, provide "sufficient" evidence --

DR. KHACHATURIAN: Couldn't we say just one is enough, throw the other one out, or are we obligated to look at both?

DR. TEMPLE: No, you don't have to reach the decision that way. You can look at them both, you can make your decision primarily on the basis of 1200 and merely concluded that 1202 doesn't cause you to think it is not sufficient anymore. You are completely flexible on that. There is very little track record, so you are very free.

It was our thought, though, that what you said about the studies could have some importance to everybody. So focus first on is there enough evidence, is it reasonable

to have a treatment IND, which could mean very substantial distribution, and you have heard from Monroe that they don't plan to charge. We don't address that question or actually care one way or the other.

(Maybe think about that first, and then we will get to the due diligence question, which is I think a very complicated question.)

DR. GILMAN: I would like to take it step by step actually, so I would like to hear the committee's view of Study 1200. Do you think that has provided good, clear evidence of an effect?

DR. KHACHATURIAN: Yes.

DR. GILMAN: Dr. Khachaturian, yes.

Dr. Kawas?

DR. KAWAS: Yes. Can I go ahead and comment?

DR. GILMAN: Please go ahead.

DR. KAWAS: To my mind, we have been told that substantial is two studies, and substantial is what is necessary for an IND which we are not --

DR. GILMAN: NDA.

DR. KAWAS: -- NDA, which we are not discussing today.

DR. GILMAN: Correct.

DR. KAWAS: So the question is, is one study sufficient, because I think I certainly feel that the OO

study is compelling information to suggest both efficacy and reasonable safety for this compound.

The second study, however, does not provide either to my mind. I am not convinced that there is efficacy in the second study, nor am I convinced that there is a difference in the mortality rates in the second study.

So for me personally, the second study is more non-informative rather than specifically negative.

So I feel that I personally have one study, and the only question I am not completely certain of in my mind is, is one study sufficient. I think that is sort of what we are going around here with, is one study sufficient for a treatment IND, and if we suggest that it is, to what extent will that decision continue over time is another question I have. That is not our worry.

DR. GILMAN: Let me try to respond to a couple of points you made. First, the matter of what is sufficient. I would think that if we view Study 1200 as demonstrating efficacy that is convincing to us, that that is enough. Even if we have a second study that doesn't show it, I would think in my mind that would be enough to show that there is sufficient evidence for an IND.

With respect to an NDA, that is not a question before us today. It is true that we have to think about what might happen in the future, nevertheless, we are not

being asked by the FDA to make any sort of statement about an NDA, only an IND today.

With respect to the issue of substantial equating to two trials, that is, do you need two trials for substantial evidence. I think the answer to that is no. I have in my time seen one trial come here and be approved.

Dr. Leber, you are not agreeing with that.

DR. LEBER: We have several people here, one more senior than I from the agency, but I think we usually say if you look at the law, under the current law, ordinarily more than one adequate and well-controlled is the standard.

There have been occasions, which Dr. Temple will be happy to review, but we have found the evidence from a single trial so overwhelmingly compelling, robust and consistent, that even though nominally a single trial, we have decided that it served the purpose of independent corroboration and replication, which is a scientific basis, I can't say enough about the legal history to know that it was the basis in law for the requirement that we have interpreted as being more than one.

As a general rule, under the FD&C Act. Now, if you are talking about a decision made under the Public Health Service Act that dealt with the biologic product, and I think you may be, betaseron?

DR. GILMAN: I am thinking of betaseron.

DR. LEBER: That is even more complicated because that Act, which began four years before the original Food and Drug law, has a slightly different set of wording and standard, and although we are moving toward I think a common standard, that was exceptional, and I wouldn't use betaseron as a precedent. It certainly happened, but -- and it was also an accelerated approval.

DR. TEMPLE: Accelerated has nothing to do with the number of studies.

DR. LEBER: No, but it was a factor in that decision.

DR. TEMPLE: I think you are actually saying the same thing, and the usual way we say it is you need two studies, but sometimes you don't.

DR. LEBER: But the fairness is what is the most common --

DR. TEMPLE: You are right, the usual reason is that the study is very powerful, has internal replication. There is some reason that makes you think you don't, and working on defining that is of some importance, but I think you are actually both saying the same thing.

DR. GILMAN: I think we should get back to the IND and what is before us today.

In the minds of the committee, is there sufficient evidence today? Does anybody else want to comment? Dr.

Coyle.

DR. COYLE: Well, as I have heard the evidence, I would think that 1200 seems to be a positive study, and 1202 seems to be a negative study, and that is a little bit of a problem for me with regard to potential NDA in the future, and I would urge the company to consider another clinical study.

DR. GILMAN: Dr. Zivin?

DR. ZIVIN: We have been discussing the 1200 study as being positive, and by standard statistical methods I suppose it probably is, but, in fact, it is really a very weak positive result.

I believe that the reason that the 1202 study is negative or at least not positive is because just by random chance when you have only a marginal effect, that it is logical to expect that the next time around you may very well miss just because of the weakness of the overall effect.

I am a bit disturbed to hear that there isn't really a good plan for additional research in this field, because as far as I am concerned, that is the purpose of an IND, and if the company has solid plans for doing that, then, I have less trouble with approving an IND, but if they don't, then, I don't know where we are going from here and maybe it's nowhere.

DR. GILMAN: Dr. Copple.

DR. COPPLE: I would concur with what Dr. Zivin said. It is semantic somewhat. I certainly agree there was an effect demonstrated in 1200, but I regard it as weak, not compelling or robust. 1202, I don't think there was any effect demonstrated, and I too would like to see a third study, because the bulk of the evidence taken in aggregate is negative with both studies.

DR. GILMAN: Dr. Adams?

DR. ADAMS: I think the issue that bothers me in both studies is mortality, yet, I understand the primary hypothesis is to halt progression. In the safety analysis, we were told that most of the deaths were due to the effects of ALS.

I am disappointed that we do not have an effect in a positive way in mortality, and in fact, in the European study a higher mortality presumably from ALS, which to me is a sign of progression. The patient died of the disease.

I would like -- and maybe it could still be done in the afternoon -- is somehow to look at the endpoint of death being equal to at least 115, and the vital capacity as evidence of an endpoint. If these patients are truly dying of the disease which we are trying to treat, to me, this is a very important endpoint and would greatly influence how I respond to the decision.

DR. GILMAN: Other comments about efficacy?

DR. TEMPLE: My understanding is we do know that endpoint for both studies, and for 1200 it doesn't make too much difference because the deaths are approximately evenly distributed, so it doesn't make much difference, and that for 1202, as we heard, the p value already not significant, gets higher because the deaths went slightly the wrong way.

I think we know. 1202 still doesn't look so good, and it doesn't affect 1200.

DR. GILMAN: Exactly. Any other comments about efficacy?

If not, let's move on to safety. Dr. Temple?

DR. TEMPLE: I guess I hear some disparate views about how enthusiastic one should be about 1200. I wonder if we could explore why people perceive it differently, just so we will understand it.

DR. GILMAN: All right. I saw it personally as convincing with respect to an effect in the measures used, which were the slope of decline and to me the effect was positive. It did not reverse the disease. It depends on what one means by a truly magnificent effect. This is not a magnificent effect. This slowed the decline to some extent. That is how I would phrase it. I wonder if other committee members want to comment.

DR. ZIVIN: One of the biggest problems that I had

with the design in both of these trials is the endpoint, and the reason I am comfortable with it is because I am not convinced that this is a logical way to evaluate the disease.

This type of rating scale is a conglomeration of a variety of things, which wasn't necessarily logically constructed for testing drug effect. It may have been quite useful for testing natural history, but I think that it complicates the interpretation of the data, because I think it increases, as a matter of fact, the variance by putting these various different things together.

This committee struggled quite a bit with the riluzole issue last year, and the reason that I believe it got approved at that time for an NDA was because it had a hard endpoint, which this one doesn't.

I am not trying to compare the relative merits of the two drugs. All I am trying to do is compare the relative merits of the trial design, and I believe that the riluzole trial design was superior.

DR. TEMPLE: If you can get a mortality endpoint, then, you get a mortality endpoint, but you don't always have to have a mortality endpoint, and if you don't expect one, what should you do? How should you measure it?

DR. ZIVIN: I wasn't expecting a mortality endpoint. I think that time-to-criterion endpoint is a more

logical way to approach this type of a problem.

DR. TEMPLE: Actually, that was successful, wasn't it?

DR. LEBER: I would like to ask Dr. Adams something. This is actually an issue that came up a long time ago. You obviously can get continuous measures on individuals, and therefore you can have everybody contributing to the data set.

If you look at events, time-to-events, only a fraction of the individuals randomized will contribute information that counts. So, generally, to do a time-to-event, where the event is fairly uncommon over the time of the trial, requires a much larger trial to generate enough events.

So generally a trial that is powered to look at a continuous measure, as this one was, will be underpowered with respect to the ultimate goal here, which is delaying death and delaying -- another thing might be in keeping you in a stage of the illness which is relatively mild and non-compromising if you are not changing death, and making the period of time you traverse the very bad portion of the disease very rapid, but keeping you as long as possible doing well.

Now, those would be reasonable things to do. Unfortunately, or fortunately, this sponsor has a right, and

as I told you earlier, to propose a treatment that is not for everything. Remember, we approve drugs for the claim made for the sponsor. So that is legitimate.

You have a right to say that is not an appropriate way -- that is what we struggled with dementia -- to evaluate a drug for this use, but as has been put, many experts in the field thought it was, and they did it.

I certain take your point, Dr. Zivin. It would be much nicer if trials were longer, so we could really know their ultimate effect in controlled trials on mortality and the staging of disease you were in, but as somebody pointed out earlier from the sponsor, that requires that patients be assigned in a randomized way to a treatment they don't want to be on for a long period of time. So there is no easy way out of this box.

We need to know what you think of this study as designed, and I think if you are going to say you don't believe that any trial that doesn't look at mortality should be relied upon -- is that your point, Dr. Zivin, or are you willing to settle for less?

DR. ZIVIN: Oh, I was willing to settle for less. I wasn't talking about mortality. They had a variety of reasons for censoring the patients, and they might be able to collect them together.

DR. GILMAN: Other comments?

DR. TEMPLE: Have we pinned down satisfactorily the nature of the difference? I hear some people saying, well, I am reasonably impressed with 1200, and other voices that say not so.

In addition to the slope score, which was the primary analysis, there was an endpoint score, and it was favorable, right? Am I remembering that correctly? Endpoints of score over 115 plus --

DR. LEBER: The first trial used a slope analysis, and the second trial changed at --

DR. TEMPLE: I know, but if you just look at people who drop out because they have reached an endpoint, a pulmonary endpoint, a 115 endpoint or death.

DR. LEBER: Those are, in a sense, not clinical trial endpoints. Those were safety reasons for withdrawing people because they couldn't measure them. They couldn't get them back to clinic.

I think if you look at the protocols, that is not what they said they were. It is in retrospect.

DR. GILMAN: Dr. Gennings.

DR. GENNINGS: I was just going to say I think it is important for us to realize and to remember that the 1200 trial did play the game correctly. I mean they had prospective endpoints, and they showed that -- whether or not you agreed with the choice of the endpoint -- they were

able to show significance on that endpoint.

Now, I think all of us would have liked to have seen bigger differences or more effects, but nevertheless, it was significant. 1202, unfortunately, was not that clear, and I think all the -- I will use the word "games" -- that were played to show a difference just sort of muddied the water. I think that 1202 is not very compelling at all, and I am weighing what I would think about efficacy on 1200 only.

DR. GILMAN: Dr. Snead.

DR. SNEAD: I would just like to reiterate the latter part of Justin's comment, because I know it is a major concern of mine, and that is I think that 1200 showed efficacy, I think that 1202 did not show efficacy, but the problem that I have is that the sponsor doesn't appear to have a plan for another trial, which in my mind is needed.

So if there is a treatment IND, is there going to be another trial or not?

DR. GILMAN: I am not sure that we need to know yes or no with respect to another trial if we believe the evidence before us suggests there is sufficient evidence for an IND.

DR. SNEAD: I had the impression from Dr. Leber that -- I guess the question I am asking is can we make that a caveat of our vote?

DR. LEBER: You are free to do anything you want.

DR. GILMAN: I believe the sponsor is here and is listening intently.

DR. SNEAD: Because I think that is a lot of our major concern at this table, quite frankly.

DR. GILMAN: Yes. Dr. Temple.

DR. TEMPLE: Just one point. As Monroe Klein said, you could argue that the fact that an NDA is coming in represents one version of due diligence. I don't want to try to settle that issue, but I wouldn't dismiss that argument.

So it may just be that the sponsor is entitled to do that -- I mean the sponsor is entitled to submit an NDA, and it may be that we would reach the conclusion that is due diligence for this purpose, but I, nonetheless, believe it is very helpful to hear what your view of the total data is and that that will prove helpful to all of us. So I think you are doing fine as far as this goes, and I don't think you have to worry too much about some of these things.

You are saying what you think, and I think that is fine.

DR. GILMAN: I have not heard anybody in the committee say that they think 1202 is a study that shows convincing benefit, and I guess what we doing now is trying to hear what people think about the quality or the extent of

the benefit in 1200. That is what Dr. Temple was asking us to express here. Can we continue? Anybody else want comment? Dr. Kawas.

DR. KAWAS: I will just answer Dr. Temple's question. The reasons why I think 1200 is a reasonably compelling study have to do with, first of all, the fact that the measures were defined ahead of time, and the study was carried forth according to the rules.

The endpoints, while I agree with Dr. Zivin, there is not a harder endpoint than point, but the fact of the matter is that many studies like this require clinical endpoints, and in fact, the study used multiple measures, most of which supported the fact that those patients in the 1200 trial did improve.

So the 1200 study is I think a positive study, but like most people here, I don't find the other study satisfactory for compelling evidence.

DR. GILMAN: Dr. Khachaturian.

DR. KHACHATURIAN: I agree with most things that were said about the 1200. My additional comment is that I look at the weakness of the effect attributed to perhaps the heterogeneity of the disease, that there are subsets perhaps that are far more beneficial than to others, and there is that phenomenon that we need to keep in mind. For that reason I would like to give the benefit of the doubt to 1200

and make sure that there is another trial done to prove it.

DR. GILMAN: Dr. Temple, have you heard enough?

DR. TEMPLE: Yes.

DR. GILMAN: Let's deal with the issue of safety then. In my own mind, there were no compelling reasons to believe that this is an unsafe drug, as we have heard today. We heard that there were many deaths. That is the expected in the course of this terrible disorder. I didn't hear any concern except for the mild side effects, and they were portrayed as a whole list of various abnormalities, symptoms, and some signs, but they are common in the course of amyotrophic lateral sclerosis.

So I didn't have particular safety concerns. Let me hear what the committee thought.

[No response.]

DR. GILMAN: Does silence mean approval or silent disapproval?

DR. ZIVIN: It means approval for me.

DR. GILMAN: I think at this point, unless anybody wants to hear more or speak more about this, we should then turn to the people who wish to speak.

**OPEN PUBLIC HEARING**

DR. GILMAN: The open public hearing is now in progress. Seventeen individuals have notified Mr. Bernstein ahead of time and requested time to comment in the open

public hearing.

When your name is called, please come forward to the microphone. We will use the microphone next to Dr. Temple. Identify yourself and your affiliation and begin your statement. Please limit your comments to five minutes or less.

Lynn Klein will read the statement for James Rather and Cary Green.

MS. LYNN KLEIN: Dr. Gilman, Dr. Leber, and members of the committee. My name is Lynn Klein and I am the Executive Vice President of the National Organization for Rare Disorders, most commonly known as NORD.

I am also a nurse and have been involved with ALS patients for over 16 years including nine years as Vice President of Patient Services for the ALS Association.

It is my honor and privilege to appear before you today on behalf of James Rather and Cary Green, two patients who were unable to make the trip down here, but very much wanted to testify.

I will start with Jim Rather. Before I read Jim's prepared testimony, I would like to take a minute to tell you a little bit about this inspiring man. James B. Rather is the husband of Amelia, father of Jim, Ebgenia, and John. He is a Vietnam veteran, an attorney, and a founding partner of a major law firm in New York, the latter after he was

diagnosed with ALS.

He has handled a wide range of cases including commercial, environmental, product liability, employment, and discrimination litigation. Jim told me his favorite work was when he was Assistant United States Attorney for the Southern District of New York, where he tried numerous cases including organized crime, corruption, fraud, and RICO prosecutions.

Among his prosecutions was the conviction of a major organized crime boss and 10 of his associates for violations of the Racketeering Influenced and Corrupt Organizations Act, RICO.

Jim has faced the violations and indignities of ALS with the same strength and confidence and courage he faced organized crime. Jim is still working as an attorney, often spending all day in court.

I almost forgot to mention Jim is on life support, has a feeding tube, and speaks via a computer with a voice synthesizer. He is also the recipient of the Muscular Dystrophy Association's Personal Achievement Award among many others.

Now for Jim's testimony.

My name is Jim Rather. I have been afflicted with ALS since spring 1990. I regret that I am unable to speak to you in person, but am thankful for the opportunity to

address you through Lynn Klein.

In my youth I saw the excellent movie Pride of the Yankees about the great Lou Gehrig who was brought down by ALS in the year of my birth 1939. A scene that made a lasting impression on me then, and has come back to haunt me since, was of the kindly, sympathetic doctor telling a gracious and stoic Lou Gehrig that there was no cure for his disease. No cure.

At the time it seemed impossible to me, and it still does, although I have been witness to several hundred courageous lives cut tragically short by this most mysterious and most dreaded of diseases.

I never heard those draconian words from my kindly and sympathetic doctor, Louis Rowlin, head of the Neurological Institute at Columbia Presbyterian, but I well remember the day I first understood my sentence. I literally saw stars and my mind seemed to explode within my head.

ALS has a way of sneaking up on people. It enters the body innocently and imperceptibly and seems no cause for alarm. In my case, it struck in my left foot and I was just aware of less spring in that foot. If I had not been a long-distance runner, I might not have noticed that.

I had little concern and expected it to improve with some chiropractic adjustments. I lived on in sublime

innocence. But of course there was no improvement.

A year later it had extended up my left leg and to my right foot and leg. I had run my last marathon and wondered why I had been so slow and out of breath. Initial tests were negative for anything.

When I had my first EMG, the doctor could not conceal his concerned expression. He suggested more tests. His report stated the possibility of "motor neuron disease." I began to read some medical texts and gradually eliminated less serious conditions.

One day -- and it was one day -- it all came together and I knew I had Lou Gehrig's disease. What I could not believe was the description contained in every neurological textbook, no cure, and three to five years to live.

I read and read looking for a way out. I thought there had to be a solution. I had always found a solution to serious events. As a combat airborne infantry platoon leader, I had always found a solution and survived to tell about it. As a federal criminal prosecutor, I had always found the solution necessary to put the felons away. There had to be a solution, I thought, there is something for every disease even cancer. But there was nothing for ALS.

I decided to keep the diagnosis to myself, I just could not tell my wife. I wanted life for her and our three

children to remain normal for as long as possible. Nor did I want my four new law partners to be concerned about me during the precarious start of our fledgling law firm.

I told everyone it was some kind of neuropathy and it would soon stop bothering me. As ALS progressed, it became clear to me no cure and the unvarying sentence death in three to five years. These words haunted me every night at every moment. I felt happiness whenever my children spoke of their futures. It seemed impossible, but the ALS relentlessly progressed.

There was one glimmer of hope during that period. It was called Eldepryl, and I was in the clinical trial of the Eleanor and Lou Gehrig Clinic at Columbia Presbyterian. What a difference that small pill made. I believed it was helping, and to this day I believe it may have helped slow progression. It was my lifesaver because I felt it was doing something that might help.

When I finally faced that indescribably terrible day of telling my family, I was able to couch it with the possibility of hope. When I learned of the IGF-1 Myotrophin clinical trial, I believed it was even more excitingly hopeful than Eldepryl. I certainly was prepared to accept any risk, any risk, where there was hope to possibly retard or reverse this disease that was devastating my body at an ever-increasing pace, but I did not qualify due to my low

vital capacity.

Death did come for me, on schedule, in December 1994, however, my departure was deferred by my choice to remain alive with a feeding tube and a ventilator. It was not an easy decision and many do not choose to live this way, but I still have a strong desire to stay here with my family and try to help in an effort to find a cure. Yet, ALS is relentlessly continuing to destroy my remaining functions.

I have lost the ability to breathe, to eat, to speak, and to hug. Even my smile is fading. I have been through every state of this devastating disease, yet continue to hope that my condition may be ameliorated.

A great hope for me now, for all of us with ALS and our families and loved ones, is the potential of Myotrophin. I am in almost daily contact with the ALS community throughout the country by computer and know the great hope engendered by the potential of Myotrophin.

We see to you let us have our hope. It does not have to be with risk. We measure our lives in days, weeks, or months. We ask for you to help us give hope for one more day without delay.

We deeply appreciate the care and concern of this committee. We know you will carefully consider all the factors. We urge you to recommend early access for this

most hopeful of drugs, Myotrophin.

Respectfully submitted, James Rather.

DR. GILMAN: Thank you, Ms. Klein.

MS. KLEIN: I had the second one that I was to read.

DR. GILMAN: You have one minute left.

MS. KLEIN: Cary Green.

DR. GILMAN: Please.

MS. KLEIN: I don't know Cary personally, but I have spoken with him. He has been forced into retirement and he now spends his days watching his brother do his favorite hobby, and that is fishing.

My name is Cary Green. I am 42 years old and was diagnosed with ALS in June of 1993 at the age of 39. I have developed symptoms beginning with my right hand about a year prior to being diagnosed.

I have three children, ages 17, 15, and 13, who live with my wife in East Hampton, Connecticut. Although I have limited use of my hands and arms, I can still walk with some difficulty. I still live independently with the help of family, friends, and a home health aide. My speech has most recently become affected. I am well aware that the progression of my disease has been slower than most. For that I am grateful, for it gives me precious time to spend with my children.

I can without question attribute this slow progression in large part to the drug Myotrophin produced by Cephalon. I am in the singular position of having more experience with Myotrophin as a patient than almost anyone else in the world.

I was the first participant in the Myotrophin drug study at the University of Connecticut Health Center in August 1993. When the study ended and the results were announced in June of '95, I learned I had been on full doses of the drug for the entire 18 months of the study.

Subsequent to February '95, when I was no longer receiving Myotrophin, my deterioration became increasingly rapid and frightening. The pace at which I was losing hand, arm, and leg function was readily apparent to all who knew me. Each week I could measure my loss of strength and energy.

I was forced to retire from my work as CFO of a large company in October '95. By January '96, I was no longer able to dress or feed myself. It was obvious to me that Myotrophin dramatically slowed the pace of my deterioration and I was naturally anxious to get back on the drug.

I lobbied extensively with University of Connecticut, Cephalon, and the FDA to restart the program and release the drug for compassionate use. Although my

friends and family couldn't understand the delay, I soon learned and accepted the complexities inherent in the process. Finally, after much frustration with misleading information, the restart program was approved and I once again start receiving the drug in February '96.

I was told that had I not made the efforts I did, the program, at least at the University of Connecticut, would not have been revived.

After being on the drug again for four months, I have noticed my deterioration has once again slowed. Although it is in no way getting easier to live with ALS, I am able to do things now that I never thought I would be able to do given the pace at which I had been previously deteriorating.

It has given my friends, family, and myself renewed hope in an otherwise hopeless situation. It is extremely important to note that after taking Myotrophin for almost two years, I have had no adverse side effects. Concern with side effects with a disease as insidious as ALS should, in my opinion, have reduced focus anyway.

Realistically, all one can hope for is a few extra days of quality life. If, by releasing this drug on a compassionate use basis, the FDA has the opportunity to offer this gift to other ALS sufferers, it would be inhumane not to do so.

Respectfully submitted, Cary Green.

Thank you.

DR. GILMAN: Thank you.

Janice Dorfman, please.

MS. JANICE DORFMAN: My name is Janice Dorfman. I am very grateful for the opportunity to be here today speaking for myself and 30,000 known Americans suffering from ALS.

Each of us has a story to tell, the story of how our lives and the lives of those who love us were forever changed. The details are different, but the story tells of a past that held a promise of a future. For me it was the invitation of my beloved husband, grow old with me, the best is yet to be.

But it was not to be. ALS, like a thief, robbed me of a future, made the past too painful to revisit and the present a day to day existence on which I am dependent on a caregiver to provide all physical needs, such as bathing, toileting, dressing, and feeding. My young adult son toilets me, my elderly parents feed me 50 years after we began that way.

My husband maintains a full time job out of the home and manages all household responsibilities in addition to caring for me. My ALS friends and I have no illusion about our future. Without intervention, early death is

certain.

When Myotrophin was first considered for approval, I was able to stand, to walk, and to speak without impairment. Anything that slows the daily loss of function by this dread demon of disease must be made accessible to patients on a fast track regardless of the risk involved.

Dr. Kessler himself has said that the greater the risk, the greater the benefit. The light of hope provided by Myotrophin gives us back the future, the promise of a future. For those in the early stages of disease, it means being able to maintain independence longer, being able to use arms to hug the kids a while longer.

For me, I know I won't be able to walk down the aisle at my son's wedding, but I want to be there. I won't be able to find my daughter's first child, but I want to see my beautiful grandchildren. I want to say to my beloved, grow a little older with me. Having this time is a gift.

Please, give us the gift of time. Give us the promise of a future. Give us the light of hope. Give us early access to Myotrophin.

Thank you.

DR. GILMAN: Thank you.

Next is Mary Beth Parks.

MS. MARY BETH PARKS: Good afternoon. My name is Mary Beth Parks. By profession I am a nurse and I am the

owner of Gulf Coast Medical Personnel in Houston, Texas.

Gulf Coast Medical Personnel is a home health agency that specializes in the care of ALS patients. Since 1983, I have had day to day contact with ALS patients.

ALS is a family disease. It may only affect one person physically, but it affects the entire family including the extended family of friends and colleagues.

It is a disease that leaves us all with a feeling of powerlessness since the cause and cure remain unknown. The treatment has been aimed at managing the symptoms, assisting the patient to remain as independent as possible for as long as possible with dignity and quality of life.

ALS is commonly known as Lou Gehrig's disease or, what some people say, Stephen Hawkins has. I know ALS as Jim Martin disease. After a five-year battle with ALS, Jim, age 36, lived just short of two weeks after holding his first child.

Or William Gray, an Exxon executive, who discovered his ALS while training for his third triathlon. ALS has also claimed my lovely Lydia, who was a county clerk in Brezoria, Texas for 33 years, suffered the initial symptoms of tremors in her hands, and eventually was locked in entirely except for the slight eye blink.

There is one thing that ALS cannot take away from these patients, and that is hope, hope that medical science

will find the answers in their lifetime, hope that drug companies will take the risk and join the fight, and achieve success in developing a treatment that will have some effect in altering the course of ALS.

This is not about analyzing data, this is about patients living longer and having a better quality of life, and so, members of the committee, today you have the opportunity to recommend early access to Myotrophin for the treatment of this hideous disease.

In the words of Atouchette Dish, "I implore you, I shall pass through this world but once. If therefore there be any good I can do, let me do it now. Do not defer it, do not neglect it, for I shall pass this way but once."

This your chance. Thank you.

DR. GILMAN: Thank you.

Next is Linda McKnight.

MS. LINDA McKNIGHT: Good afternoon, ladies and gentlemen. Please allow me to introduce myself. I am Linda McKnight from Seattle, Washington area.

I lost a wonderful sister to this monstrous disease. Since that time, almost four years ago, I have worked extensively with ALS patients across the United States, Canada, and Europe. I am here to speak on behalf of thousands of Americans, the ALS afflicted, their families and their loved ones.

It is not my role nor do I have the expertise to address safety and efficacy, but if I could, there is one more thing I would include in there, and that would be the need for this drug. I think that is equally as important as the two other items, and I think Myotrophin is the drug that we all believe could help many people with ALS to fight for a longer and better life.

When I first heard of this disease, I was only told half-truths. I was told it was a disease that paralyzes the muscles of the body, and I am sure that you are familiar with this. But that wasn't the whole story I found out later. It also paralyzes emotions, futures, and dreams of all of its victims. It paralyzes what we call life.

As I look at you, each of you around this table, I see the same needs that an ALS person has or any human beings have. I see you want to see your family grow to adulthood, to share the joys, the triumphs, and even the disappointments of their lives.

It doesn't matter what age ALS strikes. To each age we have our own private dreams and reasons to continue our lives. To be able to share these moments is what it is all about.

It is not just the people you see around me here today. It is the thousands of ALS patients spread all

across America. They are so immobile or without speech that they could not be before you today to express what they wanted you to hear. They wanted so bad to be heard.

I had calls from all over America from the people that knew I was going to be at this meeting today, pleading with you that you would hear the message that is sent to you today.

I promised each one of them, yes, they are going to be heard today, because I packed every one of them in my heart and I promised each one of them that, that I would speak to you, but it is your voices that they are hearing today. Each one of them stand before you.

It is my heartfelt hope that you would take the great consideration, the right of ALS patients to make choices. That has been so denied ALS patients for over a century. All they want is the right of choice. Their physical sense may be in array, but they and their physicians are 100 percent capable of making these informed choices that so affect their future and control of their own bodies within this life struggle.

Ladies and gentlemen, because ALS is a smaller population disease, it is overlooked by so many of the drug companies. I so respect and applaud every step that Cephalon has put forth for all ALS patients to bring this drug before you today.

I fully realize what these trials entail and without them we would be lost forever to this devastating disease. I thank you, Cephalon, from all the patients across America. Thank you.

One thing that I didn't have, that I was going to say to you, and it happened to me last night. We had a dinner and at the dinner a patient walked up to me and handed me a picture of his two little children. Somehow with my travels in the ALS community I guess I kind of lost track of the fact I was so involved that it was a patient and give help to the patient, that somehow I had forgotten the children of all these patients.

So this meeting isn't just about the patient, it is about the children. Give them a choice also to have their parents be with them and to do things with them, because it is about the children of these patients, too.

Also, I talked at length, about an hour and a half, just before I caught the airplane, which was real early a patient called that had been on the Myotrophin trial. He has been on the trial since the beginning of it, and he mentioned to me, he said, Linda, he said you have got to do something, you have got to let these people know that if it wasn't for the Myotrophin, I wouldn't be talking to you right now, and I feel in my heart that is the only reason why I am talking to you is because of Myotrophin.

So if you find that this drug in any way may in any little way may be effective, these people want so much this option of choice.

Yes, I realize that there are many variances in any drugs, but I carry the belief along with patients within my heart today that many are willing to take a greater step for a drug if a potential of even just a touch of benefit is there.

Ladies and gentlemen, we look towards this panel to give the ALS community the availability of that choice.

Thank you from all of us for your time and patience.

DR. GILMAN: Thank you.

Don Altier.

MR. DON ALTIER: I was asking Linda if you had all gotten a picture like the one I showed Linda last night of me and my sons.

My name is Don Altier. I am 36 years old and I have ALS. I have traveled across the country to ask for your help in my battle to live each day God gives me as fully as possible. I was diagnosed with ALS on October 13, 1992, one day after my wife Carrie and I found out that we were expecting twins.

My wife and I had long looked forward to being parents. From the time I was a young boy I had always

wanted to be a daddy. We were both thrilled to find out she was going to have twins. Only 24 hours later, we were devastated by the prospect of my impending paralysis and ultimate death as predicted by the diagnosis of Lou Gehrig's disease.

We were both only 32 years old and had just found out our dream of being parents had come true and now we were being faced with the nightmare of my having a terminal illness with no known cause of available treatment.

I sought out hope even though the situation appeared to be hopeless. Our unborn twins cried out to be from my wife's womb don't give up on us, daddy, don't give up.

One doctor advised us that this was no time to be having a baby. I advised him that we were going to have twins and that furthermore I was going to find a way to win my battle with ALS.

My research led me to late Dr. Forbes Norris, a renowned ALS specialist who was involved with a clinical trial of IGF-1. There was hope. Due to the fact that my disease progression was slow, however, I did not qualify for the Myotrophin study.

I was able to participate in another clinical trial for CNTF. Unfortunately, I got placebo for a nine month double-blind period. After one year on open label, I

was told that CNTF had not shown efficacy. I take Eldepryl, neurontin, lots of vitamins, practice yoga, and pray for the strength and wisdom to make it through another day smiling despite the muscle and joint pain that is constantly trying to get me to give up. Every day is a victory.

Being able to see my sons' birth and to hold them and give them their first bottles was a miracle I will never forget. On May 13th, we celebrated Trevor and Brian's third birthday. We have been constant companions since the moment they were born.

My wife works full time and I stay home and take care of them, and I hope that I will be able to do that for a long time. They have filled our lives with their joy, their innocence, and their endless love of live. They have given me the inspiration to fight, to live and love life with an energy that I did not know I ever possessed.

Sometimes I am overwhelmed by how hard simple tasks become as ALS progresses, and I say to my wife 'I have had enough, I give up. She replies look your sons in the eye and say that, and I immediately realize that giving up is not an option for me.

Today, when you cast your vote, look at the picture of me and my sons' smiling faces, and I believe you will decide you cannot give up on us. Remember, there are thousands of families like ours waiting for anything that

will help ALS victims stronger and more independent.

I will accommodate this disease, but I will never surrender to it.

ALS patients have had patience enough. It is time to take the next step towards defeating ALS and approve a drug shown to be safe and effective in slowing down the muscle weakness that plagues those affected by Lou Gehrig's disease.

Many people have said to me since my diagnosis that they wish there was something they could do to help. Today, you have the opportunity to do something. By helping to reduce the rate of progression, Myotrophin can help us battling ALS, to hug a loved one for longer, to be able to play with our children, to enjoy the simple pleasures that most take for granted, eating, talking, and breathing for a bit longer is all we are asking for.

All we are saying is give us a chance. Let's put Dr. Kevorkian on terminal hold by giving people with ALS and their families hope. Suicide is not the solution to ALS. Access to effective drugs is the key part of keeping us alive and full of hope to await the next breakthrough in ALS.

We are fighting this disease with all our will and spirit. We are counting on you to fight for us, too.

In the words of Dr. David Kessler, Commissioner of

the FDA, as quoted in Newsday, March 1st, 1994, "When people are suffering and dying from a devastating disease, we cannot wait for all the evidence to come in, for all the i's to be dotted and all the t's crossed. We must be prepared to accept greater risk from a drug when greater benefits are possible.

I am here today to cross a t for my son Trevor, give you a B for my son Brian, and a C for my wife Carrie, and lastly, to dot an i for all the eyes focused on the hope that today the next step towards a cure for ALS will be taken.

On behalf of all the ALS families fighting for hope, I thank you for your compassionate consideration of our situation.

DR. GILMAN: Thank you.

Ben Gill, please.

MR. BENJAMIN GILL: Ladies and gentlemen, my name is Benjamin Gill. My speech is slow and tortured. I will focus on two issues, time and hope.

I was diagnosed with ALS two and half years ago. ALS patients understand the relentless, progressive nature of this disease. We know well that in the next several years or less, several of us here today will not be here.

Will there be time, will medicine provide the answer to ALS in our lifetimes? We do not have the answers

to such questions, but all of us have hope. Hope is the most precious possession of an ALS patient. That is why we are here today, hope.

Last summer, the FDA approved access to riluzole. I was a lucky one out of the lottery to receive this drug while the approval process continued.

I started Rilutek in October and continue it today. Rilutek has been of modest benefit for ALS patients and we know that your decision was a close one. I submit modest is a relative term, particularly to an ALS patient who can find hope in many small things including a drug that might retard progression of the disease, a drug which researchers may find even more definitive benefits, and a drug that with other drugs may be the combination that actually arrests progression. That, I submit is real hope.

It also buys time. Even if Myotrophin only has mild benefits, has only several months, those extra months of modest treatment may allow parents to share a little bit mortality of a child's life, may enable an individual to enjoy a few more good days on this earth. You can't measure that.

Quite frankly, unless you know today that Myotrophin is a fraud or is unsafe, the decision on early access should be made. The manufacturers are willing to make it available, and it has demonstrated some positive

characteristics in dealing with ALS. It provides hope and may well provide additional time to ALS patients. There is no doubts on it.

But you may say the FDA does not want to raise false hopes among ALS patients and that you wish to protect us. I submit that we are experts in the category of realistic hope. We know Myotrophin is not a magic bullet. We know it may end up providing only modest benefits or non-robust benefits.

We accept that as a risk, are more than willing to take those risks for giving a potential reward involved.

[Portion not understandable.]

That is not a false hope, but rather a rational request for immediate action. I would be remiss if I didn't take this opportunity to also request the FDA to immediately adopt new criteria that will allow for expedited approval.

Thank you for your attention.

DR. GILMAN: Thank you, Mr. Gill.

Christopher Pendergast.

MR. CHRISTOPHER PENDERGAST: My name is Chris Pendergast and I have come here to address this distinguished panel, to present the perspectives of a 32-month combatant of the war on amyotrophic lateral sclerosis.

I am in the front lines, down in the trenches, and fighting like hell for my life. Though perhaps I might be

already mortally wounded, I have refused to yield.

I, as well as 30,000 fellow Americans, have been called to do battle with this horrific, seemingly invincible and damnable foe and battle we will. We will challenge it on every front. Some of those challenges will be poignantly personal as we come to terms with living with ALS, and some of those challenges will be very public, as is this forum today.

The battle is intense and the time is bitterly short, but before I succumb to this monster, I will do everything in my power to see it defeated. I will not go lightly and I will not go quietly.

So I stand here before you today because by the grace of God I can still stand. I can plant my two feet firmly in front of you and I can stand up and I can ask to be counted. I am talking to you today because by that same grace, I have a voice that can still be heard.

I have not yet been silenced and therefore I can be a clarion and cry loudly and clearly our unified appeal. You realize, of course, that I am a lucky one. I know not why, but I am. There were four patients who began this struggle with me two and a half years ago. We were a group knotted in hope and in fear into a support session. They are all dead.

Their names I shall forever remember: John

McPartland, Ronald Lichtenberg, Pat Stevens, and just last month, the last member of our group, Paula Shefrigo.

Since my diagnosis on Columbus Day in 1993, perhaps 15,000 others have died. Going all the way back to Lou Gehrig himself, felled in less than two years in the prime of his life, at 37, perhaps 300,000 have died.

Who have lamented their passing except our own tiny band? Who marshaled energy in support for them? Nobody. How can I let these fallen friends be forgotten? They had no voice, they had no mass protests, they had no media focus. They had no stamps. Instead, they had obscurity and benign neglect.

What have we done to deserve this disease or what have we done to develop it? We relentlessly recall each detail of our own lives searching for answers. Did we innocently expose ourselves to toxins, are we victimized by pesticides or attacked by a slow-acting virus?

Is it genetically coded? Do we have faulty immune systems? Ah, like so many other top killers, heart disease, lung cancer, and AIDS, mostly they result from lifestyle choices, and they could be nearly eradicated with a change in those choices. Oh, if we only had that choice. But no, our sufferers slip into their graves hushed in silence and despair, and their numbers are only medical enigmas.

But no more, never again. I am here for them. I

am also here for the person who is going to die in the next 90 minutes as we deliberate, and that person who will die 90 minutes thereafter, day in and day out.

I am here, too, for the 6,000 who will be diagnosed this year. But be clear, I am not here as a statistic, I am a vital human being. I am your neighbor. I am your child's teacher. I am a volunteer naturalist. I am the gentleman at the end of the two at church.

I want you of the panel to look at my face and to see me. I am real. When this disease kills, it doesn't kill a number, it kills me. We are not just case numbers or a data point on a statistical curve. We have faces, we have names, and we have families who love us, and we have jobs left unfinished, gardens that wasted hands can no longer till, children to lift but arms too weak, paths to journey but legs unable to bear, voices to sing, songs to sing, but voices too frail.

We have breaths to breathe and lungs and chests too weak to draw. Look at my face and see us all. We have suffered and we have died tormented. No cures, not even potent treatment, absolutely nothing. How much longer we ask.

Well, you might say this has been an unparalleled period of research and pharmacological activity. Research, regulatory agencies, medical communities are working hard to

conquer ALS, and this may be so. But who here would deny me if I held up that glass with water at the midpoint, and I claimed it to be half empty even though we both knew it was also half full.

And similarly, who can deny me that we have done too little too late? It is too late for my friends back at the support group, it is too late for that person dying this 90 minute, and it may well be too late for me.

Yet, before you again is a compound that holds promise in intervening in this disease process. You have the statistics, and the scientific studies, black and white tables, plots of curves are there in front of you on that paper.

But let me ask you, is my picture there with them? Do you see my 11-year-old son held tightly in my arms after he has won a hockey game? Do you see my 19-year-old daughter and I walking proudly arm and arm as she graduates college next year?

I am those numbers, those charts, those statistically significant data, that is my life. Don't we have a right to ask then, are we too impertinent to want? Can't we be so bold as to wish?

You have the most difficult task. You are a regulator, and you must assess and protect. A better medication for an ingrown toenail, a quicker removal of

warts, or something Americans have been waiting for, a cure to baldness.

Well, then yes, regulate us, assess us, do strict objective, hard science, but, panelists, this, this is a medication for ALS. Where will the balance lie and how tightly are you willing to walk that rope?

Let us be part of this solution. Let us continue to have use of the medication. Give us access to a promising compound. If there is reasonable belief in its efficacy, don't hold it back in bureaucratic limbo while we endure a living hell.

What else is there for ALS sufferers, pages of regulations and justifications?

I said earlier we will fight. Put a weapon in our hands. Access hope and promise.

I want to conclude with a brief metaphor using baseball. Just as Lou Gehrig did for over 2,000 games, each one of us is in our own batter's box, and the count is 3 to 2, 3 balls and 2 strikes. It is the last inning, the last game, it is the end of our career. And, distinguished panelists, you are our umpires at home plate.

We have one pitch left. It all comes down to this. Let me swing at that last ball. Please don't call me out on a questionable strike. Don't make me stand there at home plate with my bat slung idly over my shoulders. Don't

end up as I have to passively watch that ball zoom by.

Let me home run. Let me strike out. If I must go down, then, I will, but in heaven's name, please, let me go down swinging.

I want to thank you in advance of your decision.

DR. GILMAN: Thank you. I believe we have an hour for the open hearing, so please limit your comments to five minutes.

Dee Holden Norris.

MRS. DEE HOLDEN NORRIS: After such eloquence, it may be hard to follow.

I am Dee Holden Norris. I am an R.N. and the Executive Director of the ALS Research Foundation in San Francisco, a nonprofit medical research foundation which I co-founded with my late husband, Dr. Forbes Norris, a neurologist some of you on this panel may have known.

I was involved with my husband for over 20 years and remain actively involved with literally every aspect of ALS, the scientific research, the clinical management, the health care, the educational and patient services program which continue at the Forbes Norris, M.D.A. ALS Research Center.

Some of you who may have known of my husband knew of his long-time efforts and diligence in pioneering some of the early scientific research in this disease, but most

especially in the later years of his advocacy for aggressive clinical management and intervention to alleviate the major degrading symptoms associated with increasing paralysis and muscle wasting, the hallmark of this disease.

I am pleased to say that this philosophy of active symptomatic management has come to be more and more accepted and advocated by the ALS medical community and will probably be my husband's legacy.

He resorted to these efforts out of a compassion and desperation because there was nothing else to offer until now. Patients were, and are, given this diagnosis as an automatic death sentence. They were old that there was nothing that could be done, so go home, take care of yourself, and, by the way, you had better stop off at your lawyer's office and write your will because you are going to be dead in three to five years. But before that happens, you are going to progressively become paralyzed, wind up in a wheelchair, unable to move your arms or legs, hold up your head, or scratch your nose, gradually losing your ability to speak or chew or swallow, and you will start choking on your own saliva and lose your ability to cough or even to take a deep breath.

All the while you will remain perfectly alert and aware of yourself, your body, and everyone around you. cognizant of your increasing entrapment and impending death,

cognizant that you have become a major financial and laborious burden to your family, cognizant that your physician, not wanting to deal with the daily horrible dilemmas and the mundane problems, knowing full well that he or she has nothing else to offer, generally doesn't.

To a healthy man or woman who has never been sick a day in their lives, who is active, successful, and leading a healthful, family-oriented life, this is an all unacceptable, unbelievable, immeasurably horrible, and the ultimate demeaning indignity.

For the physician, the nurse, the caretaker who must hold these people's hands and watch helplessly as this inexorable process occurs, this is the ultimate nightmare.

Thank God, at last we are entering a new era when this all too frequent, dismal scenario of utter helplessness and hopelessness is changing. With your insistence on an approval today for a treatment IND for Myotrophin, the first we hope of several possibly helpful drugs to stem the mercilessly relentless, downhill course of this scourge, we can for the first time look these patients in the eye and say that even though we don't have a cure, we can offer something that gives a glimmer of hope for living with ALS until we can find the cause and most importantly the cure for this disease.

We who have working for so long and so hard in

what my husband called the dark hole of ALS, and most importantly, these desperate people who live and are dying in that dark hole, who have never had anything to offer them hope before, need this drug. They deserve this drug, and they demand this drug.

I ask on their and our behalf that you give immediate approval to this IND for Myotrophin.

Thank you.

DR. GILMAN: Thank you.

David Coleman.

MS. SUSAN GRAHN: My name is Susan Grahn, and I am speaking for David as he can no longer speak.

Dear Members of the Committee: On February of 1995, I began to have speaking problems. I went to my family doctor who sent me to a neurologist. After several tests that included an MRI of the brain and a spinal tap for Lyme disease, and other related diseases, and after everything else was eliminated, it was determined that I had amyotrophic lateral sclerosis or ALS.

It was in May of 1995 that I was informed that I was diagnosed with ALS. Since that time, my life as I knew it has changed in many ways. I can no longer dress myself, walk freely, swallow solid foods, drink liquids, or speak. I own my own business, which is a construction company, which took many years to build, and I can no longer run that

either.

In December of 1995, I entered the hospital for a period of time to have a tracheostomy and a feeding tube put in. I could not clear my throat any longer and the phlegm was blocking off the airway. The feeding tube was to get the nutrients into my system that I so desperately needed.

I have the bulbar form of ALS which affects the muscles of the throat first and very slowly spreads to the rest of the body. I have been told that I have two to five years to live from last May. I think with that kind of fatality rate, someone has to come up with a cure.

I have personally known three people that have died from ALS. While I have participated in the Rilutek drug study and continue to take the drug today, the life expectancy, as I understand it, is an additional three months. This is very little compared to a lifetime of hope and dreams.

I would just like to say that I have been dating David for two years now, the second year dealing with disease. He was a very strong man one year ago, but he still remains strong inside. That strength keeps me going.

A lot of people say to me you have to look out for yourself, Susan, you have to think about yourself, and I just think when do we think about others. I think we need to think about others and help them fight for their life.

If you have something that can help, I hope you will give it to them.

David has typed out one sentence. Well, he was going to type out "Please help us."

Thank you.

DR. GILMAN: Thank you.

Steven Stricter.

MR. STEVEN STRICTER: Boy, it is going to tough to follow all the eloquence and sincerity that I have heard this afternoon.

My name is Steve Stricter. I am from near Trenton, New Jersey. I would like to say that I am very impressed with the level of expertise that I have heard in the discussions today in the fields of medicine, pharmacology, philosophy, statistics, and I am also very impressed with the dedication of the developers of this medication, and I am very impressed with the families and fellow patients, and I have to applaud everything that I have heard so far.

[Applause.]

As for myself, now I have got to get to the written form. I am 53 years old and I live near Trenton. I have a lovely wife Judy in the audience and two kids, six adorable grandkids. I was the part owner of a small business, a very skilled worker in my time in my line of

work.

My wife and I have traveled extensively throughout the U.S., Canada, Mexico. We have been to the Holy Land, to Europe, Australia, many other fun spots and sun spots. I have enjoyed and been satisfied with all of the above, and I certainly am not ready and willing to give it all up.

But something entered my life recently which has started to turn my life upside-down and screwy, and that is something is ALS. I was first diagnosed with this impediment to my happiness in July of 1993.

It started with a weakness in my hands and arms, kind of clumsiness that I had never experienced before. From all the information I could gather three years ago, the disease might lead to the ultimate unhappiness, my death, in about five years, the average life left after the initial diagnosis.

The progression of the disease in my case has been fairly slow and still concentrated in my upper limbs. I have had to quit working at this point and travel is not the easy fun that it was when I was younger, but I sure don't want to give up the good times with my wife, the kids, the grandchildren, and family members and friends.

I was hoping that maybe I could pop a pill and my symptoms would just go away, but it is not that easy. Thanks to the research and development efforts over the last

few years, there are a few drugs which may show some promise in slowing the progression of the disease, and I am presently taking one of these drugs, Rilutek, which became available to me under an early access program.

I am hoping that that drug is effective in slowing the advance of the disease. I urge that the same early and expanded access availability be afforded to patients that my be helped by taking Myotrophin. When precious little time is left in one's life, it is a matter of great urgency to have access to whatever tools may become available to treat the disease and that as many people have access to the drugs as soon as the research deems that it is safe to take these drugs.

I dread facing the inevitability of what lies in store for me and not being able to enjoy the good things that life has to offer. My hope is that the drugs that may offer increased efficacy will soon be developed and that they will be made available to patients like myself.

I thank you very much for the opportunity.

DR. GILMAN: Thank you, Mr. Stricter.

Joseph Polizzi.

MR. JOSEPH POLIZZI: Hello. My name is Joe Polizzi. I am from Philadelphia. I was diagnosed three and a half years ago, and my doctor told me the same thing he told everybody else, three to five.

Well, he also told me something about Myotrophin, and he put a little bit of wind in my sails. I have been on Myotrophin exactly three years, and truthfully, I think it helped. Otherwise -- I have been in this chariot for three months. It is no fun.

I am going to be short, but try not to take the wind out of my sails. Okay?

Thank you.

DR. GILMAN: Thank you, sir.

Karen and Fred Micale, Jr.

MR. FRANK MICALE: Good afternoon. My name is Frank Micale and I am here today with my wife Karen. I would personally like to thank Cephalon and the Greater Philadelphia ALS Chapter for extending to me this opportunity to speak to you today.

I was diagnosed with limb onset ALS on July 12, 1995. Since then, Karen and I have struggled immensely in dealing with this disease while at the same time trying to keep our family's daily routine as normal as possible.

At the time, our daughter Lauren was 9 and our son Christopher was 3. One of the hardest things we had to do was to go home and finally explain to our daughter what was wrong with me. After Karen told Lauren in very simplistic terms what ALS was, she responded in a positive youthful manner and said, "But dad can just take medicine from the

doctors to help him get better," to which Karen had to respond, at the time, "But there isn't any medicine dad can take to make him better."

Receiving the diagnosis of ALS with all its implications is very devastating. To further be told that there is no treatment at the time was even worse. Since then, as most of you know, we have seen the approval of riluzole. Even so it is hard to accept that in this age of advanced science and technology, there is only one drug for the treatment of a disease that was first identified 127 years ago.

In our lifetime alone, we have seen the rewards of pharmaceutical intervention. Karen has been a registered nurse for 17 years. She experiences first-hand in the hospital setting the benefits of dedicated research and development as newer and safer drugs are introduced and older drugs are improved upon or replaced for the treatment of chronic diseases and life-threatening illnesses including cancer and AIDS.

For most ALS patients and families, it is a truly helpless and frustrating experience to wait patiently for the treatment. How has my life changed in the last year? I consider myself fortunate that I can stand here before you today. I am still able to work because I have a desk job and my company has been supportive. I would like to

continue to contribute to society and work as long as possible.

The most difficult changes have been those at home. Karen elected 10 years ago, and I concurred, to give up her full time job and stay at home with the children. She continue to keep her nursing skills intact by working weekends. We have always worked together as a team in raising our children and I consider it the most important thing I do. However, it is becoming harder every day for me to participate in the daily routine with the children, something I have always enjoyed doing since the day they were both born.

Lauren is a bright, outgoing, athletic, 10-year-old child. Up until recently I have been able to physically participate with her in all her school and extracurricular activities. Sadly, she now understands that I am not able to do as much as I would like to do with her as my muscles continue to deteriorate and my fatigue increases.

Christopher is a typical rambunctious 4-year-old boy who has no idea why he is stronger and more coordinated than his own dad. One good butthead is enough to knock me to the ground, and he wins every time we wrestle.

I cannot kick a ball to him or have a catch with him. His idea of playing with his dad means sitting at a computer. As he gains his independence in dressing himself

and learning to tie his shoes, I am losing mine.

I used to take Lauren and Christopher to the parks for hiking while Karen worked on the weekends. I can no longer do that. We have always been an active family who have enjoyed the outdoors. My family has been my greatest source of joy. I know that if this disease is allowed to follow its course, I will be left totally paralyzed yet mentally intact.

I want to be there for my family both physically and mentally. Today I am here on behalf of all ALS patients that have gone before us and all present and future ALS patients. We understand the necessity of the formal FDA approval process for all drugs, however, given the aggressive and unpredictable nature of this disease, we do not have the time to wait.

If Myotrophin is found to be statistically safe and effective, we ask that you approve the early access program. Faced with the terminality of this disease, we are left with no other recourse and are willing to risk the side effects in order to slow its relentless path.

Irreparable damage occurs with each passing day. 127 years is a long time to wait. Rilutek was the first step. Let your actions today be the second step. I would like to go home today and tell my son and daughter and fellow ALS patients that yes, there is another drug

available.

You have the power to approve this program and renew our hope as we move one step closer to the eventual cure of ALS.

Thank you.

DR. GILMAN: Thank you.

Fred Kanzler.

MR. CARL MAYLE: Ladies and gentlemen, my name is Carl Mayle. I am a 28-year friend of Fred, and I am here with him today. He has asked me to read his statement with your permission.

My name is Fred Kanzler. I live in Mt. Holly, New Jersey, and I am 69 years old. My wife Ann and I were married on June 27, 1959. We have one son who is married and are blessed with two granddaughters. On April 30th, 1993, I retired an environmental manager from a plant with about 160 employees manufacturing polyvinyl chloride.

In that capacity I was responsible for the plant's industrial hygiene and environmental programs. I was diagnosed by Dr. David Lee of Mt. Holly on June 25th, 1991, with sporadic ALS. His diagnosis was confirmed by Dr. Shartland of HUP in Philadelphia.

Under the guidance of my physical therapist, who is trying to improve my gait, I started working out at a gym in September 1991. My wife was determined to find something

which, in her mind, would give us hope. Her efforts culminated with the discovery of the ALS Association, the Greater Philadelphia Chapter.

Among others she spoke to, the ALS Chapter nurses suggested that I get in touch with Dr. Howard Netter at the Hahneman Hospital ALS Clinic. Dr. Netter asked me if I would have an interest to participate in a drug study. My screening trips to Hahneman started in the summer of 1992.

The results of the tests seemed to show a rather rapid loss of strength in the legs and, to a lesser degree, in the arms. Around February or March of 1993, I started using a cane. Based on my rapid rate of deterioration I was accepted on April 8th, 1993, to participate in the double-blind study for IGF-1.

With the exception of the first four or five weeks where the thigh inject sites showed a reddening the size of silver dollar, I experienced no other side effects. The blush of the thigh inject site would abate after about 8 hours. The abdominal inject sites remain normal.

About three to four months after the start of the study, Dr. Netter mentioned that the results of my Appel test indicated a return of strength. My own observation showed a marked reduction of fasciculations. At the end of the 9-month study period, I noticed the muscle definitions in my shoulder muscles had returned and the circumference of

my calves had increased by 1.5 complication.

After the completion of the 9-month double-blind study period and the subsequent 9 months extension, which ended October 6, 1994, I had to wait for two months to continue with the IGF-1 treatment. It was during this 2-month period that I noticed atrophy returning associated with an increase in muscle weakness and fasciculations in all limbs. In fact, I had to reduce the weights for my lifting exercises at the gym and the distance traveled in 25 minutes on the stationary bike dropped by one mile, which represented nearly a 20 percent reduction.

No longer was I able to walk with a cane. Rather than using a walker, I taught myself to walk with Canadian crutches. During the same time, I also noted symptoms of a bulbar onset. It is my understanding that my extrapolated Appel curve indicated I would have expired in June 1994, therefore, I am thankful. If it was to be, I was stricken with ALS at the right time and in the right place.

Had I not had the IGF-1 treatment, I would have missed two dance recitals of my older granddaughter, and I would never have known my younger granddaughter, missed the wedding of my son's best friend to the sister of my daughter-in-law, and all the wonderful days I was able to spend with my family, not to forget all the friends I made at the ALS Association and the gym and the visits with

friends from Canada and Germany.

It is to me rather sad that despite the demonstrated efficacy, the access of Myotrophin is denied to wives or husbands, to mothers or fathers of young children, and to older children of parents my age. I have seen young men at the age of my son, with children the same age as my grandchildren, wither away, despite the fact that there is something out there that would buy them a longer life, more time with the people they love.

Not to speak of the countless who have already gone because of the denial of access to, in my opinion, an effective treatment. I am almost ashamed to tell anyone afflicted with ALS about my good fortune and my success. Do we really want to continue to play God based on statistics?

Based on my own successful experience with Myotrophin, isn't it time to have some compassion with all the ALS patients out there who wait for a miracle to happen right here in this room right now.

Thank you for the opportunity to appear.

DR. GILMAN: Thank you, Mr. Kanzler.

Dr. Gerald van der Vlugt.

DR. GERALD van der VLUGT: Good afternoon. My name is Gerald van der Vlugt. I am 57 years old and I come from a medical family. My mother and father were both physicians. My father died at the age of 55 from heart

disease and smoking, and my mother received the Outstanding Alumnus Award from the University of Oregon in 1994.

My wife just retired two years ago as medical director of the United States Peace Corps for eight years, and my daughter is a third-year medical student in the top of her class at Stanford.

I graduated from medical school in 1963 and retired in 1989 from the Senior Foreign Service. During that time, I had the distinct pleasure of dealing with the FDA on getting approval of such things as depo provera, and I understand the politics of the FDA, as well as ivermectin, and other drugs in my capacity as a senior executive service officer.

When I retired in 1989, I took my RV and my motorcycle and I traveled to all of the 49 states that are accessible by RV, and had a wonderful five years of retirement before I had the onset of ALS.

In June -- June is my anniversary month -- in June 1994, developed a right footdrop. I was very physically active and physically fit, and like I say, I serve on several public service committees, which I continue to serve on. I am on the executive board of the Public Employers Roundtable, on the executive board of the Federal Physicians Association, so I am active in those things even today. But I always used to arrive on my motorcycle. Now I arrive in

my wheelchair with my wife pushing me, which is not quite the same, but I still am able to serve.

My right footdrop began in 1994. I had a workup and a diagnosis was made in March 1995. I was begun in September 1995 on BDNF trials, double-blind, and I began on the Rilutek shortly after it was approved by the FDA. I am on high doses of vitamins because my medical family would want me to be that way.

When I was given the opportunity to come here originally, my firm intent was to think of my background in dealing with the FDA and its timidity in approving drugs, and encouraging you to move forward with a great vigor and approve this drug.

However, as I have researched the drug more -- and IGF-1 has been around for many years -- I am very thankful that the FDA has no vested interest in either the patients' view or in the company's view, but is looking for safe and effectiveness, and does not want to put something on the market that would be a cruel hoax, raise hopes that would not be true.

So as a patient, I would encourage you to go forward with Myotrophin and approve it. As a physician, I think there are serious concerns that I trust you all have more information than any of us, and will make a wise decision.

I note that when I began my BDNF trials that they also placed me on neurontin, 2400 mg/day, and I will leave you with this experience. I began in September taking neurontin. In the middle of December I suffered the rapid onset of bilateral visual field loss, went blind to the point where I could not see TV or my computer monitors.

Luckily, when I stopped taking the neurontin, my vision came back. So I am very happy to be able to see and talk and get around this way. But I think that we have to be careful, and I trust again the FDA will make the right decision with your technical information and your background.

I certainly want to stay active as long as I can and appreciate the new drugs that are coming down the pike, and I hope the drug companies keep up their good work to work on making more drugs available and help us as we go forward.

Thank you.

DR. GILMAN: Thank you.

Dr. Theodore Munsat.

DR. THEODORE MUNSAT: Mr. Chairman, members of the panel, thank you for allowing me to speak briefly. It has been a long day and I shall my remarks very brief.

I am Professor of Neurology and Pharmacology at Tufts University and Director of the Neuromuscular Research

Unit at New York Hospital.

I have spent most of my professional life involved in experimental therapeutics of ALS and I am pleased to be here today and take part in this meeting.

I have heard these data presented many times at scientific meetings in the United States and elsewhere, and I have heard them presented again today. I would like to join those of you on the panel and FDA in giving my support for acceptance of the 1200 study, which I think is scientifically sound, it is statistically robust, and the drug is safe.

Let me make a few remarks about another issue that was touched upon and that has to do with further trials. I have the pleasure of serving as Chairman of a World Federation of Neurology Committee that has been involved with therapeutic trials for several years. Our mission is to try to maximize resources for ALS trials and to bring together the skills and expertise of the private sector and the academic community, so that when further trials, future trials are presented to this committee, they won't pose as many problems with methodology and statistical analysis, and so on.

We have indeed had preliminary discussions with the sponsor of this drug, and are very willing to continue on discussing with them, as well as with other companies and

with FDA, trials that will be scientifically sound, statistically robust, and trials that will be economically and time efficient.

As a matter of fact, we have a preliminary draft of the study already. Let me just make one additional remark about the thinking of those of us who are involved with ALS trials. We do believe we are in a very new and promising era.

I think most of us believe that no single drug is going to provide the kind of major functional improvement that we all want, but we believe we are beginning to see drugs that have modest effects and that we must move very quickly into combination trials.

I think approval of the IND of Myotrophin will allow this momentum to continue. It will be a bad time to interrupt the momentum of drug development at this point. So I hope you will vote in favor of this. Thank you.

DR. GILMAN: Thank you, Dr. Munsat.

Dr. Robert Brown.

DR. ROBERT BROWN: Thank you. I am a neurologist from Boston where I see a large number of patients with Lou Gehrig's disease and conduct a research program investigating genetic factors that are predisposed to this illness.

I had the pleasure of collaborating with

scientists at Cephalon, but I want to mention that I have absolutely no financial interest in that company, nor do I stand to have any change in my financial status as a result of your deliberations today.

I want to say simply that I too have had an opportunity to review the results of Study 1200 and I would agree that it is well designed and that it shows clear statistically significant benefit and a benefit which is probably also clinically significant. It may be of only a modest benefit, but it is nonetheless real.

I think it is quite extraordinary sitting in the back of the room this morning to hear FDA's own experts review the study and agree that it showed clinical efficacy. I would share your view that Study 1302 is at best equivocal. That said, I would urge two things. Like Dr. Munsat before me and many others, I would urge that Myotrophin be approved.

I would equally urgently urge that you invoke some mechanism to insist that a third study be done, so that once for all we can settle with finality the question of efficacy, because I think it is unconscionable to provide this to our patients, presumably who have considerable expense, without knowing once and for all whether indeed it is helpful.

Thank you.

DR. GILMAN: Thank you, Dr. Brown.

Has anyone else any comments or statements to be made during the open portion of the meeting? Dr. Brooks.

DR. BENJAMIN BROOKS: Thank you. I faxed yesterday a request to speak.

I am Benjamin Brooks, Professor of Neurology and Director of the ALS Clinic at the University of Wisconsin Hospital and Clinics in Madison, Wisconsin. This is a region of the USA that has a high rate of ALS.

Our patients don't view their disease across their latest version of SAS. They view it from their wheelchair or behind by that machine. There are four points I want to make.

First, we needed an open public discussion of a separate independent review of all this data. It was absolutely necessary. At day's end, within the caveats given by Drs. Leber and Katz, there are no safety issues, and 1200 seems to have made the day.

The second issue, Dr. Zivin's issue, is, is this a significant clinical effect, and we see it primarily in the upper extremity function, in cutting, feeding oneself, these are clinically significant, and I would opine that they probably explain the fact that an independent quality of life measure was somehow positive in 1200.

The third point I want to make addresses some of

Dr. Munsat's issues. There is symptomatic, palliative, and restorative therapies that may be available to these neurodegenerative diseases. At the present time we only have one palliative therapy, and no restorative therapy. We need this added to your armamentarium.

The fourth and final point I want to make relates to the issue of the calculus of clinical trials and the issues of how analysis can affect bias of outcome.

There are three types of analysis: primary endpoint analysis, secondary endpoint analysis, and exploratory endpoint analysis. The primary and secondary endpoint analysis are usually in the clinical protocol. We know from today's discussion that 1200 made that. I would say that this provides substantial evidence for efficacy of this drug.

The issue before the committee that I see is whether exploratory analyses is supportive or negative, and I would opine and recommend that the committee look upon them as supportive.

Thank you.

DR. GILMAN: Thank you. Any other commentary? Dr. Jubelt.

DR. BURT JUBELT: I am Burt Jubelt and Professor of Neurology at SUNY-Syracuse and run an ALS clinic and see ALS patients on a weekly basis.

I wanted to comment just briefly from the scientific standpoint that, as all of you have heard, and I want to make it very brief, that from my standpoint, the 1200 study, the North American study is clearly efficacious and we have a second study that is either negative or supportive depending on your point of view, and the drug has minimal side effects.

From the personal standpoint, I want to mention that in the last year, I have had a family member that I had to care for as the physician, who had ALS, and seeing ALS patients dying every week, month. From the patient advocate standpoint, I think it is important to keep in mind that here you have a disease in which everybody dies. From that standpoint, and they die in three to four years. So it is worse than AIDS, it is worse than most cancers in this day and age, and here is a drug that if I had ALS tomorrow, I would want to try this drug, because it appears from my standpoint that it is efficacious and has little side effects.

Thank you.

DR. GILMAN: Thank you.

Yes.

MS. ABBIE MYERS: My name is Abbie Myers, President of NORD. I had requested time on the program about three weeks ago, and I guess I never heard from you.

So I would like to just give you this written comment, but I would also want to say that the last time I was here at a committee meeting, I remember the chairman of the committee, Dr. Fahn at the time, in voting about Rilutek, said I cannot vote for approval of Rilutek because the North American study shows it doesn't work in North America, it only works in Europe.

So here we have got exactly the opposite. This drug seems to work in North America.

DR. GILMAN: Is there any other commentary from the floor? Yes.

DR. BARRY FESTOFF: My name is Barry Festoff, Professor of Neurology at the University of Kansas Medical Center and the VA Hospital in Kansas City, and I have been involved with ALS patients for more than 20 years in clinical trials and bench research and have been actively investigating IGF-1 for the past 10 years beginning with studies with a predecessor hormone, Human Growth Hormone.

You have heard a little about the Human Growth Hormone study, which was negative, but in fact, showed that the axis for IGF-1 in growth hormone was intact in ALS patients and suggested that there was a window of treatment opportunity there for IGF-1.

I have been involved in Phase I and Phase II studies with Cephalon, and we currently have now four

patients out of the initial seven that entered the study. It was a double-blind study, and these patients have received over 980 doses of 0.05 mg twice a day almost two years on open label and extension, and the blind is still coded, so we don't know the blind, whether or not these patients in the nine months prior to that also received IGF-1.

These patients have essentially stopped in terms of their maximum progression rate on the Appel Scale. All of them fit the criteria for the large 1200 study in terms of entry, and although one patient is bedridden, still is able to feed himself with assistance.

The other three patients are ambulatory. Just to give you that sort of notion that long term IGF-1 administration seems not to have any significant side effects.

DR. GILMAN: Thank you, Dr. Festoff.

Thank you all very much. We thank the patients who have testified before us. We certainly appreciate the desperateness of this disease and we want to do all that we can to help make progress in this area.

**COMMITTEE DISCUSSION (CONTINUED)**

DR. GILMAN: Now, I think it is time for the committee to continue its discussions and deliberations.

Let me try and precipitate, again by being

provocative, in my own mind, Study 1200 has shown that Myotrophin is effective, that is, it shows a benefit over placebo in altering the slope of the clinical scale that was used, the Appel Scale.

The study was done utilizing the statistics that were designed prospectively. Safety is not an issue, and so I would conclude that the 1200 study did show effectiveness. The 1202 study still in my mind did not show effectiveness. So I wind up looking at one study that showed effectiveness and the other one that did not.

On this basis, I am inclined towards approval in that these two studies, taken together, have shown one that clearly shows effectiveness, and the other one I think we need to put aside for now because we do have a positive study. Moreover, we are looking towards the request for approval of an IND, not an NDA.

That being the case, then, I would be in favor of approval at this point.

I would like to hear from the other committee members. I am stating my own personal opinion only, not that of the committee.

[No response.]

DR. GILMAN: You either all disagree or all agree.

DR. KAWAS: I would just say I think I agree with you, Dr. Gilman. I think that the agency has told me that

two studies is substantial and that what we needed to decide was whether or not there was sufficient, and since one is less than two, I think the criteria has been met.

DR. GILMAN: Thank you.

Dr. Khachaturian.

DR. KHACHATURIAN: I was expecting you to be provocative, but you weren't. I think I agree with you.

DR. GILMAN: All right. Other commentary from the committee?

MS. PHILLIPS: I think as a consumer representative, it is obvious that the consumers, the patients made their case that they want the drug, and as a representative, I would concur with you also that the Study 1200 showed effectiveness.

Based on that, it would be very, very difficult, if not unconscionable, to not continue to proceed with the IND. I think also for me personally, hearing other doctors, Dr. Brown, Dr. Munsat, who are eminently respected in the community, come forward with their statements would certain help me to approve.

DR. GILMAN: Well, I want to emphasize here that when I speak for myself alone, I am speaking on the basis of the data that I have heard today. I appreciate what a difficult, disastrous disease ALS is, and I want to do whatever I can to help patients with this disorder, but also

I want to base my own personal decision upon the evidence, and I hope that is what the rest of the committee will do today.

Dr. Coyle.

DR. COYLE: Can the panel also make a recommendation that a third study be done?

DR. GILMAN: We can certainly discuss that. We have been asked whether evidence is sufficient to have us support a treatment IND. The tenor of the discussion today certainly does suggest that the company might consider a third trial because I, for one, do not see adequate evidence to have me, at this point in time, favor an NDA. If that were the question before us, I would say no, I don't think we have substantial evidence. We have evidence, it is not substantial in my own mind.

That is not the question before us, though, but I believe the company has heard that multiple times today.

Other commentary? Dr. Adams.

DR. ADAMS: I would encourage the neurological community, who does this research, Dr. Munsat, and the other experts who have addressed us, to seriously talk to Cephalon about doing a third trial that is amply sized to test the effect of this drug, not only on progression, but on mortality, and because there is some concern about the tremendous heterogeneity of the disease, that they consider

a trial with some prestratification by rapidity of progression, so that there is strong evidence that there may be some people with ALS who may benefit more or less, and it may very well be that those people that are rapidly progressing are the individuals that are most likely to benefit, and I think that is very important knowledge for me and probably for any other physician who deals with this illness.

DR. GILMAN: Thank you.

Other commentary? Dr. Gennings.

DR. GENNINGS: I think it might have been Dr. Dobbins earlier today was saying that at the time, if he could have chosen a repeated measures analysis when the 1202 was designed, he would have done that, and I think that now, maybe if we are talking about a third study, those kinds of thoughts in terms of statistics could also be placed in there, which should be very helpful.

DR. GILMAN: Other comments?

All right. That being the case, let me ask the committee whether there is any other evidence you wish to hear or anything else any of you wish to say?

Let me ask the sponsor if there is anything. Yes Dr. Snead.

DR. SNEAD: I have one question of the sponsor. There is talk about a combination study in the offing. Do

you have drug-drug interaction data on these two compounds?

DR. GILMAN: Did you hear the question? The question is, if you are considering a two-drug trial next, are you concerned about drug-drug interactions?

DR. GRANEY: I think we are at the point where we are just considering it. We are aware that some toxicology would be needed. We don't have the anticipation, but we have not discussed the specifics of the preclinical studies with the agency yet.

DR. GELINAS: If I could speak. Some of the patients who were in the original Myotrophin study are still living, and are taking Rilutek at my center, and are tolerating it without difficulty.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: If there were not another trial, and you note the subjunctive for the condition, contrary to the fact. If there were not another trial, what would then happen, what would the duration of the treatment IND be? We were carefully warned that this is a temporary or transitory phase.

DR. LEBER: That is a very good question, and you may get more than one answer because I don't know. If the NDA was submitted, and the NDA were approved on the basis of this evidence -- and I am not clear how that would go, we might come back to the committee, we might do a number of

things -- then, clearly you don't need the treatment IND.

The problem comes up if the NDA were disapproved on the basis of the evidence in the hand, and I -- Bob, do you know what is anticipated? Would we suspend the treatment IND at that point?

DR. TEMPLE: I would say that is relatively unlikely, but we would stamp our feet a lot in the hope that further studies would get done.

DR. LEBER: I don't recall the regs participating in this.

DR. TEMPLE: The regulations don't say that. What they say is that there is a responsibility to move forward in developing the data needed for approval, but at that point you would have a different set of information, and you would have to then decide what to do with it.

DR. DRACHMAN: What if they did nothing at all, how long would it go on?

DR. TEMPLE: What do you mean nothing at all?

DR. DRACHMAN: I mean if they did not submit another study.

DR. TEMPLE: Well, as we have been saying, that is not the only question. They plainly are committed to submitting a new drug application.

DR. DRACHMAN: Right, but there are, in fact, three choices. One is simply delay it, and how long would

that work? What I would worry about is that we would be holding out a false hope that the drug would available, and it would be available for a long period of time without the final decision regarding it.

DR. TEMPLE: We haven't had cause to worry about the possibility that no application would be submitted, so we haven't worried about that, because we have been told to expect one. If they change their mind and did no further work, and just let it sit, that would be a problem. That is really not what the regs contemplate, but there is a lot of contingencies in there.

DR. GILMAN: Are there other questions or comments from the committee now?

Anything further from the sponsor? Anything you would like to tell us that has not been said before?

DR. GRANEY: No, there is nothing else.

DR. GILMAN: Anything from the Pharmacology Division, Dr. Katz, Dr. Leber anything further you want to tell us?

DR. LEBER: We have had our say.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: Only one thing actually, and it was Mr. Gill's comments that make me want to say this. I will be very brief.

Despite a perception that only drugs for AIDS and

cancer get any attention, I want to make it very clear that that is not so. The last drug we had for a bad neurological disease Rilutek was approved in less than six months. Drugs of that class are regularly treated as priority reviewed drugs, which means we intend to respond to them in less than six months.

Treatment INDs of the kind we are considering are most common for AIDS and cancer, and the third most common use is one or another neurologic disease. We are prepared to accept both survival and symptomatic improvement as bases for approval. If anybody could think of a good surrogate, we would certainly consider ti.

I just want to make sure everybody knows that we are very concerned about these diseases for the reasons that we just heard for an hour, they are terrible diseases. They are as bad as anything in the community. So there is no lack of will, interest, or the personnel to do it.

DR. GILMAN: Thank you. Dr. Leber.

DR. LEBER: Speaking about things you can learn from what patients tell you, one of the individuals testifying mentioned that because of the hiatus of availability that he had to come off the drug, and he reports measurable changes in the status of his disease from fasciculations, competence of his cath, and the like, which brings to mind the possibility within subject designs.

I just want to mention that because, you know, we are locked into this few in may ways parallel studies, although I realize there are alternatives, but another compelling design provided it is done the right way is within subject change, that is, replicable and not occurring under the circumstances the blind is penetrated.

So people have done them, and that is another source of evidence that we might consider looking at, that doesn't expose large numbers of patients to no treatment at all.

**RECOMMENDATION AND VOTE**

DR. GILMAN: If the committee is ready, then, there are 11 voting members of us.

Let me see a show of hands. All those who favor a treatment use of the product under an IND treatment protocol, please raise your hands.

[Show of hands.]

DR. GILMAN: I believe it is unanimous.

[Applause.]

DR. GILMAN: Any opposed?

[No response.]

DR. GILMAN: It is unanimous.

**CLOSING REMARKS**

DR. GILMAN: Dr. Leber, Dr. Temple, any further questions for the committee?

DR. LEBER: I have a very important announcement.

DR. GILMAN: Dr. Leber.

DR. LEBER: I wouldn't want this day to end -- and I understand there is a lot of joy and happiness in the room about the decision -- I want to talk about something else totally unrelated to ALS, but something that is not so a moment of happiness on our part.

I don't know how many of you on the committee know that, Mr. Bernstein, this is his last time as our Executive Secretary. He has decided after many years of government service to give up the ghost, to leave Washington to head home toward Texas.

So we will not see him again in this capacity, I hope we will see him as a friend, but I want to say this, that over the years that I have been here, there have been few executive secretaries or colleagues that have done such a good job for so many times, so well.

I thank you.

[Applause.]

[Whereupon, at 5:30 p.m., the proceedings were adjourned.]

# *CERTIFICATE*

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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