FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FORTY-SIXTH MEETING

OF THE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM ADVISORY COMMITTEE

8:31 a.m.

Thursday, May 8, 1997

Holiday Inn-Bethesda

8120 Wisconsin Avenue
Bethesda, Maryland

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C O N T E N T S

NDA 20-654, MYOTROPHIN
mescasermin (recombinant DNA origin)
Injection for the Treatment of
Amyotrophic Lateral Sclerosis

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P R O C E E D I N G S

(8:31 a.m.)

DR. GILMAN: I would like to welcome everybody to this meeting of the Food and Drug Administration's advisory committee.

I'm Sid Gilman, a neurologist and Chairman of the Department of Neurology at the University of Michigan Medical Center.

I would like to go around the table to have you meet the members of the advisory committee. We'll start with Dr. Khachaturian.

DR. KHACHATURIAN: I'm Zaven Khachaturian, Director of the Ronald and Nancy Reagan Research Institute of the Alzheimer's Association.

MS. PHILLIPS: I'm Ellyn Phillips. I'm the consumer representative. I'm with the ALS Association in a volunteer capacity.

DR. GENNINGS:

I'm Chris Gennings. I'm an associate professor in biostatistics at the Medical College of Virginia.

DR. ZIVIN: Justin Zivin. I'm a neuroscientist

at the University of California, San Diego.

DR. COYLE: Pat Coyle. I'm a neurology professor at the State University of New York at Stony Brook.

DR. KAWAS: Claudia Kawas. I'm a neurologist at Johns Hopkins.

MS. McGOODWIN: Ermona McGoodwin, FDA.

DR. ADAMS: Harold Adams, a neurologist at the University of Iowa.

DR. DRACHMAN: David Drachman, Chairman of Neurology, U Mass in Worcester.

DR. HOBERMAN: David Hoberman, Division of Biometrics, Food and Drug Administration.

DR. FEENEY: John Feeney, medical reviewer, FDA.

DR. LEBER: Paul Leber, Director of the Division of Neuropharmacological Drug Products, FDA.

DR. KATZ: Russ Katz, Deputy Director, Division of Neuropharmacological Drug Products, FDA.

DR. GILMAN: Thank you all, and I'd welcome members of the press, of the company, Cephalon, and other

visitors.

I'd like to give some ground rules for the day today. Will the presenters both from Cephalon and from the FDA please make your presentations as crisp and clear as you possibly can? I'm sure you will do that but I just wanted to say this.

Second, will you please respond to questions from the panel at the time that they are posed to you. We have read the material, I can assure you. We know it very well by this point. It would be helpful for you to review it and tell us all that you wish to tell us, but please stop and answer our questions at the time they are posed.

I will ask that members of the panel either raise your hand for me to acknowledge you or if the lights are down and I can't see you, you can simply speak up and ask your question.

Please speak into the microphone. All presenters should speak into the microphone so that we'll have a transcript of this proceeding.

We have an agenda that consists of the presentations, first with the Food and Drug Administration,

Dr. Leber, then Cephalon-Chiron Partners' presentation, followed by the FDA's presentation with Dr. Feeney. The committee will then discuss all that we have heard.

We'll then have an open public hearing. We've had requests from 22 people to speak. That is a very large number and in the interest of time and effort, I ask that each of the presenters in the open public hearing please keep your remarks as brief as you possibly can. We would prefer to have the remarks down to two or three minutes, if that is at all possible, so that the committee can get its work done.

Finally, we will have committee further discussions, recommendations, and our vote. We'll then have closing remarks.

With that I will ask Ermona McGoodwin to read the conflict of interest statement.

MS. McGOODWIN: Thank you, Dr. Gilman.

The following announcement addresses the conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of a conflict.

1 Based on the submitted agenda and information
2 provided by the participants, the agency has determined
3 that all reported interests in firms regulated by the
4 Center for Drug Evaluation and Research present no
5 potential for a conflict of interest at this meeting with
6 the following exceptions.
7 In accordance with 18 U.S.C. 208(b)(3), full
8 waivers have been granted to Dr. Sid Gilman, Dr. Justin
9 Zivin, and to Ms. Ellyn Phillips. A copy of these waiver
10 statements may be obtained from the agency's Freedom of
11 Information Office, room 12A-15 of the Parklawn Building.
12 In the event that the discussions involve any
13 other products or firms not already on the agenda for which
14 an FDA participant has a financial interest, the
15 participants are aware of the need to exclude themselves
16 from such involvement and their exclusion will be noted for
17 the record.
18 With respect to all other participants, we ask
19 in the interest of fairness that they address any current
20 or previous financial involvement with any firm whose
21 products they may wish to comment upon.

1 Thank you.

2 DR. GILMAN: Thank you.

3 Dr. Temple has just joined the table. Please

4 introduce yourself, Bob.

5 DR. TEMPLE: I'm Bob Temple. I'm Director of

6 the Office of Drug Evaluation I.

7 DR. GILMAN: Thank you.

8 I'd like also to note that we have had requests

9 from six parties to have statements read into the record.

10 I will not read these names. We will appreciate seeing

11 your remarks in the transcript and they will be so

12 recorded.

13 With that, I'd like to turn to Dr. Leber for

14 the FDA introductory remarks.

15 DR. LEBER: Good morning, everybody. I welcome

16 the committee. This shall be a long day and I'll try to be

17 as brief as possible.

18 At the outset let me say this is not a

19 presentation of the FDA's case but probably should be

20 viewed as a basic charge and overview of where we stand and

21 how we approach this issue.

I think we ought to begin with what the regulatory requirements for the approval of a new drug are. The federal Food, Drug and Cosmetic Act says in section 505 that the FDA may not approve a drug under an application for a new drug unless there is substantial evidence of effectiveness. The act defines in the act itself what that substantial evidence is, and as we said in our mailing, the definition is somewhat convoluted. And I put it up there for all to read for themselves.

But basically it says that experts qualified in the disease for which the treatment is being offered as a treatment and considered as a treatment should be able to reach a conclusion based on the evidence adduced in adequate and well-controlled investigations, including clinical investigations -- note the plural nature of "investigations" -- that the drug has the effect or benefits claimed for it by the sponsor in the labeling that will accompany the drug if marketed.

Now, there are many who wonder why the act asks for investigations plural. All I can say is that over the many years that we have operated under this provision of

the act, first passed in 1962, and the Kefauver-Harris amendments, the agency has generally interpreted this as a requirement for independent substantiation. In fact, the evidence document mailed to the committee, a recent proposal from the FDA that discusses this standard, points out that this requirement is not some peculiar bureaucratic rule devised in some way to delay or act as a sea anchor on the development of new drugs.

To the contrary. The concept of independent substantiation, replication of experimental result, arises not from bureaucrats or regulators, but is a principle of standard scientific inference that is recognized in every area of scientific investigation. As the carpenter rule says, measure twice, cut once. Try to make certain that what you observe is true.

Now, this isn't because we disbelieve the results of experiments, but I think a point I'd like to make is we rely in our methods of inference on results of experiments and the experiments are usually set up in such a way that we try to associate proof that a drug works with a finding of a between-treatment difference between the

drug or levels of exposure to the drug and some control. And it is in the showing of the difference that we find the persuasive evidence of effectiveness.

Now, there are exceptions to this. There are circumstances where it's so obvious that a drug has an effect that you don't need a concurrent control, but of the five control designs recognized by the Food and Drug Administration as legitimate designs for adequate and well-controlled studies, three of them allow comparisons under blinded conditions and all of these depend upon the showing a difference to demonstrate effectiveness.

But when you find a difference, every analyst knows, from the very first times this was considered, that that difference need not be due to the applied treatment. In fact, there are four reasons that you could see a difference.

Bias, which by all means is always present. It's not something you can exclude. There's always a chance that something didn't go right in experimental randomization processes, something doesn't go right in the conduct of a trial, and the results you attribute to the

assigned treatment is not due to the treatment at all.

There's always a chance for fraud. There is no suggestion, by the way, that fraud operates in this case. I just mention it as one of the alternative explanations for a difference other than the assigned treatment.

Finally, of course, there's chance. And we rely upon various analytical methods based upon probability theory, and assumed distributions for errors in experimental observation allow us to reach conclusions that chance is not a likely explanation for the finding of a difference.

I'm laying all of this out because it becomes a central theme here about whether or not the evidence found in the present circumstances is possibly due to chance or to bias or the treatment effect. That's probably the theme that underlies most of today's arguments.

Now, all of this again, as I want to emphasize, is not something that came out of the FDA. The point made here is I'm quoting from something that was written in 1929 by someone who many would agree is the father of current concepts of inference in science, Fisher, who was talking

about how we think about findings of differences and what we should do for them. And I happen to like this. Maybe it isn't truth. He doesn't know what the world is, but this is a point he made which I think will stand us all in good stead, and I quote.

"It is a common practice to judge a result significant if it is of such magnitude that it would have been produced by chance not more frequently than once in twenty trials. This is an arbitrary but convenient level of significance for the practical investigator, but it does not mean that he allows himself to be deceived once in every twenty experiments. The test of significance only tells him what to ignore, namely, all experiments in which significant results are not obtained."

And to an extent ignoring them is a funny word. It's for purposes of inference, not for purposes of estimation of effect size.

But the important line I think that we ought to remember, "He should only claim that a phenomenon is experimentally demonstrable when he knows how to design an experiment so that it will rarely fail to give a

significant result."

I think for all the reasons we know, people who've thought about this question value independent substantiation, and this is just showing that it has its origins well back in the past and is not something that arose with the passage of the Kefauver-Harris amendments.

Nonetheless, there are many in society who reasonably ask why, if lives are at stake, it would be necessary to seek confirmation of an apparently promising experimental result in an adequate and well-controlled trial, why do you need to confirm it. Is not the risk that you take, if acting on one study, you increase the risk of falsely concluding the drug is effective, worth taking if you could save lives or have an impact on a devastating disease for which there are no satisfactory or effective alternative treatments?

In short, in the assessment of any potentially promising new drugs intended for a disease that kills or causes irreversible morbidity, does it not make sense to step away from this epistemological principle and consider rather the risks and benefits of making the wrong decision

and worrying about it in that perspective?

Now, it's critical for you all to understand that that is the case being made by the firm in the present situation. The ordinary standards of evidence that we would rely upon, more than one adequate and well-controlled trial, have not been met, and I think they agree to that. What they're saying is that this is one of those circumstances where it would be reasonable to do that, and in principle, that is to surrender -- to modify one's standards to be flexible.

I think insofar as the principle of flexibility is concerned, when lives are at stake, the agency wholeheartedly agrees. It's not only that it agrees, but as the evidence document that was provided to you in the mailing says, we've done it before. This isn't anything new. When the evidence and facts and circumstances allow, we will act and have acted on the basis of one compelling, strong piece of evidence derived from a single trial that shows an effect, an important effect, on the course, signs, and phenomena of disease, usually an effect on mortality, but it could be an effect on irreversible morbidity.

However -- and this again is the yin and yang. There is a difference between doing that when there is but a single trial providing very strong results and the condition where one has a trial providing what you might call modest evidence of a difference between treatments that could be interpreted as evidence of efficacy when that effect is not on survival or irreversible morbidity and when, in face of that, there is a competing trial of apparently equivalent capacity to find a difference that fails to find one. And that I think is almost the status that we find ourselves in today.

The real punch line is this. My little schematic is intended to point out what's going on. If you look at the large circle, it represents the universe, if you will, of patients now and in the future who have ALS, or actually now who have ALS or could be considered to have ALS. A process goes on by which we take a sample of that patient. How representative that sample is I know not. We know it is not a truly random sample, and we obtain in the case of study 1200 a sample of some 3 times 90, 270 or so, patients, and in the case of study 1202, we obtain a sample

of about I guess 130 and 60, say, almost 200 patients.

We then go through some process by which we assign patients to a group that's going to get treatment so that we have in 1200 even assignments so that one-third get the high dose, another third get the mid-dose, and a third third gets placebo. In the study 1202, for whatever reasons, the balance is not even, but instead 2 patients for every 1 given to placebo get the dose of Myotrophin labeled as .1. In that case, 1202, there are approximately 130 patients assigned to the dose of Myotrophin and about 60 assigned to placebo.

On the basis of these two experiments, we seek to know whether the drug has an effect, which I've just called phi. The problem for us -- and that's what this morning's discussion is about -- is that the estimate provided by 1200, phi 1200, is clearly different in our view, distinguishable, from that for phi for study 1202.

Now, this issue is not an easy one. It entails all sorts of levels of questions of evidence, the weighing of evidence, inference, how one combines discrepant results, whether they are in fact a discrepant. What will

1 happen this morning, as I expect, is that the firm
2 logically will come to you and say, look, you are to
3 believe 1200. 1200 is a strong study. It's going to
4 provide evidence that Myotrophin is an effective treatment
5 for a devastating disease and you should act upon its
6 results.
7 Now, in doing that, you've got to say that
8 1202's results are dismissible, or if not dismissible,
9 acceptable in light of what happens or explain why it is
10 what it is.
11 The other side of the coin clearly, the
12 agency's review team, for whatever reason, reaches a
13 different view of this evidence. Our view is the fact that
14 1202 does not corroborate independently the findings of
15 1200 is very disconcerting when one wants to make a
16 judgment about evidence. Accordingly, when we get up,
17 we're going to tell you why, one, we find 1202 not to be a
18 positive study and not to be consistent with the findings
19 of 1200, and we're going to try to explain why, if you're
20 going to turn on 1200 alone, it is not as strong a source
21 of evidence as perhaps the firm's view of it is. That's

understandable because a lot of how you see something depends upon your prior beliefs about it.

So, with that in mind, having said that, let me lay out just specifically what the questions are because they track very clearly, if I can get my overhead here, the very points I've been making. I had the overhead here a second ago, and it's possible that it disappeared. Anyway, I can tell you basically what they are without the overhead. They are three in number and they make sense.

(Laughter.)

DR. LEBER: The questions make sense. The answers are not necessarily known to me.

The first, of course, is whether or not there is more than one adequate and well-controlled trial that would demonstrate that Myotrophin is effective.

The second question, if not, is there a single trial, adequate and well-controlled, that lends support to the conclusion that Myotrophin is effective?

And if so, what is it about that study that would lead the committee to conclude whether or not that study is a source of substantial evidence on its own.

Now, those are basically the three questions. They follow this cascade of logic that the ordinary standard is two. If not two, then on special circumstances we will consider one, and if so, is the current set of circumstances and the current situation one in which one could make a reliable inference on one study?

Well, that basically concludes the introduction and charge.

One other thing I'd like to mention. This work doesn't get done in a vacuum, and over the almost two years that we have been considering the issue of Myotrophin -- although the NDA was only submitted in February, discussion on this began long ago when we learned the results of study 1200 -- there are two people who really have done extraordinary work and spent a tremendous amount of effort and I want to single them out. I think throughout today's discussion, when we address the data, you'll understand how much they must have done to understand it so well. And that's Dr. Hoberman who is the biomathematical statistician who's worked on this and Dr. Feeney, the clinical reviewer, and they have literally worked nights and weekends.

1 That concludes my opening remarks and I turn
2 the floor back to the Chair.
3 Sorry about the questions.
4 DR. GILMAN: Thank you, Dr. Leber.
5 Next we'll have presentations from Cephalon-
6 Chiron, Drs. Graney, Scharschmidt, Braekman, Vaught, and
7 Miller.
8 DR. GRANEY: Thank you, Dr. Gilman. Good
9 morning.
10 We're pleased to be presenting to you today the
11 evidence that we believe demonstrates that Myotrophin is
12 safe and effective in slowing the progression of the
13 morbidity in ALS. As you know, this tragic disease affects
14 thousands of Americans, many of whom will be with us today.
15 There is currently no therapy which slows the devastating
16 loss of function produced by this disease.
17 Through our presentation today, we'd like to
18 point up four issues that we believe bear on the
19 consideration of ALS and its treatment with Myotrophin.
20 The first and central one is that ALS is a
21 devastating disease which cripples and then inevitably

1 kills.

2 You'll also see today that there is a strong

3 preclinical rationale for the use of Myotrophin in the

4 treatment of ALS that in vivo and in vitro models show a

5 favorable effect of IGF-1 on all the components of the

6 motor unit, the neuron/axon junction, and the muscle

7 itself.

8 We'll also show you that we believe Myotrophin

9 does slow the progression of the signs and symptoms of ALS

10 as perceived by the patient in health related quality of

11 life and as seen by the physician with the Appel ALS scale,

12 and that these signs and symptoms are not indications of

13 transient discomfort, but that they represent irreversible

14 functional loss.

15 Finally and very importantly, you'll see that

16 Myotrophin is safe and is well-tolerated by the patients

17 with ALS.

18 Since we last presented to you, we've

19 accumulated new data and conducted analyses that we believe

20 are pertinent to the committee's consideration today.

21 First you'll see a more detailed presentation

of the preclinical rationale and its experimental basis.

Next we have more information on the survival experience of patients in our trials. In the North American trial, we now have three years or greater experience for most of the patients, and in Europe, we have two years or greater. This has provided us with a more mature database that has allowed us to conduct analyses which take into consideration established risk factors for survival in ALS.

Finally, you'll see that we have conducted an analysis of the interaction of pharmacokinetic and pharmacodynamic activities which provide information on the relationship between the blood level of IGF-1 and the therapeutic effect.

We want you to know that we did hear the message from the committee last year that further clinical research in this area is clearly indicated, and we have been conscientiously working with a working group from the World Federation of Neurology to come up with a design and lay the underpinnings for a study of Myotrophin in combination with riluzole to expand our information on the

1 use of both of these drugs. This was done as an attempt to
2 follow up on the indication that you gave us of the
3 importance. Later in the presentation, you'll hear some
4 additional detail on the study that's proposed to be
5 conducted in the post-approval environment.
6 We'll begin our program today with a
7 presentation by Dr. Bruce Scharschmidt from Chiron who will
8 talk about the clinical course of ALS and its assessment
9 using the Appel ALS score for physician assessment and the
10 Sickness Impact Profile to assess the patient's perception
11 of health-related quality of life.
12 Dr. Jeffry Vaught will then review the biology
13 of IGF-1 and review the considerations relating to the
14 rationale for clinical use based on preclinical findings.
15 Dr. Scharschmidt will then review the strong
16 evidence for efficacy from the clinical program, including
17 the North American and European trials.
18 He'll be followed by Dr. Rene Braekman who will
19 talk about the analysis of the pharmacokinetic and
20 pharmacodynamic interaction.
21 As your documents indicate, safety is an area

of agreement and we'll be presenting only a summary of the safety factors today, although we'd be happy to answer questions.

After the safety presentation, I'll discuss the survival analysis and Dr. Bruce Scharschmidt will then give the consideration of the risks and benefits involved in the treatment of ALS with Myotrophin.

We'll close with a discussion by Dr. Robert Miller from the point of view of an ALS caregiver of all of the elements that we've presented.

I'll now ask Dr. Scharschmidt to come to the mike to give the consideration of ALS and its evaluation.

DR. SCHARSCHMIDT: Good morning. My name is Bruce Scharschmidt. I represent a new face for the panel, and I'm pleased to be participating in today's presentation.

As you heard from Dr. Graney, ALS is a devastating disease. It disables and kills thousands of Americans every year.

Now, most of us here today are familiar with ALS but some may not be, so in the first few minutes I'll

1 briefly summarize the clinical manifestations of this
2 disease and I'll also describe the two measures used in the
3 Myotrophin trials to assess progression of these clinical
4 manifestations, one from the standpoint of the patient and
5 one from the standpoint of the clinician.
6 This slide summarizes the clinical
7 manifestations of ALS and its demographic features.
8 Patients with ALS experience progressive loss of upper and
9 lower motor neurons and progressive paralysis. They
10 experience impaired speech and swallowing. This is a first
11 symptom in about a quarter of patients. ALS strikes the
12 respiratory muscles and causes progressively impaired
13 breathing. Patients experience progressive weakness and
14 ultimately paralysis of their arms and legs and weakness or
15 clumsiness of the arms and legs as a first symptom in about
16 two-thirds of patients. Regardless of where the symptoms
17 begin, they tend to spread and ultimately involve all of
18 these muscle groups.
19 Now, the impaired ability to swallow, to
20 breathe, and to move about is a devastating combination.
21 Patients with ALS ultimately cannot swallow their own

saliva. These secretions tend to enter the lungs and cause pneumonia, and respiratory insufficiency often complicated by pneumonia is the major cause of death.

The median survival of patients with ALS is about three years. This is shorter than the survival of patients with HIV infection and many forms of cancer.

Among the various prognostic factors which predict survival, age and respiratory function have been consistently identified as important, and we'll see later in Dr. Graney's presentation that these are important in understanding the survival of the patients who participated in the Myotrophin trials.

ALS usually begins in the peak productive years, but it can strike adults of all ages. Each year in the United States it's estimated that up to 10,000 patients die of ALS and up to 30,000 patients suffer from the disease.

Now, the goal of the trials that we will present today was to measure the effect of Myotrophin on the morbidity of ALS and to measure it from two standpoints, one from the standpoint of the clinician and

the other from the standpoint of the patient. This is a challenge because the severity, diversity, and rate of progression of these manifestations vary greatly from patient to patient.

Now, several approaches have been developed to assess progression of clinical manifestations, and for the studies we'll be describing today, the sponsors chose the Appel ALS rating scale, or Appel scale. It was originally developed by Appel, et al. at Baylor and is specific for use in ALS patients. The Appel scale is a physician-based assessment of muscle strength and function. It consists of five separately graded components shown at right which assess the strength and function of the muscles which are involved in patients with ALS.

The bulbar component assesses speech and swallowing. Speech is graded from normal to unintelligible. Swallowing is graded based on diet ranging from normal to pureed to tube feeding.

The respiratory component is graded on the basis of the ability of patients to move air, measured as forced vital capacity, or on the need for special

respiratory support.

Function of the upper and lower extremities is based on activities of daily living. In the case of the arms, this would include the ability to raise a glass to the mouth to drink, the ability to propel a wheelchair, the ability to dress oneself. In the case of the legs, this would include the ability to climb stairs or to walk unassisted. And finally, individual muscles in the arms and legs are tested directly.

The Appel total score reflects overall clinical morbidity of the disease. It ranges from 30, which is normal, to 164 which represents complete paralysis.

The Appel scale has been used in prior clinical trials and studies by Appel indicate that measurement of the total score is reproducible.

The Appel score correlates with both muscle innervation and with mortality. Studies by Felice, shown at left, demonstrate that serial measurements of the Appel score -- in this case increases over time in a cohort of 21 patients correlate with decreases in the number of motor units estimated by serial EMG analysis.

At shown at right, Haverkamp, et al. have demonstrated that patients with an Appel score greater than the median -- that is, patients with more rapidly progressing disease -- have a survival which is worse than that of patients with Appel scores below the median. This latter observation was corroborated by the long-term follow-up of patients in the Myotrophin studies.

Now, what clinicians measure is not necessarily the same as what patients themselves perceive. Therefore, in the studies we'll be describing today, the effect of Myotrophin was also measured on morbidity as viewed by the patient, and for this purpose we used the Sickness Impact Profile, which we'll also refer to as the SIP.

Now, unlike the Appel scale, which is a physician-based, disease-specific measure, the SIP is a broadly applicable, patient-based assessment of health-related quality of life. It consists of 136 yes/no questions designed to assess the effect of quality of life in three dimensions: physical, psychosocial, and a third independent category.

Now, what sorts of questions does the SIP ask?

1 Well, patients assess their physical function by answering
2 questions regarding their ability to get about, to dress
3 themselves, and to tend to their bodily needs. For
4 example, I am very clumsy in body movements. I do not
5 bathe myself at all, but am bathed by somebody else. I
6 stay within one room.
7 Patients answer questions regarding their
8 psychosocial function which deal with their ability to
9 communicate, to interact with others. For example, I'm
10 doing fewer social activities with groups of people. I
11 isolate myself as much as I can from the rest of the
12 family. I act irritable. I'm impatient with myself. I
13 blame myself for things that happen.
14 In a third independent category, patients
15 answer questions about their ability to eat, to work, to
16 manage a household, and to participate in recreational
17 activities. For example, I am not working at all. I'm not
18 doing any of my usual physical recreation or activities.
19 I'm eating no food at all. Nutrition is taken through
20 tubes or intravenous fluids.
21 Now, ALS patients might answer yes to all of

1 these questions. Yet, many of these activities of daily
2 living which reflect the impact of ALS on patients, on
3 their families, and its cost to society are not directly
4 measured by the Appel scale.
5 The SIP overall score is scaled from 0 to 100
6 and like the Appel scale, higher scores indicate worse
7 patient-perceived quality of life. In the Myotrophin
8 studies we'll be describing, the SIP was administered by a
9 trained and blinded third party who was independent of both
10 the sponsors and the trial sites and when administered in
11 this fashion, the SIP has been shown to be reproducible.
12 Now, what do these SIP scores mean and how has
13 the SIP been used by other investigators?
14 Patrick and Deyo reviewed experience with the
15 SIP as applied to a variety of different patient
16 populations. Their findings in group health enrollees in
17 the general population would indicate that we can take SIP
18 scores of 3 or under to be consistent with normal function.
19 Among the various patient groups that they surveyed,
20 patients with ALS, in this case advanced ALS, had the
21 highest SIP scores of all those recorded. It was higher,

for example, than the score for patients with end-stage renal disease requiring hemodialysis and higher than the score for patients with end-stage pulmonary disease requiring portable oxygen.

In separate studies, Jurkovich, et al. and Wu, et al. used the SIP to assess outcome of over 4,000 patients following major trauma or discharge from an intensive care unit. In their studies, a SIP score of 4 to 9 was defined as consistent with mild dysfunction and a SIP score of 30 or more was taken to be evidence of severe functional limitation.

In prior clinical trials involving other diseases, the SIP has been used in a fashion complementary to disease-specific measures and this information has been useful for clinical decision making. So, collectively these findings demonstrate the impact of ALS on quality of life. They also demonstrate the ability of the SIP to register the broad range of dysfunction experienced by patients with ALS as well as its value as a measure independent of the Appel scale.

Now, finally, let's consider the clinical

course of ALS in the context of the Myotrophin trials. This represents the course of a typical ALS patient as reported by Appel, et al. and Haverkamp, et al. For the first few months after onset, patients with ALS typically have troublesome symptoms, but they're usually able to live independently. Some may work, and speech and eating may be nearly normal.

As strength and muscle function deteriorate, patients spend much of their time in a wheelchair, speech is severely slurred, and the diet may have a pudding-like consistently.

Eventually, if the patients survive long enough, he or she is bed-ridden, totally paralyzed, unable to speak, dependent on a ventilator, and dependent for nutrition on a tube passed into the stomach either through the nose or a specially created port in the abdominal wall.

The average Appel scores which correspond to these states of dysfunction are shown here, and the months from onset to complete paralysis shown here are derived from the median rate of progression observed in the Baylor population.

1 Now, the Myotrophin trials span the first three
2 stages shown here. As we'll see in a few minutes, patients
3 were required to have an Appel score of 40 to qualify for
4 the trials and one of the protocol-specified termination
5 points was an Appel score of 115 or greater. Patients with
6 Appel scores greater than 115 are usually too debilitated
7 to make it into the clinic and reliably participate in
8 clinical trials.
9 Also, note that these stages are separated by
10 an average of about 20 points. Therefore, a 20-point
11 increase in the Appel score was used as an efficacy
12 variable indicative of clinically significant disease
13 progression.
14 Now, let me emphasize several caveats before we
15 leave this display.
16 First, these stages are not distinct entities.
17 They're part of a continuum. Patients with ALS don't
18 represent a single population. The mix of symptoms varies
19 from patient to patient, and this display depicts primarily
20 motor manifestations.
21 Second, death is increasingly likely to occur

as patients approach end-stage disease but can occur earlier depending on respiratory complications and a variety of other risk factors.

Finally, because the SIP registers the patient's own perception of their quality of life, it's not possible to fairly represent it on this display. But as we'll see in a few minutes, the average score at randomization of the patients randomized to the Myotrophin trials was in the high 60s for the Appel scale and it was about 20 for the SIP. This would be consistent with moderate disability, as defined both by the clinician and as perceived by the patients themselves.

Now, as the disease progresses, we would expect both the Appel score and the SIP score to increase. If Myotrophin slows progression of these clinical manifestations and if it slows the deterioration of the patient-perceived quality of life, we would expect this to register both as a lesser increase in the Appel score and a lesser increase in the SIP.

Now, the nature of ALS is such that there has been little to offer patients other than supportive or

palliative care. These measures include physical therapy, speech therapy, nutritional therapy, respiratory therapy. They also include the administration of agents to decrease muscle spasm, to aid digestive function, or to treat depression.

Not all patients receive such supportive measures. Rather, their use varies with the wishes of the patient, with the recommendations of their physician, with local standards of practice, and with the facilities at which the patients receive their care.

In the Myotrophin trials, these supportive measures were not standardized among study sites. Rather, they varied in accordance with all of these factors.

Now, riluzole was recently approved by the FDA based on its effect on survival in patients with ALS. However, riluzole was not demonstrated to preserve muscle strength and function or to prolong the period of relative self-sufficiency or mobility of patients with ALS. Thus, the unmet medical need is great.

In preclinical studies, recombinant human IGF-1 has been shown to enhance or preserve neuromuscular

function.

If there are no questions regarding these introductory remarks, which I'd be happy to entertain, I'd like to introduce Dr. Jeffry Vaught who will describe these preclinical studies.

DR. GILMAN: Are there questions?

(No response.)

DR. GILMAN: All right. Please proceed and please be as brief as you can.

DR. VAUGHT: Thank you, Dr. Scharschmidt, and good morning. I too am a new face for the panel. I'm Dr. Jeff Vaught.

I'd like to briefly review with you the relevant aspects of the neurobiology of Myotrophin which led us to and continues to support the clinical evaluation of Myotrophin as a treatment for ALS.

Now, as I'm sure you're well aware, Myotrophin is recombinant human insulin-like growth factor 1, and I will abbreviate it as IGF-1. It is a 70 amino acid protein with the molecular weight of approximately 7.6 kilodaltons. Now, although it was originally isolated in part due to

some metabolic and endocrine similarities to insulin, we now know that it is mechanistically, biochemically, and pharmacologically distinct from insulin. IGF-1 is a normally circulating protein with prominent neurotrophic activity.

Although within the last few years the precise intracellular signal transduction pathways which mediate the neurobiological effects of IGF-1 have been more fully elucidated, it's not the focus of this particular presentation, but I think it's important to point out that IGF initiates the effects on cellular activity by binding to a specific membrane-bound receptor.

This particular receptor is a heterotetrameric tyrosine kinase receptor which belongs to the insulin IGF receptor family. It's a so-called type 1 IGF receptor. This particular family of receptors differs from the tyrosine kinase family of the neurotrophin family through which BDNF binds and is quite distinct from the cytokine receptor family through which CNTF binds. This is important for a couple of considerations.

The first is that it's probably inappropriate

to generalize growth factor activity across all growth factors. The receptor specificity provides the opportunity for mechanistically distinct events.

And secondly, the specificity of IGF-1 for the type 1 IGF receptor and its low affinity for the insulin receptor provides an explanation for the lack of insulin-like side effects that we've observed clinically.

Now, as Dr. Scharschmidt has carefully demonstrated to you, the devastation of ALS involves the entire neuromuscular axis. There's motor neuronal death. There's axonal dysfunction. There's loss of neuromuscular innervation and there's muscular atrophy. Since the precise cause, the etiology, of sporadic ALS is not known, it's difficult to assess which of these parameters would be the most important to intercept pharmacologically to produce a therapeutic benefit. Thus, a pleotrophic molecule that could affect a variety of these components would seem to be an appropriate choice.

I'm going to provide you with some evidence very briefly, Mr. Chairman, that shows you that IGF affects each of the components affected in ALS, that IGF affects

motor neuronal death and promotes survival of motor neurons, increases axonal regeneration, provides for re-innervation of previously denervated muscle, and although not presented here, it's well known that IGF can affect an increase in muscle mass and strength and decrease atrophy.

This slide clearly demonstrates the motor neuron survival effects of IGF-1. When motor neurons are cultured after a couple of days, in the absence of trophic support, what occurs is that the neurons die, and these are the demonstration of dead neurons. As one can clearly see, there's a loss of cellular morphology, a loss of phenotype, and if one carefully examines this particular panel, there's no neuritic extension. However, in the presence of IGF-1, there's a robust cellular morphology that's obtained by these particular motor neurons, as well as the elaboration of neuritic extensions as can be clearly seen here.

Now, if one were to take these data visually presented and quantify this, there's clearly a dose-concentration-dependent survival effect produced by IGF-1 on motor neurons in culture.

Now, in addition to the in vitro survival-promoting effects of IGF-1, it also produces in vivo motor neuron survival effects. Now, there are several ways of killing motor neurons in vivo. A convenient way is to cut the sciatic nerve of a neonatal rat. That's demonstrated in this next slide.

When the sciatic nerve of a neonatal rat pup is severed, there's a marked loss, and in this instance -- along this axis is motor neuron survival -- about a 55 percent loss in the number of motor neurons in the ventral part of the spinal cord. Administration of IGF-1 subcutaneously, which is a clinically relevant route, in a dose-dependent fashion increases the survival of motor neurons following sciatic axotomy.

Now, these particular experiments here have been replicated by Li and colleagues at Wake Forest, as well as the fact they're not limited to spinal motor neurons. Hughes and Mikel Sendtner and Hans Thoenen at the Max Planck have shown that in a facial axotomy there's a loss of motor neurons, and IGF-1 can prevent the loss of these facial motor neurons as well.

Arlene Chui and colleagues have shown in a hypoglossal nucleus axotomy that IGF similarly has a beneficial effect on motor neuron survival. Thus, brain stem motor neurons are also affected by IGF-1.

Now, since ALS is a progressive loss of motor neurons, this particular attribute of IGF-1 is important in maintaining the survivability and function of the motor neuron unit. However, reality of ALS is when patients present, there's been some denervation that has occurred prior to any treatment.

So, what's the natural process when there's a muscular denervation physiologically to try to re-innervate existing muscle? What happens is very simply that the denervated muscle is re-innervated by healthy muscle fibers called the process of sprouting. Perhaps one of the best known aspects of IGF is its ability to induce sprouting.

This slide was provided to me by Dr. Pico Caroni. It was published in the Journal of Neurobiology in 1994, and what we see here is this is an axon leading to a neuromuscular junction, which is the end part of the motor unit itself. Administration of IGF-1, as is demonstrated

in these two panels, show that this is a particular axon -- I'd like to draw your attention to these bifurcations, which is the administration of IGF-1 which induces sprouting. Thus, the physiological process of healthy muscle sprouting to denervated muscle can be enhanced by IGF-1 treatment, as is demonstrated here. This is a particular axon again with a sprout leading to a neuromuscular junction.

Now, of course, the consequence of sprouting must lead to a functional result, and this can be demonstrated in a variety of animal models when one looks at the regenerative capacity of an animal and its ability to be enhanced by the administration of a trophic substance.

This was performed by Contreras and colleagues, as is demonstrated in the next slide, where the sciatic nerve of a mouse can be gently crushed, and the behavioral manifestation of this is the inability to cling to an inverted screen. Now, over the course of 17 to 21 days, since this is a gentle crush that has occurred, this gradually recovers which shows the endogenous regenerative

capacity that exists physiologically. So, what one would look for then, if one had an agent that enhanced axonal regeneration, would be the ability to enhance this particular process.

So, in this instance what we're looking at on this axis by these bars is the percent success at day 10 in the ability to grip the inverted screen. Now, in a control situation without IGF-1, only 48 percent successful attempts were performed by these animals. However, the administration of 0.1 or 1.0 milligram per kilogram subcutaneous IGF-1 markedly enhanced the success rate up to over 85 percent.

Now, inserted in these bars is also the plasma concentrations of IGF-1 which I'd like to demonstrate a simple point. First of all, the effects on regeneration are dose-dependent as well as relate very closely to plasma levels. As dose increases, plasma levels increase and response increases.

Now, this is a traumatic induced injury of the nerve. There are also spontaneous models of neuromuscular dysfunction. One of these particular models is the Wobbler

mouse. The Wobbler mouse does have several aspects that are relevant to ALS, such as neuromuscular dysfunction. After about 3 weeks of age in this particular animal, there's a gradual loss in ability of the animal to grip a dynometer. This is a measure of the grip strength of that particular animal. That's depicted on this axis and I will simply describe it as grip strength. So, in the Wobbler mouse, which is a spontaneous neuromuscular degeneration, there's a gradual deterioration over time in the ability of this animal to grip.

Administration of a milligram per kilogram IGF-1 subcutaneously once again markedly improves and prevents the deterioration of this grip strength in the Wobbler animal.

So, whether it's traumatic injury or spontaneous injury, IGF-1 seems to have a beneficial effect on the regenerative capacity of the nerve system.

Now, as I started off by saying, we don't know the etiology of sporadic ALS. Thus, it's very important that the mechanism that's chosen in order to treat the disease is not dependent on the type of insult we've

1 produced preclinically to induce that particular insult.
2 IGF-1 from a variety of laboratories, regardless of insult,
3 has shown beneficial effects on motor neuron axonal
4 regeneration and re-innervation.
5 Now, although the etiology is not quite yet
6 fully understood, it presents challenges to us as to how to
7 target this particular disease. I think it's particularly
8 important -- I'm going to take you back now to some in
9 vitro experiments where Dr. Jeff Rothstein has recently
10 published in the last couple of years that one component of
11 sporadic ALS could be due to excessive extracellular
12 glutamate. That's an elevation of glutamate in the
13 cerebral spinal fluid.
14 Now, this can be modeled in an in vitro
15 situation in organotypic cultures, and various agents that
16 might affect this glutamate excitotoxic response, where
17 this elevation of glutamate causes a loss in neuronal
18 viability, can in fact be modeled.
19 In this particular situation, these are
20 organotypic cultures in which the spinal cords from rats
21 can be cultured for very, very long periods of time. Now,

this is quite different than the first slide I showed you which was over 2 days. I hope the panel can detect the differences between these panels. In the first panel here, MN stands for motor neuron, and what it's pointing to are healthy motor neurons in the control situation.

Now, to mimic that which is believed to occur in sporadic ALS, pharmacologically you can inhibit the ability of the motor neuron to clear glutamate, so you elevate the levels of glutamate and one sees that there's a tremendous loss of motor neurons in these organotypic cultures with no neuritic extensions.

When IGF-1 is incubated in the presence of this pharmacologic agent which elevates glutamate, there's a marked nerve protective effect. So, we're comparing this effect where there are motor neurons clearly present to the control situation and that after excessive glutamate.

This suggests that in fact that if in sporadic ALS excessive glutamate is responsible for motor neuronal death, IGF-1 has the opportunity to prevent this particular neurotoxic event. Now, although visually very obvious here, it can be quantified in a couple of ways. Number

one, you can count the number of motor neurons, or two, you can use the biochemical marker, choline acetyltransferase, which marks for motor neurons.

Can I have the next slide please?

DR. GILMAN: Before you move on, let me ask you about that previous slide. It looks as if there are lots of cells sprouted in the intermedial, lateral, and dorsal columns too. Is that correct?

DR. VAUGHT: In which panel are you referring to, Dr. Gilman?

DR. GILMAN: The far right panel.

DR. VAUGHT: Far right? That could very well be in this particular slice. That's correct.

I think what's important is that as you look in the far right column with IGF-1, these motor neurons tend to -- since these are prolonged cultures, there's a lot of neuritic outgrowth and extension that occurs. In the panel where there's no IGF-1 in the presence of excessive glutamate, there are no motor neurons and there's no neuritic extension. So, it clearly demonstrates the protective activity that's occurring here.

DR. GILMAN: So, these have all been incubated the same period of time.

DR. VAUGHT: That's correct.

DR. GILMAN: The same age.

DR. VAUGHT: That's correct. Same age, same period of time, the only difference being -- to answer your question directly, this is 3-O hydroxyaspartate which inhibits the transport of glutamate into accessory cells.

DR. GILMAN: Thank you.

DR. VAUGHT: These data can be quantified and I'll show you very quickly. If one looks at a variety of neuroprotective agents in this model, the two which have shown most significant effects are IGF and riluzole.

Now, are there any other components of the IGF system that we might apply to the human situation of amyotrophic lateral sclerosis? And I can provide simply one.

Adem and colleagues, as well as independently Dore and colleagues, have demonstrated that in spinal cords taken from ALS patients, there's a marked elevation of IGF receptors. This is demonstrated by this slide, which this

is control spinal cord, age-match controls, and these are ALS spinal cords. I draw your attention, since this is autoradiography, to the red color in which it clearly demonstrates from ALS patient to control a marked elevation in the ventral horn, as well as other areas of the spinal cord, of the IGF receptor system.

I think these data are important for two reasons. First of all, it demonstrates that in the spinal cords from ALS patients there are in fact IGF receptors present on motor neurons, and secondly, the IGF receptor, consistent with what happens in peripheral systems, has been activated and is responsive in part of the regenerative process.

So, as I've tried to very briefly review with you, ALS affects all components of the neuromuscular axis. It affects motor neuron survival, axon, causes denervation of the neuromuscular junction, and muscular atrophy. IGF-1 in preclinical studies has provided evidence that can affect each of these components affected in ALS. This includes the promotion of motor neuron survival. It promotes axonal regeneration. It induces motor end-plate

sprouting and can increase muscle mass and strength.

It is based on these data that provided the preclinical rationale that led us to evaluate Myotrophin clinically for the potential therapeutic utility in ALS.

Dr. Scharschmidt will now describe these studies to you.

DR. GILMAN: There's a question from Dr. Drachman.

DR. DRACHMAN: I for one would be very interested in the evidence of surrogate activity that you may have. The notion of sprouting is certainly a very interesting one. What evidence have you accumulated that there is in fact sprouting in ALS when you use IGF-1?

DR. VAUGHT: That's a very good question. In fact, in actually looking at the sprouting response in patients -- and I could defer this to my clinical colleagues. I'll take a crack at it here -- we did not look directly at sprouting in ALS. Clearly the sprouting response in ALS is part of the regenerative process that occurs naturally in the disease. We've not looked directly at that.

As we discussed earlier, the data by Felice, et al. looking at motor unit would be a way of approaching that very question of have we affected the motor unit directly in ALS. That was not evaluated in our current clinical trials.

DR. DRACHMAN: No biopsies that you're aware of, no studies, no EMG studies that have been done to demonstrate a change that you're aware of?

DR. VAUGHT: With IGF-1? No, not to date. Those studies are certainly very important and studies which we're considering doing.

DR. GILMAN: Does anybody else in the sponsor's group want to address that question?

(No response.)

DR. GILMAN: All right. Thank you, Dr. Graney.

Then Dr. Zivin has a question also, Dr. Vaught.

DR. ZIVIN: A couple of questions. Do you believe that the Wobbler mouse is an adequate model of ALS?

DR. VAUGHT: I think, Dr. Zivin, I would answer that by saying I don't think there is a model of ALS. As we looked at IGF-1, we think that the pleotrophic

activities of IGF-1 and effects across the entire neuromuscular access, as well as looking at several animal models, that in the aggregate all of the data provided the rationale for clinical evaluation. We don't weight any one model greater than the other. I actually look at the entire body of evidence. But it's a reasonable model that resembles certain aspects of disease.

DR. ZIVIN: Having said that then, my understanding of ALS is it is both an upper and motor neuron problem, and what I'd like to know is, do you have evidence that IGF-1 gets into the central nervous system and does anything about the upper motor neuron problem?

DR. VAUGHT: Yes, let me take that in two parts. First, does it get into the central nervous system? Several pieces of information suggest that in fact it communicates to the central nervous system.

First of all, Carolyn Bondy and colleagues have in fact demonstrated that IGF can cross the blood brain barrier. We know that along the endothelial cells and the choroid plexus, there are specific transport mechanisms that bring IGF-1 into the central nervous system. Now,

whether or not it does so in concentrations sufficient to activate the receptor we don't know.

Secondly, we know that neurotrophic factors can access the central nervous system via retrograde transport. Since in ALS the projections of these motor neurons lie outside the central nervous system, it's very well demonstrated for a variety of growth factors, including IGF-1, that retrograde transport can occur, and in fact if you block that, you block the physiological and pharmacological effects of a variety of growth factors, including IGF-1.

Thirdly, our data on motor neuron survival promoting activities by subcutaneous administration further exemplifies that in some fashion there's a communication to at least the spinal cord motor neuron.

We also know that by sprouting we can turn on GAP 43 and alpha tubulin which are markers for a sprouting response which are nuclear events, again suggesting that there's a signal back to the central nervous system.

We've not looked directly at the upper motor neuron effects of IGF-1. So, in the last part of your

question, do we affect upper motor neurons, we've not looked. In the Wobbler mouse, it's predominantly a motor neuron deficit of the cervical region. It's a four limb dysfunction.

DR. GILMAN: Do you have another question?

DR. ZIVIN: No.

DR. GILMAN: Dr. Leber?

DR. LEBER: I have a question because of just a balance of this. Clearly a lot of preclinical work is done to justify investment in the development of a new drug in clinical trials. However, it's also true in reductionist research that in addition to models where the drug has an effect, there may be those in which it has failed to show on, and you rarely hear about those.

I just wonder if anyone knows whether there are models that have been proposed to represent this disease where you can't find an effect of Myotrophin, whether they've been done or whether they haven't, and whether they exist or not.

DR. VAUGHT: We have looked at a model that has been reported to resemble the familial aspect of

amyotrophic lateral sclerosis. In that particular model, which is an over-expression of a mutated gene, copper-zinc superoxide dismutase, which clearly links to familial ALS, which is approximately 2 percent of the overall population. We've not as yet seen an effect of IGF in this particular model.

We've looked at other agents as well and not seen effects of those agents.

I think that as far as its relevance to disease, we could go back to the point that it is one of many models in which we evaluate in aggregate the overall activity of the agent.

So, your point is well taken, Dr. Leber, but in essence, if you look overall, we're not using one model to predict one way or the other.

DR. GILMAN: Dr. Leber?

DR. LEBER: One follow-up question because again it sort of lies on the table unanswered. We seem to be assuming -- or at least that's my presumption -- that sprouting is a benefit. But sprouting might not be a benefit if it didn't occur in the right relationship in the

right way, and I thought Sid was raising the possibility that there may in fact be sprouting in areas that would not necessarily be beneficial. Were you trying to make that point?

DR. GILMAN: I was trying to make two points that I didn't really make very well, so let me ask again.

I was wondering whether, first, the Rothstein experiments consisted of injecting the agent into a leg, and if so, did that then show result in sprouting within the lumbosacral segments? And did injection into the leg result in sprouting in the cervical segments also? In other words, to what extent will this agent track up the cord? That's an important question I think clinically. If the agent is given in a leg or an arm, does it then affect bulbar musculature?

DR. VAUGHT: First of all, maybe a point of clarification. The Rothstein experiments were organotypic cultures. So, those were not in vivo.

DR. GILMAN: Oh.

DR. VAUGHT: All right? So, in that regard, it was perhaps the Caroni experiments you were thinking about,

and those were injected on the muscle. What we were looking at there, Dr. Gilman, was the ability of sprouting at the neuromuscular junction rather than in the spinal cord, in the central nervous system.

But in relationship to abnormal sprouting, we must remember that in ALS there's been denervation, so we're not looking at abnormal sprouting. We're looking at a reinstatement of normal neuromuscular function, trying to normalize a deficit.

We also have no evidence after long-term administration of IGF in a variety of models that abnormal sprouting has occurred because in all functional assessments -- one would have to assume that there would be a functional abnormality with abnormal sprouting. In all of our functional assessments, such as looking at the sciatic nerve crush and a variety of other models, we've seen benefit rather than deleterious effect.

DR. GILMAN: Well, to follow up again, is there evidence then that this neurotrophic agent, if injected into a leg, will activate receptors that are in the cervical spinal cord?

DR. VAUGHT: No. If it's going into the leg muscle, those predominantly innervate motor neurons in the lower part of the spinal cord, as you know.

DR. GILMAN: Yes.

DR. VAUGHT: Once transported to the central nervous system, it's not believed that it's trans-synaptic, that it leaves the motor neuron and then enters the CSF.

DR. GILMAN: Well, again, I think that's an important issue because if the agent is given into the left leg or the right leg, can it affect the upper extremities or the bulbar musculature?

DR. VAUGHT: Yes, I see where you're at. Where we're administering it subcutaneously -- it's not over a muscle per se -- it reaches the general circulation.

DR. GILMAN: And does it penetrate sufficiently then to show that you activate the receptor with the agent?

DR. VAUGHT: Yes. We know we can promote motor neuron survival. Now, your question as far as bulbar, we have not looked at bulbar motor neurons -- or upper motor neurons. Excuse me.

DR. LEBER: Promotes survival where?

DR. GILMAN: Yes. That's the question.

DR. VAUGHT: Based on the model in the spinal cord.

DR. GILMAN: Where in the spinal cord?

DR. VAUGHT: From the brain stem to lower sacral regions.

DR. LEBER: In what species?

DR. VAUGHT: Mouse and rat.

DR. GILMAN: Are you going to review those data?

DR. VAUGHT: I can go back over it again. We did.

DR. GILMAN: No, no. You just made an assertion that injection subcutaneously of this neurotrophic factor --

DR. VAUGHT: That's correct.

DR. GILMAN: -- will prolong motor neuron survival in the cervical as well as lumbar musculature. I did not see that presented.

DR. VAUGHT: Yes. Those data were the rat sciatic axotomy experiment where we axotomized the rat

sciatic nerve, injected IGF-1 subcutaneously, looked at motor neurons in the ventral horn of the spinal cord --

DR. GILMAN: Of the lumbosacral spinal cord.

DR. VAUGHT: That's correct.

DR. GILMAN: But the question is, to what extent does this effect generalize? In other words, do you affect neurons in the cervical cord as well?

DR. VAUGHT: The only data we would have there would be on brain stem motor neuron, which would be a facial axotomy or hypoglossal nucleus axotomy.

DR. GILMAN: Well, but again, that's an axotomy experiment.

DR. VAUGHT: Yes.

DR. GILMAN: Dr. Drachman?

DR. DRACHMAN: I'm a little puzzled. Just a follow-up to Dr. Zivin's question, you said that the retrograde passage of the IGF-1 was important and that's one of the major ways that IGF-1 reached the central nervous system. How does that work when you've done a sciatic nerve section? Could you explain that?

DR. VAUGHT: Sure. Let me, first of all, say

it's a way. Whether it is the major way I think would remain to be proven. It is a way that you can communicate that forward.

In fact, the whole concept of neurotrophic factor biology suggests that there's neurotrophic support for the motor neuron. Thus, on denervation it provides for the ability to be taken up by the nerve stump and transported retrogradely to the central nervous system. Now, whether that occurs or not, Dr. Drachman --

DR. DRACHMAN: The line of questions here is whether it spreads, and that's really the key. If the sciatic nerve is sectioned and the IGF-1 does not get in through that route, how exactly does that work? I'm not quite clear unless you're either suggesting that it does get in or that it spreads within the central nervous system, one or the other.

DR. VAUGHT: Perhaps I can readdress rather than talking about the sciatic nerve. When we do a sciatic nerve axotomy, we're looking at a specific set of motor neurons and asking a very specific question, not does it affect amyotrophic lateral sclerosis, but can we show

activity that we can promote motor neuron survival in the part of the spinal cord to which the sciatic nerve projects.

So, the administration of IGF-1, however it communicates to the motor neuron, whether it's via retrograde signal, via retrograde transport and/or crossing the blood brain barrier, the end result of which is motor neuron survival in this particular model -- there aren't good models for motor neuron death along the entire axis of the spinal cord preclinically.

DR. GILMAN: Can I ask Dr. Drachman's question again? I think Dr. Drachman is saying, if the sciatic nerve is sectioned, then how is the agent getting into the motor neurons that are represented in the sciatic nerve? Is the agent getting into the proximal stump? Is it getting directly into the central nervous system, or how does it get there?

DR. VAUGHT: The data would support both of those as possibilities, as well as the fact that it doesn't even have to get to the nervous system because not all growth factors are transported, but there can be a

1 retrograde signal that's produced in the motor neuron. For
2 example, if IGF is applied to the proximal stump, if one
3 looks at nuclear markers in the motor neuron, there's an
4 elevation of, say, GAP 43 that induces sprouting. Now, if
5 that's due to the transport to the central nervous system,
6 that's one way. Crossing the blood brain barrier is
7 another way and/or a retrograde signal that also signals
8 the motor neuron to induce these nuclear events.
9 DR. GILMAN: Finally, let me just ask one last
10 question about sprouting versus motor neuron survival. Do
11 you think that the two are connected? First, does
12 sprouting promote motor neuron survival? And do you have
13 evidence that sprouting in fact promotes any recovery of
14 function in the models that you have discussed with
15 administration of this neurotrophic factor?
16 DR. VAUGHT: Yes. Can I deal with those
17 independently, sir?
18 First of all, does sprouting promote motor
19 neuron survival? I think the answer would be it's an
20 independent event. You can have a sprouting phenomenon
21 independent of motor neuron survival.

What we've noted and what's now being recognized in the literature is that merely survival of a motor neuron does not necessarily mean the elaboration of its axonal extension. For example, certain trophic factors and certain elements that are involved in the survival of the cell body. You could have very nice surviving motor neurons with no axonal extension. Those are data that are there.

It was recently published in Science with another trophic factor that in fact you could have a profound sprouting response by simply looking at sprouting in a particular animal model and have a very prominent effect in a model of neuromuscular dysfunction. This was in the PMN mouse.

So, the idea that IGF produces sprouting, if we just look at that, I'm not sure that we would say that its preclinical rationale for looking at its effect in clinical disease. We go back to the combined effects of motor neuron survival, axonal regeneration, sprouting, and the prevention of muscular atrophy is really where we would say in the aggregate would -- since this is what's affected in

ALS, a clinical evaluation of IGF-1 in that.

Now, as far as your last question, as far as the regenerative capacity of IGF-1, if you administer IGF-1 in, say, the slightly crushed sciatic nerve, you can find nerve segments that have been denervated that following IGF-1 -- and this is a natural recovery process -- this is enhanced, which would suggest sprouting, yes.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: A couple of questions, and since I'm having some difficulty following this, just tell me if they're silly.

You made the point that the protection or encouragement of growth ideally should be independent of the kind of injury. What's your view about the failure to see much in the familial ALS model? Does that shake your faith at all? A silly question perhaps. What's your response to that, though?

DR. VAUGHT: Well, it's a very good question. To date the reported agents in the familial ALS model have been riluzole and vitamin E. I do know of several other things that have been looked at and tried, but they've not

been published, so until that occurs, it would probably be inappropriate to discuss.

I guess we would view it and I would view it from a discovery aspect. FALS models just that: familial ALS. It does not model sporadic ALS. Clearly there are other mechanisms involved in sporadic ALS. In the aggregate of all of the activities, it's of interest to us to further study this FALS model and understand its predictability to human disease. We simply don't know enough about it, but in the aggregate we'd say we didn't see activity the way we looked at it in this particular model, but a variety of checks on the side that there are other models that show very robust activity.

DR. TEMPLE: Okay. I guess I thought your point was that none of these are models of ALS. None of the animal models are true ALS.

DR. VAUGHT: That's right.

DR. TEMPLE: But that didn't matter so much because you got growth in any kind of injury by severing the sciatic nerve. Okay.

DR. VAUGHT: That's correct.

1 DR. TEMPLE: The second question is there have
2 been other growth factors where the animal data have led
3 companies to spend vast resources on doing trials and maybe
4 some of those have been conspicuous failures that you read
5 about in the Wall Street Journal. What do those results in
6 the animal models look like in comparison? You did show
7 one where IGF and riluzole were clearly better. Is that
8 true in the other models too, or do those all sort of look
9 pretty good for the brain-derived growth factor and all
10 that?
11 DR. VAUGHT: Yes. If we look at each component
12 individually, you could compare across. I think what I'd
13 like to impress upon the panel, as well as those gathered
14 here, as well as our own observations, is that the
15 pleotrophic effects of IGF are unique to IGF. We look at
16 motor neuron survival, but muscle cells are dying as well
17 in ALS. IGF has profound effects on muscle cell survival
18 as well as motor neuron survival. No other growth factor
19 has this attribute.
20 It's the combined activities of motor neuron
21 survival, axonal regeneration, sprouting, and the effects

on muscle, along the entire neuromuscular unit, that we think distinguishes IGF from the other trophic factors. We know that in injury IGF receptors are up-regulated and sustained over the entire course of injury chronologically as well as temporally related to recovery. This is not true for other growth factors.

We also know, as I'm sure well aware to the agency as well as to the committee, apart from mechanisms which are quite distinct for IGF-1, there are other pharmaceutics reasons why certain substances work clinically besides the strong preclinical rationale.

But I think it's the pleotrophic effect of IGF-1 that clearly distinguishes it from other growth factor substances.

DR. TEMPLE: Okay. Actually the last thing you mentioned leads to my next-to-last question and then I'll have one more, which is how many of the models involved administration at a site distant from what you were trying to influence, such as a subcutaneous injection? I guess the sciatic nerve injury one represented a subcutaneous injection.

DR. VAUGHT: That's correct.

DR. TEMPLE: So, it must travel through the systemic circulation to get there or something.

DR. VAUGHT: That's correct.

DR. TEMPLE: Do any of the other models have that characteristic too?

DR. VAUGHT: Yes. The Wobbler mouse was subcutaneous administration. The sciatic nerve crush injury was subcutaneous administration. All those were.

DR. TEMPLE: Okay. And my last question is, it's sort of conspicuous that there's no human data correlating to any of these things. Could you or could somebody subsequently say how one would go about looking for these kinds of effects which might be considered plausible surrogates in human trials if one wanted to? I'd also be interested in why no one has tried. Maybe it's very difficult and there's probably no precedent for it. That might be a reason, but it's worth thinking about what one could do because, among other things, these effects are probably seen fairly early. Right?

DR. VAUGHT: The effects?

DR. TEMPLE: Well, the effects you've seen in the animals occur right away.

DR. VAUGHT: They occur after administration, yes. It takes some time to develop, but they --

DR. TEMPLE: Some time? Days, weeks?

DR. VAUGHT: Days. So, in other words --

DR. TEMPLE: That's really compared to 9 months. Okay?

DR. VAUGHT: Yes, that's correct. Very good.

In answer to your question, I would defer that to my clinical colleagues since that is more of a clinical question.

DR. GILMAN: Does somebody want to answer that from the clinical perspective? Dr. Graney?

DR. GRANEY: Dr. Gilman, we have no specific plans right now. We're considering a range of electrophysiologic explorations in future trials. But the survey of the literature doesn't indicate that we could reliably use them as a major component of a trial right now. It's really a technology that's in development, as far as its application to ALS.

1 DR. GILMAN: Dr. Leber?

2 DR. LEBER: Since Dr. Temple brought up

3 surrogacy, which I think we were indirectly discussing,

4 surrogates and what they are is still a matter of some

5 contention. It's interesting that although we recognize

6 surrogacy as a basis for accelerated approval, the agency

7 doesn't have any regulations yet specified that I know of

8 -- and Bob can correct me -- about how one really knows

9 that something is or is not a valid surrogate.

10 As a result, I feel unencumbered in suggesting

11 that there's a difference between a surrogate where one has

12 good evidence showing that something that can be measured

13 in humans reliably predicts toward the future what will be

14 the state of a patient at a later time and an observation

15 that suggests something as a candidate or putative

16 surrogate that might be predictive if one collected the

17 evidence to document it. For example, just measuring

18 something that the drug produces as a change in no way can

19 logically say that that change will in any way predict the

20 future state of the patient unless you do clinical studies.

21 I think that part of this -- I think the soil

of why one develops a drug makes a lot of sense in terms of reductionistic preclinical models, but the first question is whether or not a drug works and then if it works, perhaps you can understand how it works. Another question is, why would I waste my time and effort developing a drug unless there was good reason to believe it? But the issue still ultimately has to be that in spite of all the predictive hope is there evidence that the drug works.

And I think we're sort of stuck. We'll go round and round on postulated mechanisms, all of which may be quite reasonable, rational, would lead a logical person to invest time and effort in it, but the question is do we yet have findings that suggest that we have anything to test any of our surrogates against. In a way it's a plea to get us back on what has been the spirit of the agency and that is relying on studies in humans that would allow us to conclude that the drug is effective or not effective.

DR. GILMAN: All right. Any other questions, comments from the panel?

(No response.)

DR. GILMAN: If not, let's proceed.

1 DR. SCHARSCHMIDT: Based upon the preclinical
2 studies, which Dr. Vaught has summarized, the efficacy of
3 Myotrophin was studied in patients with sporadic typical
4 ALS in two multi-center randomized placebo-controlled
5 trials. Apropos of the questions by Dr. Leber and Dr.
6 Temple, I would mention that patients with familial ALS
7 were specifically excluded from these trials.
8 Now, these two trials had many similarities, as
9 well as some important differences. Protocol 1200 was
10 executed at eight sites in North America and we'll also
11 refer to this as the North American study. Protocol 1202
12 was executed at eight sites in six different European
13 cities, and we'll also refer to this as the European study.
14 Recall that supportive measures were not standardized among
15 study sites.
16 In the North American study, 266 patients were
17 randomized equally into three study arms: placebo, 0.05
18 and 0.10 milligrams per kilogram per day. And I'll refer
19 to these later two as low dose and high dose treatment
20 groups. In the European study, 183 patients were
21 randomized on a 1 to 2 basis into placebo and high dose

1 treatment groups.

2 In both studies, the Appel score was the

3 primary efficacy measure. Recall the Appel score assesses

4 morbidity from the standpoint of the clinician. And in

5 both studies, the SIP was the secondary efficacy measure.

6 The SIP assesses morbidity from the standpoint of the

7 patient.

8 Appel measurements were made at randomization

9 and monthly thereafter. SIP measurements were made at

10 randomization and every 3 months thereafter, and in each

11 case the SIP measurement was made within the 7 days

12 preceding the clinic visit at which the Appel measurement

13 was made.

14 Now, this presentation will focus on

15 prespecified efficacy variables. The primary efficacy

16 variable in the North American study was the Appel slope.

17 The primary efficacy variable in the European study was the

18 change from baseline in the Appel score.

19 If we look at secondary efficacy variables in

20 the two studies respectively, they included the change from

21 baseline in the Appel score and the Appel slope. So, these

two primary and secondary variables were mirror images of each other.

Additional secondary efficacy variables included the time to protocol-specified markers of advanced disease, specifically an Appel score of 115 or greater and an FVC of less than 39 percent, and the time to 20-point progression on the Appel scale.

The increase from baseline in the SIP score was also included as a secondary measure in both studies. I call your attention to the fact that 20-point progression on the Appel scale was a prespecified marker for the European but not for the North American study.

Now, this schematic depicts examples of study patients which we think are helpful in understanding the design and analysis of the Myotrophin trials.

First let's consider issues related to randomization and stratification. In order to qualify for the study, patients needed to have an Appel score between 40 and 80. Patients also needed to demonstrate progression as demonstrated by an increase of 5 points on the Appel scale during the 2 to 3-month prerandomization period.

1 Patients who did not progress, so-called non-progressors,
2 were not randomized.
3 Note that some patients progressed to scores
4 above 80 by the time of randomization, so patients with
5 scores over 80, in some cases over 100, were randomized,
6 and this reflects the intrinsic heterogeneity of this
7 patient population.
8 In the North American study but not in the
9 European study, patients were also stratified at
10 randomization into upper and lower strata depending upon
11 whether their Appel score was greater or less than the
12 value of 60. The stratification was done for the purposes
13 of helping to ensure balance among the study arms. It was
14 not done with the intention of separately analyzing the two
15 strata.
16 Note that some patients with initial scores
17 below 60 actually progressed to above 60, that is, to the
18 upper stratum, by the time of randomization, so the upper
19 stratum included about twice as many patients as the lower
20 stratum. Also because patients who progress more rapidly
21 would be more likely to enter the upper stratum by the time

of randomization, the upper stratum not only included more total patients, but a disproportionate number of the rapidly progressing patients.

Now, what happened after randomization? About half the patients that were randomized completed the 9-month protocol. Most of the remaining patients reached protocol-specified markers of advance disease, termination points consisting of an FVC of less than 39 percent or an Appel score of 115 or greater.

Patients who either completed the trial or reached these protocol-specified termination points were eligible for high dose Myotrophin treatment as part of one of the open label protocols, and in the North American trial but not in the European trial, patients had at 3-month intervals for a period of time Appel scores during open label.

Now, finally, this display helps illustrate the three different kinds of efficacy variables, which you'll be seeing in just a minute. Measurement of the Appel slope, a primary efficacy variable in the North American study, required three post-randomization Appel measurements

as assessed by simple linear regression and the vast majority of patients who qualified for this efficacy analysis had -- 90 percent or more of patients had four points or more.

Now, note that there was month-to-month variation in the scores, but overall the slopes tended to be linear. Examination of all the patients randomized in both trials suggested that there was no systematic deviation in linearity up or down with time.

The time-to-event analysis reflects the time between randomization and the time that patients reached protocol-specified termination points, such as an Appel score of 115 or greater or an FVC of 39 percent or the time required to progress 20 points on the Appel scale.

Finally, the change from baseline analyses reflect the difference in Appel or SIP scores at the time of randomization and at the time of completion of the study.

Now, for patients such as this one, who terminated early, their value at termination would be carried forward to the final analysis. This last value

carried forward approach has the potential to introduce bias, for example if there is uneven dropout from the study arms either in terms of numbers or patient characteristics, for example, the Appel score or the Appel slope.

However, examination of the patients who exited the trial prior to 9 months indicates that attrition did not contribute to the observed treatment effect in the North American study. Moreover, there was internal consistency in both trials with respect to all efficacy variables with respect to either the presence or the absence of statistical significance.

Now, of the 266 patients who were randomized in the North American trial, 88 to 90 percent had at least three post-randomization Appel measurements and qualified for the primary efficacy analysis. Recall that better than 90 percent of this group also had four or more points.

Of the 183 patients randomized in the European study, 88 and 84 percent qualified for the slopes analysis.

Among all patients in all trials, better than 90 percent had at least one post-randomization Appel measurement and qualified for the change from baseline

analysis.

In the North American trial, 36, 39, and 23 percent of patients respectively in the placebo, low dose, and high dose groups reached prespecified Appel or FVC endpoints, and the corresponding numbers in the European trial were 41 and 25 percent.

Finally, in both trials between 76 and 83 percent of patients qualified for the SIP analysis.

Now, let's consider the results of both of these trials and we'll start with the North American trial.

This slide depicts the primary efficacy analysis for the North American trial, namely the post-randomization measurement of Appel slopes. These three bar graphs correspond to the three different treatment groups. The slopes in the three groups were 4.2, 3.8, and 3.1, and the slope for the two treatment groups combined was 3.4 points per month.

Now, please note that in this display, as well as the subsequent displays I'll be showing you, these error bars correspond to 95 percent confidence intervals.

The primary efficacy analysis called for a

comparison of the placebo and the treatment groups combined. The p value for this analysis was 0.05.

The high dose treatment group had a decrease in the Appel slope compared to placebo of 26 percent, and this was significant at the .01 level.

The low dose treatment group registered an Appel slope that did not differ from the placebo group but was intermediate between the placebo and high dose group, consistent with a dose-related pattern of response. We'll hear later from Dr. Braekman that this dose-related pattern of response was accompanied by a blood level-response relationship.

Now, this is a cumulative distribution --

DR. GILMAN: Dr. Drachman has a question for you. Excuse us.

DR. SCHARSCHMIDT: Sure.

DR. DRACHMAN: Would you go back one slide please? I was a little confused by one thing. That is, it looks as if the placebo group is lower than the baseline slopes. Is that correct?

DR. SCHARSCHMIDT: That's correct. In fact,

the pre-slopes turned out to be not a terribly faithful reflection of the post-slopes for all the various treatment groups.

DR. DRACHMAN: So, the notion of linearity then is not as accurate as we might hope.

DR. SCHARSCHMIDT: Well, let me remind you that in some cases the pre-randomization slopes were defined just on two points. This is a really crucial point.

DR. DRACHMAN: What?

DR. SCHARSCHMIDT: In some cases, the pre-randomization change is based on two or three points. So, we knew the lines less accurately.

But, Dr. Hines, could I ask for a slide showing the patient slopes? This is a crucial point, so a picture may be worth a thousand words here.

While we're waiting for the slide, the findings reported by Haverkamp, et al. at Baylor suggested that 80 percent of patients had an R squared value for the Appel slope of .8 or more. This finding was basically replicated in our studies, but R squared has its failings as an analysis of linearity.

1 So, what we're looking at here are the actual
2 slopes of all patients, both placebo and treatment, which
3 clustered near the median. Of course, there were patients
4 with flatter slopes and patients with much steeper slopes.
5 You can appreciate that there was month-to-month variation,
6 but on balance there did not appear to be any systematic
7 deviation upward or downward with time.
8 Let me just also remind you that in order to be
9 eligible for this analysis, patients required three points.
10 Better than 90 percent of patients had four or more points.
11 So, we know with much greater accuracy the post-slope than
12 the pre-slope.
13 DR. DRACHMAN: The other part of that was that
14 it appears that in the North American study, some 29
15 patients had slopes of less than 5 points per 3 months.
16 Where did they end up?
17 DR. SCHARSCHMIDT: Maybe I can just ask us to
18 go back to the slide showing the display, the study design.
19 DR. DRACHMAN: Wasn't that a criterion for
20 entry?
21 DR. SCHARSCHMIDT: It's a critical point. Let

me just expand on it a little bit in the context of the study design.

I think the important point in here -- and it's pointed out in the briefing document -- is that there were protocol violators of two different kinds. Let me indicate what they are in the display and then summarize what the results of a per-protocol analysis would be. Remember, what we're looking at today is really an intention-to-treat analysis.

So, there were protocol violators of two kinds. There were patients who were continued on double-blind medication while awaiting for open-label medication to become available. So, in this case we're for the most part dealing with data points not patients, although if we exclude these data points, we actually chose 3 patients because they no longer had the three post-randomization Appel slopes.

There were a larger number of patients who were otherwise judged to be suitable candidates for the trial but did not demonstrate, as you indicated, the 5-point progression.

When an efficacy analysis is done which excludes both types of protocol violators -- it includes data points for patients who were double-blind data points beyond the point they should have reached termination or patients who were randomized with slower slopes than the protocol specified -- the p values for both treatment groups are under .05. They're .02 and .03. So, we're focusing today on intention-to-treat analysis but that's the result of the per-protocol analysis.

If we exclude just one group or the other, then the p value for the high dose treatment group remains significant, and the p value for the low dose treatment group is not significant but somewhere between that I just showed you in the bar graphs and .05.

DR. DRACHMAN: So, once again, where did those 29 end up? Were they in placebo groups? Were they in the high dose group? There is a very significant or a very notable -- notable, not significant --

(Laughter.)

DR. DRACHMAN: -- difference between the slopes I gather of those on placebo and those on 0.1. Those on

placebo had a pre-study slope of 4.9. Those with .05 had a slope of 4.9. Those with .1 treatment milligram per kilogram had a pre-study slope of 4.5. How did you deal with that and does this really mean that a large number of the non-progressors or those who are protocol violations ended up in the 0.1 group, or how did that work out?

DR. GRANEY: Dr. Drachman, I can address your question. While it's true that there were a substantial number of patients who did not reach the 5 points within 3 months for a variety of reasons, including a patient not being able to get in at a given month, essentially all of those patients with just a few exceptions had 7 points progression over the course of 4 months. It was simply an accommodation that had to be made to the practical considerations. So, the impact is not as great as it would seem.

While we certainly would have preferred to have everyone qualify strictly, a logistic decision was made that if those patients had a missing visit or couldn't come back, they could go to a total of 7 points in 4 months in place of 5 in 3. It's certainly not perfect but it was

more an accommodation, and the patients were then treated like other patients. So, we believe that it does not represent a sort of selective bias source of slow progressors.

DR. GILMAN: Dr. Adams has a question.

DR. ADAMS: I have unfortunately about four. Let's do them in sequence.

Would you discuss the slope acceleration again for me? If somebody has a baseline score of 95, will their slope in the next 3 months be different than if they have a baseline score of 60 on the Appel scale? In other words, does the scale by its very nature start accelerating, or is there some anticipation in the scale so that points will start to be accumulated very quickly when you get to a certain level?

DR. SCHARSCHMIDT: Dr. Hines, could I have the slide which shows the Appel slopes, let's say, if we look at patients with higher slopes?

So, what I showed you, Dr. Adams, before were the slopes for the patients clustered around the median, and what we'll look at here are the actual data for

patients who had steeper Appel slopes. So, we're looking here at patients who had Appel slopes in the very most rapid group, 7 to 8 points per month, and this is what they looked like.

Note that patients who reached these points at termination often have an up-tick and therefore are not in a position to see the next point, but by and large, examination of all 266 slopes data points in the North American trial didn't suggest deviation from linearity upward or downward with time.

DR. GILMAN: Dr. Hoberman wants to respond here.

DR. HOBERMAN: I can't give a definitive answer to your question, but I can say that one of the things that I looked at was taking the data from patients up to about 5 months after randomization and then taking the data after about 5 months and seeing whether there was an accelerated curve just in terms of a breakpoint over getting worse. And it turns out that that occurred in both trials. But again, it's a descriptive thing, but I don't know whether it's an indication of the course of disease.

DR. GILMAN: It happened in all groups?

DR. HOBERMAN: Yes. I was looking only at the .10 milligram and the placebo, but it did happen in both groups.

DR. GILMAN: Both of those.

Dr. Leber, do you want to respond to this issue?

DR. LEBER: Yes. I just want to clarify. Under the assumption that this is a linear scale over most of the range of pathology that we are likely to observe, it has to be no correlation between. That's what it should be in theory. No correlation between the intercept as an artifact of when the patient happened to get in the trial and their slope because you can pass with this disease through every one of the points of ALS score. So, it would make sense that someone can approach a score of 60 at a very flat trajectory or at a very rapid one, and they should be independent.

In this particular data set, you may see one trend or another, but it's a sampling problem. I don't know what the state of nature is, and I think we have to

admit given the linearity that has been postulated to exist for the scale over most of the range, you shouldn't see a correlation with the intercept.

DR. SCHARSCHMIDT: As I pointed out when we were speaking about the design of the trial, the fact that there was a relationship between the strata and the slope is really a function of the trial design. Intrinsically they should be different entities since all patients pass through all stages.

DR. GILMAN: That was question one of four from Dr. Adams.

(Laughter.)

DR. ADAMS: The question is, if somebody has a score of 95 when they enter the trial, are they likely to get 20 more points, which is one of the endpoints in the European study, more rapidly than somebody who generally comes in at a score of 60? We'll stick with just placebo. I'm not talking about active treatment.

DR. SCHARSCHMIDT: About 10 to 15 percent of patients overall reached Appel endpoints before progressing through 20-point progression.

1 Dr. Yoshizawa, did you want to comment?

2 DR. YOSHIZAWA: Yes. Carl Yoshizawa from

3 Chiron.

4 Because of the design of the trial, patients

5 who are at randomization at a score of 95 have increased by

6 at least 50 points because they had to be no greater than

7 80 at the start of screening. So, by their very nature,

8 they are faster progressors.

9 DR. GILMAN: Dr. Hoberman, wants to respond to

10 this.

11 DR. HOBERMAN: I have an overhead showing the

12 course of patients who drop out at different times and

13 their baseline scores that may be illustrative, but I need

14 an overhead to show it.

15 DR. GILMAN: Perhaps you could get back to it

16 when you can sort through that. It's a very important

17 point. We'd like to see what you have.

18 DR. ADAMS: I guess I'll get rid of one of my

19 questions, but this leads me to my third question which is

20 my key question for the North American trial which is from

21 our briefing document from Dr. Feeney. Of the 14 worst

patients by baseline Appel scores, 10 were in the placebo group at randomization, and I would like to know how we handle the fact that 10 out of the 14 worst patients on entry into the trial were in the placebo group.

DR. SCHARSCHMIDT: Let me consider this in relation to the different efficacy variables we're talking about. The Appel slope, which is the primary efficacy variable and the subject of the primary efficacy analysis, is at least subject to study dropouts. It captures 88 to 90 percent of all patients in the North American trial. To the extent that there is uneven distribution of patients with different Appel scores at randomization, it would manifest itself primarily in the time to endpoint analyses.

When we get, Dr. Adams, to the last value carried forward, what I'd be happy to do is just show you the attrition analysis and the characteristics of the patients who exited the trial on a month-by-month basis.

DR. GILMAN: Does that answer your question?

DR. ADAMS: Yes. Well, did you want to comment?

DR. FEENEY: It's basically all a function of

the fact that there was no upper limit on baseline Appel score by nature of the inclusion criteria. You had to raise by a minimal amount on the Appel scale over those 2 to 3 months during screening, but you could raise by any amount at all. And it just so happened that in study 1200 there was this group of outliers that begged some exploratory analysis early on because they did seem to have such a strong impact on the time to event analyses.

Now, the interesting thing is those people, by nature of their rapid progression, ended up for the most part not having a minimum of three on-study Appel scores over time. So, they ended up not being in the protocol-specified slopes analysis. That's just the way it turned out.

So, you have to kind of distinguish between the time-to-event analyses that are done today and the slopes analyses. They may be very different groups of patients in the different ones.

Now, the sensitivity analysis you're talking about -- it was an early exploratory analysis. The important thing is that in study 1202 time-to-event

analyses were negative; in study 1200 they were positive, but as soon as you took out the outliers, the time-to-event analyses tended to be more negative. An exploratory analysis.

DR. SCHARSCHMIDT: Dr. Temple?

DR. TEMPLE: I just want to be sure I'm following this and that everyone else is.

The people who were very bad in terms of Appel score at baseline, according to Dr. Feeney, don't show up in the primary analysis because they don't have three points.

DR. SCHARSCHMIDT: Correct.

DR. TEMPLE: So, to the extent that the placebo group is worse on that baseline parameter, they don't show up anymore in the analysis, but they do show up in the endpoint analysis because they do reach whatever the endpoint is faster. I think that was a point you made. Is that right?

So, the placebo group is arguably disfavored for the endpoint analysis and there's an inadvertent but existing baseline imbalance for the endpoint analysis.

DR. SCHARSCHMIDT: For the endpoint analysis.

DR. TEMPLE: For the endpoint analysis. But that disfavor doesn't show up anymore in the primary analysis because they're --

DR. FEENEY: Well, again, let's just leave this as an exploratory analysis for now. I don't want to make too much of that.

DR. SCHARSCHMIDT: Perhaps I could just reemphasize Dr. Feeney's point. We focused here specifically on prespecified analyses, but this is an awfully important point. So, when we get to the dropouts in the course of the study, which is coming very shortly, I can show you the characteristics of the patients who exited.

DR. GILMAN: Well, let's proceed for another 10 minutes. Then we will need to take a break.

DR. SCHARSCHMIDT: Okay.

So, let me just reset the stage. We've presented the bar graphs which depict the findings of the primary efficacy analysis in the North American study. We're looking here at the same findings in the context of

the cumulative distribution function.

So, here the y axis represents the cumulative percent of patients with Appel slopes corresponding to the values shown here along the x axis. The advantage of this is that it allows one to see all the individual slopes that comprise those bar graphs that we just looked at. A shift to the left, a shift toward lower slopes would be consistent with a treatment benefit, and here there is separation between the curves in favor of the Myotrophin group which is consistent with the results of the primary efficacy analysis which I just showed you.

Now, this will give us an opportunity to expand on some of the important questions raised. This display depicts the change from baseline analysis, that is, the increase from baseline in the Appel score. We're looking here not only at 9 months, which is the prespecified analysis, but also the month-by-month changes.

Note that the difference between the groups is visible and significant beginning at 2 months, and it's sustained throughout the 9 months.

Notice also that, as in the primary analysis,

the lower dose treatment group registers an effect at each month which is intermediate between the placebo and the high dose.

Now, this reflects all the patients who were still in the analysis. At the June meeting, Dr. Leber made the apt analogy that this allows us to see patients who were still in the race, still in the trial, but it doesn't allow us to capture so well the patients who were exiting from the trial.

Dr. Hines, could I have the backup slide which is the attrition analysis for the change from baseline?

So, what we're going to look at in the next slide are the numbers and characteristics of the patients who exited at each 9-month period, the patients, if you will, who are no longer in the trial or in the race.

So, let me just set the stage here. We're looking at each of the 9 months of the trial. Below we have the numbers of patients, and the yellow represents Myotrophin and the red represents placebo. What this shows here is both the numbers of patients who exit at each month and the change in the Appel slope registered by the

1 patients who exit at each of those 9 months. I think there
2 are a couple of points to be made here.
3 First, with the exception of month 5, the
4 pattern that we see throughout each of the months is
5 similar to that at the 9-month analysis; that is, we're
6 seeing bigger change scores in the placebo group than in
7 the treatment group. To the extent that we're losing
8 patients with greater change scores, it would tend to
9 dampen the effect registered by treatment.
10 We looked not only at the total change from
11 baseline in the Appel scores on a month-by-month basis, but
12 also the slopes of the patients as they exited, keeping in
13 mind that absolute scores and slopes are not definitely
14 related. What we found was that the slopes were very
15 similar for the first 2 months but then consistently each
16 month thereafter, the slopes tended to be higher in the
17 placebo group. This reflects the nature of the last value
18 carried forward analysis, so that to the extent that
19 patients were exiting from the placebo arm with greater
20 slopes, we sort of lose the impact of those patients at the
21 9-month --

DR. DRACHMAN: You're using slope and score interchangeably. Is that correct? Or what do you actually mean? Aren't these scores or are they slopes?

DR. SCHARSCHMIDT: I spoke about both, yes. I spoke both about scores and slopes. Again this is an important point, so if I wasn't clear, let me try again.

We're looking here at the patients who exited at each of the 9 months and these are scores. These represent the change between baseline and the last recorded value while the patient was in the study. These are not slopes. These are changes from baseline.

So, this is very similar to the analysis we just showed except it's the mirror image looking at the patients who left the trial, the point being that the pattern was very similar throughout with the greater change scores in the placebo patients.

What I was referring to but did not show was we were interested in trying to understand this analysis. We looked at the slopes of the patients who exited, and with the exception of the first 2 months, those also tended to be higher in the placebo groups.

DR. DRACHMAN: Right. What I am more interested in is change in slope. Do you have that available? Change in slope.

DR. SCHARSCHMIDT: Let me share with you what I do have and it may or may not directly address your question. Dr. Hines, could I have the attrition analysis where we're looking at slopes?

So, let me again set the stage. Here we're looking at the patients who exited the trial on a month-by-month basis and we're considering the slopes of the patients in each of those groups. These are the slopes registered at the time they exit from the trial. Note that here we're starting at 4 months because it takes at least 3 months to have a slope measurement.

We see that at the earliest period, the slopes are very similar, and then later in the trial, the slopes are greater in the patients exiting from the placebo group.

I made this point to illustrate again the nature of the last value carried forward analysis. To the extent that we're losing more patients with greater change scores or greater slopes from the placebo group, the nature

of the analysis is that it tends to dampen the treatment effect.

DR. DRACHMAN: Are these differences significant or not?

DR. SCHARSCHMIDT: I think we were interested primarily in patterns in understanding the analysis rather than significance.

DR. ADAMS: Dr. Scharschmidt, could you go back to the previous slide?

DR. SCHARSCHMIDT: Sure.

DR. ADAMS: I think the 9-month is 38 and 39. Those are the actual patients that got through the whole study for 9 months. Is that right? Those are the people that reached the entire trial period, active exposure to study drug.

DR. SCHARSCHMIDT: You don't mean the backup slide. You mean the --

DR. ADAMS: Well, no. I was talking about the one immediately before this one. You had the change of score.

DR. SCHARSCHMIDT: Right.

DR. GILMAN: It was the score.

DR. ADAMS: It was the absolute score and then you had the numbers below. It said numbers of placebo and number of -- there were 38 placebo patients and 41 active treatment patients that reached the entire 9 months of treatment. Is that correct? They would have theoretically ended the trial at that point.

DR. SCHARSCHMIDT: These are the numbers of patients who exited the trial.

DR. ADAMS: Are these premature terminations, those last 38 and 41? Are those the patients that finally got to the end?

DR. SCHARSCHMIDT: Those would be patients who reach protocol-specified endpoints.

Carl, is that correct?

DR. FEENEY: It looks to me that those are the cumulative numbers of people that left the trial by 9 months.

DR. SCHARSCHMIDT: Correct.

DR. ADAMS: No, no. It can't be. No, that can't be. No.

DR. HOBERMAN: The answer to the question is yes. Those are the number of patients, according to my records, who actually did get 9 months of treatment and had a last visit. They completed the trial.

DR. SCHARSCHMIDT: Thank you.

DR. ADAMS: Now, was there a difference at 9 months between the 38 patients in the placebo arm and the 41 patients with active treatment with 9 months of exposure? Is there something that's statistically different in those two groups of patients' outcomes?

DR. SCHARSCHMIDT: Yes, absolutely. That was the analysis that I showed earlier which is the last value carried forward where the change scores were significantly greater in the high dose treatment group -- significantly lower in the high dose treatment group --

DR. TEMPLE: That's not the same thing.

DR. ADAMS: That's not the same question. I'm asking is you have 38 placebo patients and 41 active treatment patients who went through the entire trial for 9 months. What were the results in comparison of those 38 placebos versus 41 active treatment patients? Is there a

1 significant difference in the outcomes in those patients
2 who completed the entire trial as planned?
3 DR. SCHARSCHMIDT: Carl, did you want to
4 comment?
5 DR. YOSHIZAWA: It's my understanding that was
6 not statistically significant, but I'd like to point out
7 that the sample sizes at that point are relatively small.
8 DR. GILMAN: Dr. Temple?
9 DR. TEMPLE: Well, that's always a troublesome
10 analysis. If people are leaving because they reach an
11 endpoint, the people who complete are only the people who
12 haven't led to an endpoint. So, a drug can be considerably
13 better. The completer analysis is always ambiguous for
14 that reason. So, that's one of the reasons that people
15 like LOCF. But every analysis has its own problems.
16 DR. SCHARSCHMIDT: Before we leave this point,
17 maybe I --
18 DR. GILMAN: Yes, go ahead.
19 DR. SCHARSCHMIDT: I'd just like to emphasize
20 the core message here. The last value carried forward
21 approach certainly is subject to bias if there's uneven

1 dropout of patients either in terms of numbers or their
2 characteristics. The dropout analysis that we saw here
3 would, if anything, tend to dampen the treatment effect, or
4 to put it another way, certainly the treatment effect we
5 saw was not a result of this particular last value carried
6 forward method. That's the message I'd like to leave with
7 the panel regarding this particular last value carried
8 forward analysis.
9 DR. LEBER: And I think we want to stipulate
10 that's exactly how we see it. The patterns of dropouts
11 across the course of this trial do not favor the drug.
12 They are, if anything, underestimating. If Myotrophin has
13 an effect that accounts for these differences, they
14 underestimate it. This is a classical dropout cohort
15 analysis that Dave Hoberman has been doing for years in
16 antidepressants, and I think the pattern shows that this is
17 unfavorable. When people are censored, so to speak, they
18 in general are censored with worse scores if they were
19 assigned to placebo, the point Dr. Temple was making
20 before.
21 We have never disputed this study finding a

1 difference between .1 and placebo. The question that
2 remains is what is the difference due to.
3 DR. GILMAN: Dr. Hoberman, did you want to
4 comment?
5 DR. HOBERMAN: Well, perhaps part of the spirit
6 of the question was not so much statistical significance,
7 but the actual magnitude of the treatment effect or the
8 treatment difference in the completers. My figures are
9 that in the last 4 to 5 months, the difference between the
10 treatments was about .04 units per day and for completers
11 it was about .02 units per day.
12 DR. DRACHMAN: But does that represent a slope,
13 a change in slope --
14 DR. HOBERMAN: That represents slopes.
15 DR. DRACHMAN: Well, I was more interested in a
16 change in slope. In other words, what is the benefit?
17 What is the difference between where they started, and
18 since the slopes of the placebo group started lower, I
19 really wondered whether the change in slope differed. Did
20 it?
21 DR. HOBERMAN: That slide unfortunately we do

not have. We showed it at the last committee.

DR. TEMPLE: But it's in the handout. The committee got it. It's in Dr. Feeney's --

DR. HOBERMAN: The change in slope?

DR. TEMPLE: Sure. It's in Dr. Feeney's --

DR. LEBER: (Inaudible.)

DR. TEMPLE: Well, my memory may be wrong, but I believe the material that reflects what was presented at the previous meeting includes Dr. Feeney's best shot analysis using pre-slope versus post-slope and comparing the difference. Right? We'll find it.

DR. LEBER: We're running through it right now.

DR. HOBERMAN: The company may have a different analysis, but when I looked at this data a long time ago, my analysis was an analysis of variance and the p value was .15.

DR. DRACHMAN: So, not significant.

DR. HOBERMAN: Not according to my analysis.

DR. SCHARSCHMIDT: Dr. Hoberman, I haven't had a chance to see that analysis. Could you please describe what you did for me?

DR. HOBERMAN: Unfortunately, my reviews were not submitted.

DR. LEBER: Take a look at page 25 under tab D in your manuals, briefing books.

DR. HOBERMAN: I'll simply quote from my review. "Since the slopes taken over the 3-month screening period were available, it is possible to ask whether or not there is a difference between the high dose and placebo groups with respect to slopes preceding randomization and those observed during double-blind treatment. Using analysis of variance, the p value was .15."

DR. TEMPLE: Can I ask, is that the statistical analysis of what Dr. Feeney's review shows on page 24-25?

In tab D, there is an exploratory analysis using the baseline slopes, but we know the baseline slopes are not as reliable as the on-study slopes. There are fewer values and all that. So, there is reason for caution in doing that, and that's why Dr. Feeney called it an exploratory analysis. But you have it with you in tab D. It went to the committee.

DR. HOBERMAN: Okay.

DR. TEMPLE: And the pattern, if you look at the cumulative distribution of effects, looks the same. It's got a little belly in the middle like all of them do.

DR. HOBERMAN: Same effects as what? It looks like what?

DR. TEMPLE: Well, it looks like the analysis of slopes.

DR. HOBERMAN: No, actually it doesn't. The distinction between the analysis of slopes and the analysis of change is that the 60th percentile of the slopes is exactly the same in both treatment groups. So, in a sense --

DR. TEMPLE: No.

DR. HOBERMAN: Yes. Wait a minute.

DR. TEMPLE: Look at page 25. Look at page 25.

DR. HOBERMAN: No. I'm not talking about that.

DR. LEBER: He's talking about something else.

DR. HOBERMAN: I'm talking about the slopes, not the change in slopes. I'm talking about page 23.

DR. LEBER: The general position of these two distributions is not that different between the two.

DR. HOBERMAN: The only distinguishing feature is that in the slopes analysis, the 60th percentile is the same in both groups. It's as though the medians were very similar in both groups. However, there's a difference in the tails.

In the change in slopes on page 25, it doesn't have that feature. There is a more uniform difference, and an analysis of variance gives a p value of .15. That's simply the way it turns out.

DR. TEMPLE: Okay. So, for the figures shown on page 25, which is the change in slopes from the baseline slope, a comparison of that --

DR. HOBERMAN: Right.

DR. TEMPLE: -- you're saying that was .15.

DR. HOBERMAN: Right, according to analysis of variance.

DR. TEMPLE: The general image is the same but a different p value. But that's clearly an exploratory analysis and it is what it is. Okay.

DR. HOBERMAN: Yes. It's simply the result.

DR. TEMPLE: But it partly goes to what Dr.

Drachman was asking about. That was our best shot at trying to look at comparison of initial baseline slope with final slope. But it has its limitations because that wasn't the intended analysis. There aren't necessarily a lot of values, and there's some uncertainty in the baseline slope. So, it is what it is.

DR. SCHARSCHMIDT: So, perhaps I could follow up on Dr. Temple's comment and refocus us for just a second.

As I mentioned at the outset, we focused on prespecified analyses so as to allow the panel to come to grips with some of the clinical issues. There are a lot of complex biostatistical issues which tend to emerge when you look at after-the-fact analyses. That's why we focused on prespecified analyses.

My understanding, based on Dr. Temple's comments, is that the last value carried forward analysis is viewed by both the sponsors and the division as yielding a statistically significant result. My understanding also is that the slopes does as well. Is that correct?

DR. GILMAN: Dr. Feeney?

DR. LEBER: Post-randomization slope is the protocol-specified analysis, comparison of the groups combined .05 and .1 versus placebo. I believe our p value for that analysis is something like .055 or .064 depending upon which one you interpret the protocol, which allows some argument to be and John will present that later.

That was the gate, by the way, for looking at the between-groups contrasts of .1 versus placebo and .05 versus placebo. You have to attain statistical significance on that gate to get to the second pairwise analysis, and those numbers are different depending upon which group you're comparing. And we'll discuss that later.

But I want to go back again and say there has never been a dispute that 1200 was a study providing evidence that in the context of an ordinary application would be considered one of several more studies that would constitute support for substantial evidence. So, we were not fighting about this.

In fact, when we saw the results, just to bring a little history, we went to the firm and said, look, this

is the kind of thing that demands treatment IND use. So, we have never said what this study would on face be interpretable. It's the question of can it stand alone I think.

DR. TEMPLE: I guess the other thing to point out is that we give special primacy to the intended analysis. So, it certainly is interesting to look at an analysis that takes into account the pre-randomization slopes. Of course, they're likely to be more variable, and that's very interesting. It's not a silly question. But the primary analysis is the ones that we basically agreed on, and we tend to give primacy --

DR. LEBER: There's a little more historical justification, however, for why we would have chose to look at an other than primary specified endpoint. As it often happens, a protocol is not as precise as one would want it to be. Or we'd have to combine across studies where there are different, as there are in this case, primary specified analyses. So, we may as "disinterested" parties to it try to find an analysis which maximizes the information provided by the study and allows us to look at the

evidence. That's why we tend to have liked the change in slopes analysis, but it is post hoc and therefore doesn't meet the rigorous test of being protocol-specified.

DR. DRACHMAN: Well, the real reason why I raise it is that there were those protocol violations leading to an imbalance or apparently leading to an imbalance. So, it raises questions about whether what is actually the secondary analysis, meaning that is of the separated groups, is as strong as one might think were one actually looking at the primary analysis with no protocol violations. Is that clear?

DR. GILMAN: Yes.

DR. TEMPLE: Could someone tell me if this is wrong? The primary analysis was a slopes analysis and that would tend to exclude a bunch of people on placebo who made the placebo look worse. That would favor the drug. John or David, tell me if this is wrong.

The analysis that uses change, however, includes those people.

DR. FEENEY: No. That's absolutely wrong.

DR. TEMPLE: Okay. What's right?

(Laughter.)

DR. FEENEY: You have to have --

DR. TEMPLE: That's why I said tell me if it's wrong.

(Laughter.)

DR. GILMAN: The answer was yes.

DR. FEENEY: You have to have three post-randomization Appel scores to get into this change in slope analysis.

DR. TEMPLE: That's what I said. So, the bad placebo patients are not in that analysis. That tends to favor the drug. So, the slopes analysis, the primary analysis, could be said to be biased in favor of the drug. Could be.

But the secondary analysis that looks at change -- not slope -- change -- doesn't have that problem. So, the worst placebo group -- they're in that analysis and it still comes out okay.

DR. SCHARSCHMIDT: Dr. Gilman, maybe I could just set the stage for --

DR. GILMAN: Let Dr. Hoberman comment first.

DR. HOBERMAN: I just want to confirm what Dr. Temple said. I believe you only needed one post-baseline observation and baseline in order to be in the change in baseline. That's right. These are different cohorts. I mean, between change from baseline and slope, yes, they are overlapping but not identical.

DR. TEMPLE: So, they have slightly different properties. One of them could be thought to be biased in favor of the drug; the other probably would not. So, one tends to take comfort from the idea they came out the same, which is part of the reason we've never particularly argued about whether 1200 is an overall favorable study.

DR. LEBER: The answer is we never have argued it.

DR. GENNINGS: But the change in slope and the slope analysis is the same cohort. Is that correct?

DR. FEENEY: Yes.

DR. LEBER: Yes. Dr. Katz makes a point. We've never argued about the directional outcome or the protocol-specified analysis of study 1200 except with some minor details, taking it as one source of substantial --

1 that could contribute to substantial evidence. We may
2 argue today about how robust a source it is, but let's just
3 get off the table this idea that we're debating anyone
4 about it being declared by ordinary standards a positive
5 trial that finds a statistically significant difference.
6 DR. SCHARSCHMIDT: Perhaps I could follow up on
7 Dr. -- excuse me.
8 DR. GILMAN: Please, go ahead.
9 DR. SCHARSCHMIDT: I was just going to follow
10 up on Dr. Leber's comment and reset the stage for a second.
11 We've discussed the primary efficacy analysis.
12 The prespecified primary efficacy analysis captured 88 to
13 90 percent of all patients. It was significant as
14 discussed. When we reviewed the analysis, in response to
15 Dr. Drachman's question I believe about protocol violators,
16 it was still significant actually for both groups. So, the
17 primary efficacy analysis appears not to be in dispute.
18 When we looked at the change from baseline
19 analysis, which also appears not to be in dispute, there
20 was a significant difference at 9 months between high dose
21 and placebo, and if we analyzed the dropouts over the

course of the study, not only does the treatment effect, not a result of the dropouts, but if anything the nature of that analysis appears to dampen the treatment effect.

DR. GILMAN: Dr. Graney?

DR. GRANEY: Dr. Drachman, I just wanted to address your question. Those patients who were violators in the sense that they took 4 months to get 7 points were evenly distributed in the North American trial across the three treatment groups. So, we checked and there was no collection of them in one particular treatment group.

DR. GILMAN: Dr. Scharschmidt, do you want to conclude this segment? I want to remind everybody that we have been discussing the clear-cut study.

(Laughter.)

DR. GILMAN: And we've been at it for two hours and a quarter. Can you conclude so that we can take a brief break?

DR. SCHARSCHMIDT: I'm right in the midst of the 1200 trial. It will take about three more slides or four to conclude the 1200 trial.

DR. GILMAN: All right, please, yes.

DR. SCHARSCHMIDT: That might be a good breakpoint.

DR. GILMAN: Let's do that.

DR. SCHARSCHMIDT: So, we've talked about the primary efficacy analysis and one of the secondary, which is the change from baseline.

We're now looking at one of the Kaplan-Meier plots which depicts the effects of Myotrophin in this case on the time to protocol-specified markers of advance disease, an Appel score of 115 or greater, or an FVC of less then 39 percent.

You can see that the high dose patients progressed more slowly toward these endpoints. The risk of the high dose treatment group reaching one of these endpoints was reduced by 44 percent as compared with the placebo group, and the lower dose treatment group again registered an intermediate effect. The difference between the high dose and placebo was statistically significant.

The effect of Myotrophin on a 20-point increase in the Appel score was very similar; that is, the risk of achieving a 20-point increase in the Appel score in the

high dose treatment group was reduced by 50 percent as compared with the placebo group.

Now, these clinical measurements were corroborated by the SIP where there was again a significant difference between the high dose and placebo group. Recall that the greater the change in the SIP, the greater the patient-perceived deterioration in quality of life. So, this effect was registered both by the clinician and by the patients themselves.

As for the Appel based measurements, the low dose treatment group again registered effect that was intermediate between placebo and high dose.

Now, to help understand what contributed to this treatment effect, the physical and psychosocial dimensions of the SIP are shown here. An apparent dose-related treatment effect was noted for both and the effect was statistically significant for the psychosocial component. Recall this registers how a patient perceives their ability to communicate and interact with others and participate in recreational activities.

This display represents a summary of all the

findings for the 1200 trial that we've reviewed to date. It depicts variables within different units. Note here that we're looking at the slope and change score analyses. These are represented as the differences in the means. Here we're looking at the time-to-endpoint analyses which are represented as the relative risk.

In order to allow these different units to be represented as part of the same display, these variables here were divided by an estimate of the standard deviation. This results in the display you see here where deviations to the left favor Myotrophin, deviations to the right favor placebo. The horizontal bars correspond to 95 percent confidence intervals.

You can see that the evidence of efficacy was registered both by the physician based measurements. These are the Appel slope, change from baseline in the Appel score, and the time to protocol-specified termination criteria or 20-point progression, and were corroborated by the SIP.

Notice also that none of these lines crossed the midline and therefore they're all statistically

significant.

Now, I'll next cover the European study, but we can do that after the break if you prefer.

DR. ZIVIN: Can I ask one question?

DR. GILMAN: Yes, please. Dr. Zivin?

DR. ZIVIN: I've constantly been trying to get at a better evaluation of the results of this trial that patients and physicians can understand rather than changes in Appel scores per minute or whatever units you have been using. What I would really like to do is have you go back to the slide that's change in baseline of ALS scores by month. It's several slides back.

DR. SCHARSCHMIDT: The units were Appel points per month.

DR. ZIVIN: Change in ALS scores. That's the slide or you could use the next one too.

As I look at it, it appears to me what you have done is shifted the patients so that they improve by approximately 3 months. Is that an accurate statement?

DR. SCHARSCHMIDT: That's the nature of the last value carried forward analysis. So, one would expect

if we look at the 9-month value, it would be 9 times the average slope, and you can see that it isn't. That reflects the fact that we're losing patients from the placebo group with higher change scores and higher slopes.

DR. TEMPLE: That's not what he's asking.

DR. ZIVIN: That's not what I'm asking.

DR. TEMPLE: It's not what he means. Look at the placebo value at 3 months. Okay? It's roughly 10. Now, carry it over to where it meets yellow, and that's at about 5 months, 6 months, whatever you want. So, you could argue that you've saved somebody 3 months. Right? That's what you're asking.

DR. ZIVIN: That's exactly what my assessment of what this means is.

DR. TEMPLE: Whether you can draw that from this I don't know, but I think that's the question.

DR. SCHARSCHMIDT: Dr. Zivin, let me understand your question. Could you rephrase it for me to make sure I get it?

DR. ZIVIN: What I'm trying to do is get a method for patients to understand how much the magnitude,

the absolute magnitude, of their improvement will be. And from looking at this data and the next slide as well, it appears to me that the patients are retarded in their progression of their disease by about 3 months.

DR. SCHARSCHMIDT: The impact on the patient is probably best captured in the slope where the relationship between slope and time is analogous to the relationship between speed and distance. And the time saved or the time preserved is a relative function of the duration of the observation period.

What I took from your question was that the effect here looks as if the groups track parallel after 2 to 3 months, and again that is a function of the last value carried forward analysis where we tend to be losing the patients with the higher slopes from the placebo group. So, we don't register their full impact at 9 months.

DR. ZIVIN: If you have a better way of expressing how much the patients improve on the basis of how long they can expect to maintain a level of neurologic function, what would be your best estimate?

DR. SCHARSCHMIDT: Dr. Williams, did you have a

comment?

DR. GILMAN: Well, let's have Dr. Leber next and then we can hear from the sponsor.

DR. LEBER: I think what you're doing is admirable. People always want to convert a scale and a rating score which doesn't map to anything that anyone could understand. There's some salvage, how much am I saving, how much more time am I delaying progression for something important.

I think one of the things you've got to be careful about, however, is that there is more than one source of information for estimating the effect size. It isn't just going to come out of the study that is persuasively positive from your point of view. It has to account other studies that provided other estimates of that.

So, I think it's a little risky to take a study that's positive and start talking about this as premature. We want to convey across all studies that are relevant to talk about the size of that effect. So, before we start flashing around 3 or 4 months, let's look at the other

study which, as far as I can tell so far, is still on the table as a source of evidence about the size of the effect that might be seen if any case is due to Myotrophin.

DR. GILMAN: A comment from the sponsor?

DR. WILLIAMS: Just a brief comment because we understand the essence of the question, and it basically is how can you translate the statistical findings into a clinical effect. Certainly the arguments about statistics are the important ones in terms of interpreting the study and how many studies you need.

On the other hand, it's our estimate that what you say is about right, that the effect -- and it's obvious when you look at this -- if you tried to use this study to translate to that effect, the translation to a clinical effect, there's about a 3 or 4-month delay in progression. That's our view of the clinical impact of this study.

DR. SCHARSCHMIDT: And, Dr. Zivin, we'll come back to that very directly later when we consider the clinical implications of the change.

DR. WILLIAMS: I'm sorry. Maybe I wasn't so clear. In the 9 months that was shown here, the delay is

about 3 or 4 months in progression of morbidity. We view this as one measurement of morbidity.

DR. LEBER: Well, it's a measure of performance. That's going to be a technical issue we really want to get into.

DR. GILMAN: Dr. Hoberman?

DR. HOBERMAN: Two things. I'm a little confused about Dr. Scharschmidt's statement that the effect of dropouts did not affect the treatment effect. I'm a little confused by what that means. I just would like to clarify in my own mind -- and I think a meaningful observation which I actually stated before, that in fact it was differences in the earlier dropout cohorts that were larger than in the people who finished the trial. In that sense when you include the people in the earlier dropout cohorts, those treatment effects, with the smaller one in the completers, then I would say that in fact dropouts do have an effect on the measure of treatment effect when you put everybody together.

DR. SCHARSCHMIDT: What I indicated was that the dropouts always affect the magnitude of the effect. To

the extent that the dropouts were among patients in the placebo group with more rapidly progressing disease, it would tend to minimize the treatment effect.

DR. HOBERMAN: Okay. I guess you meant something different from what I meant.

The last comment about the 3-month savings. I think that ought to be reserved to analyses that actually measure a time to an endpoint. It's very, very risky to look at bar graphs and means over time and compare bar graphs of means and say, well, gee, it looks like 3 months. Time-to-event endpoints are where it's at when you want to talk about time and not means over time.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: I got to say I don't think that's the only possible view. A standard scale like an Appel can be used to make some estimate of how much time along that path you're saving. To put precision on this would be a mistake. To look at it and get a ball park doesn't seem unreasonable.

DR. HOBERMAN: No. I don't think that ball parks are useful because you'd like to do the right thing.

Now, the right thing is, for instance, time to 20-point change because you've defined an event and you can measure the time to that event. If you have an inferior way of doing something, don't do it. Do it the right way.

DR. TEMPLE: Well, a 20-point change isn't the only possible measure. You could ask what's the time to a 5-point change --

DR. HOBERMAN: Absolutely.

DR. TEMPLE: -- which is basically what's being done in a crude way by looking at that.

DR. HOBERMAN: And not the proper way.

DR. WILLIAMS: Again, that analysis is on this slide.

DR. GILMAN: Well, but our point here is to assess the primary outcome measures, and I think we're spending a great deal of time on peripheral issues. So, I think maybe we ought to move along.

Dr. Leber, did you want to comment?

DR. LEBER: No. I was going to say that I think it's perfectly reasonable, if you really had a good estimate of the population's distribution of progression in

1 a disease on a well-known rating scale, if you think you
2 have it. And I mean a population estimate, not one based
3 on 77 patients following a particular registry, by the way.
4 That's a problem we had in dementia where someone might use
5 something like ADAS-COG and say it's known that patients
6 like this change 8 to 12 points a year and then someone
7 does a big placebo controlled trial two years later and
8 they change an average of 2 points per year. So, that's
9 one of the problems about talking about what you're saving
10 on some rating scale with a belief about the disease where
11 you really don't have a basis to have the belief. That's a
12 hazard.
13 But the principles of looking at the scale and
14 saying the patients move like this, this represents about 3
15 months for the population we studied, that isn't
16 irrational. It just is not perhaps the way to do it in an
17 experimental way.
18 I was trying to sort of make peace between the
19 different sides of the FDA on this.
20 (Laughter.)
21 DR. GILMAN: Dr. Adams has a question on this

slide.

DR. ADAMS: This gets back to my previous question about in this study the 10 of the 14 patients who had the worst Appel scores, that means the highest score at the beginning, were in the placebo arm. Would it be unreasonable to ask -- or maybe I am being unreasonable to ask -- does that influence this data? They're starting out with 95s and 100. Regardless of treatment or no treatment, they're going to get to 115 greater than if they started out with 60 or 70.

So, if you take this as an important secondary analysis of 115 and you're starting out with patients with 95 and 100 in the placebo arm at a higher rate than they are in the active treatment arm, how do you analyze this result? Can we really say the p value is .05?

DR. SCHARSCHMIDT: So, the time-to-event analysis is influenced by patients' initial Appel scores. That's the reason we took care at the beginning to outline the different efficacy variables. If we do a post hoc analysis -- and we've really focused on prespecified analysis -- dropping out those patients decreases the

1 treatment effect for this particular variable.

2 I'd remind the group again that the primary

3 efficacy variable, the Appel slopes, is least influenced by

4 dropouts, captures 88 to 90 percent of all patients.

5 Dr. Temple?

6 DR. TEMPLE: If you want to see the effect of

7 that, it's in tab D. If you compare page 32 with page 34,

8 Dr. Feeney has done the analysis with and without the

9 extreme values. That particular analysis is very much

10 affected by leaving them out. In fact, it doesn't show

11 anything when you leave those extreme people out. Still

12 that's not the primary analysis. It's one analysis, but it

13 shows that the initial imbalance did favor the drug for

14 certain kinds of endpoints. There are other possible

15 imbalances that you can't measure so easily. So, any time

16 you reduce data sets, you're in some trouble, but if you

17 want to know what happens if you leave those people out,

18 just compare page 32 and page 34.

19 DR. GILMAN: Yes, Dr. Katz.

20 DR. KATZ: Yes. I'd just like to make a point

21 about language and it basically echoes something that Dr.

1 Leber has already tried to make several times this morning.
2 And that is that we acknowledge that there are differences,
3 real life differences, between the treatment groups between
4 the high dose and placebo group here.
5 The question on the table is or will be
6 ultimately what is that difference due to. We are already
7 starting to refer to it in our discussions as a treatment
8 difference. At the risk of sounding picayune, perhaps we
9 can refer to them as between-treatment differences, but the
10 use of the phrase "treatment difference" implies, at least
11 permits the inference, that the difference is due to the
12 treatment applied. And that's really the big question on
13 the table. So, I suggest that we just keep that in mind.
14 DR. GILMAN: That's a good point.
15 All right. Dr. Scharschmidt, have you
16 completed your presentation then for 1200?
17 DR. SCHARSCHMIDT: For 1200, correct.
18 DR. GILMAN: Yes.
19 Are there any other questions from the panel?
20 (No response.)
21 DR. GILMAN: Let us break and reconvene at

11:20. We'll then have lunch around 1 o'clock if we can manage it.

(Recess.)

DR. GILMAN: Dr. Graney, are you ready to begin?

DR. GRANEY: Dr. Gilman, I believe Dr. Scharschmidt is walking in right now.

DR. GILMAN: Dr. Scharschmidt, please let us begin again.

DR. SCHARSCHMIDT: Thank you, Dr. Gilman. Before we go to 1202, let me just again recapture 1200 and remind the members of the panel that we're focusing exclusively on prespecified analyses. Post-specified analyses with the data in hand are always tricky. We're focusing on prespecified analyses, and in the case of 1200, each of the prespecified analyses was positive. The p value for the prespecified primary analysis was 0.01.

The findings that I'll present now for 1202 focus again on prespecified analyses.

Now, this depicts the primary efficacy analysis of the European study, that is the change from baseline in

the Appel score. This is the same format that we saw earlier.

We're looking here not only at the value at 9 months but the month-by-month changes. Notice here that at 9 months the effects were smaller than in the 1200 study. They did not reach statistical significance. Notice that in the month-by-month changes, the Myotrophin group initially had higher change scores and then the findings diverged in favor of Myotrophin. And I might add none of those changes were statistically significant either at 9 months or the month-by-month changes.

This depicts the cumulative distribution function for the Appel change scores. Recall that displacement to the left in this display is indicative of a treatment effect, and you'll notice here that the curves for the placebo and treated group were essentially superimposable up to a change score of about 30. To the extent that there is separation between the groups, it was in the patients with the larger change scores.

Now, this slide depicts the results of the secondary efficacy analyses for the European study. These

1 include the effect of treatment on the Appel slope, the
2 time to Appel or FVC endpoints, the time to 20-point
3 progression, and the change from baseline in the SIP.
4 These are the treatment effects. These p values did not
5 reach statistical significance.
6 Now, in summarizing all the results to date for
7 both the 1200 and the 1202 study, the North American and
8 the European, we'll use the same display shown earlier.
9 We're looking at variables with different units. Recall
10 that displacement to the left favors Myotrophin,
11 displacement to the right favors placebo. In this display,
12 all the results of the North American study are
13 significant. None of these yellow lines crossed the
14 midline. The results of the European trial did not achieve
15 statistical significance, but there was directional
16 consistency between the two trials with respect to several
17 efficacy variables. These include the Appel slope, the
18 change from baseline in the Appel score, and the time to
19 protocol-specified termination criteria.
20 DR. GILMAN: Dr. Adams has a question.
21 DR. ADAMS: Dr. Scharschmidt, the change in

score is the score at 9 months. Is that right? In the blue.

DR. SCHARSCHMIDT: That's correct. That is the prespecified 9-month analysis.

DR. TEMPLE: Last observation carried forward.

DR. SCHARSCHMIDT: I'm sorry, Dr. Temple. I didn't hear.

DR. TEMPLE: It's the last observation carried forward.

DR. SCHARSCHMIDT: Yes, correct.

DR. TEMPLE: It's not necessarily 9 months.

DR. SCHARSCHMIDT: Correct.

DR. TEMPLE: Okay, just making sure.

DR. SCHARSCHMIDT: Now, unless there are no more questions regarding the North American and European trials, which I'd be happy to entertain, I'd like to introduce Dr. Rene Braekman who will discuss the findings regarding a blood level-response relationship.

DR. GILMAN: Any questions from the panel to this point?

(No response.)

DR. GILMAN: All right. Please proceed then.

DR. BRAEKMAN: Good morning. I'm a pharmacokineticist and I'd like to talk to you today about a different kind of analysis, a different kind of analysis different from the type of analysis that you have heard today from Dr. Bruce Scharschmidt. This type of analysis is called a population pharmacokinetic/pharmacodynamic analysis or population PK/PD analysis.

The methodology for such an analysis of the clinical data, which really evolved in the late 1970s, has been very useful to look at pharmacokinetic and pharmacodynamic data. Before I go into that, I'd like to explain to you why this is important, why I'm even here taking some of your time to present this.

What we have there is a slide that you have already seen from Dr. Scharschmidt's talk, and it shows the placebo, Myotrophin .05 milligram per kilogram dose, and then the highest dose and it shows what the effect is on the AALS slope. There was no discussion about that, that there was an influence of dose, that at the highest dose there was a significant decrease of that slope compared

with placebo, and that the middle dose was somewhere in the middle between these two effects on slope.

This slide shows the IGF-1 trough serum levels in protocol 1200. Again, I remind you the previous slide was also protocol 1200. What you see here are the serum IGF trough levels in function of time at monthly intervals. Patients were taking blood samples and the serum levels of IGF-1 were measured. What you see here on these monthly intervals are the averages of all the patients where we had data available in the placebo group, in the middle dose group, in the high dose group.

Of course, these are different patients and function of time that contribute to that average because, as we go on in time, we lose patients because they die. You can see that there is some variability introduced by that most likely.

You also see here, however, that even with this kind of censoring, that the highest dose gives you on average higher serum levels than the lower dose, than the placebo. So, again, there is an influence of dose on the steady state trough serum levels of IGF-1.

Now, if you combine this now with the previous slide, that says there is an influence of dose on the slope, and there is an influence here on dose on the plasma levels. It's very normal to assume that there's probably a correlation between the IGF-1 concentrations and the effect on slope, that the IGF-1 concentrations are related to what you see, how the disease slows down when you have higher levels.

Now, what you see here, of course, there is some variability. There is variability in the PK between the patients. There is some variability in function of time, and you can assume that the patient that was dosed with the highest dose, for some reason because he had a low endogenous production of IGF-1 and he had a very high clearance, that that patient is exposed to a level that's closer to placebo.

And you can go to the opposite. You can imagine with the variability that you see here, that the placebo patients with a very high endogenous level of IGF-1 production, that that particular patient has a level that's closer to there. And that's what we can deal with when you

do a population pharmacokinetic/pharmacodynamic analysis.

What I want to show you, that there is for 1202 such a relationship, that higher levels of IGF-1 circulating in the serum, that they are correlated with more effect, with more decrease of slope.

So, this is very important because if we would be able to demonstrate that, it would increase the confidence that this drug works. Actually the FDA agrees with us. In their briefing book, they state if we could present evidence that there is a correlation, some relationship between exposure in serum with the effect on the disease progression, that that would be helpful. It would be a valid argument. So, that's why I'm here to do this.

DR. GILMAN: May I ask a question?

DR. BRAEKMAN: Sure.

DR. GILMAN: Is there any evidence that higher dose or higher serum level will allow greater penetration of the substance into the nervous system?

DR. BRAEKMAN: You would expect from theoretical principles of what we know how drugs work, if

you inject a compound subcutaneously, in this case Myotrophin, you would expect that you see higher levels, which is what's happening, but also in order to reach the receptor, it has to go through the blood. This is not a local effect.

DR. GILMAN: I'm not asking about theoretically. I'm asking whether in this drug there is evidence that you have greater penetration with a higher dose.

DR. BRAEKMAN: I don't think we have evidence to that.

DR. GILMAN: Dr. Drachman?

DR. DRACHMAN: You used the expression there was a greater effect on the change in slope. Did you show that? I mean, did you show that in those individuals with higher levels, the change in slope was greater?

DR. BRAEKMAN: No, I didn't not in the first slide. The first slide is actually that the slopes were different.

DR. DRACHMAN: We know the slopes were different. We know the change in slopes were not

different. Were you able to show that those individuals with higher blood levels had in fact some change in slope that was greater than those who didn't?

DR. BRAEKMAN: In the analysis that I will present, it's a different way of looking at this. It's not the kind of analysis that we heard about today. I will demonstrate that on average there is that change in slope. So, I'm interested to see what the concentration response curve is, how the slope changes in function of concentration. If that is not a flat line --

DR. DRACHMAN: Excuse me. So, then you're going to report on the change in slope not on the slope. Is that correct?

DR. BRAEKMAN: Well, they are related. If you have a concentration response curve that's not flat, if this is not a flat curve, it's not a horizontal line, then there has to be a change in slope.

DR. DRACHMAN: No, no, no. I mean a change from the baseline. Is that what you're going to show us, that the rate of change differs?

DR. BRAEKMAN: The PK/PD analysis does not make

manipulations of the data and then perform a statistical task. It uses the raw data with no bias on how these data need to be corrected, and then there is a model that's part of the whole analysis which compensates for all kinds of influences.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: I think you're being asked which endpoint is being used. As we discussed before, you can use the last value, you can use the slope, which was the primary endpoint, or you can use the change in slope from baseline. I think you're saying you used the slope, which was the primary endpoint. Is that right or not right?

DR. BRAEKMAN: The PK/PD analysis does not calculate the slope. It's an intermediate variable within. It uses the raw data which are the AALS scores as a function of time. This analysis takes into account the time factor. You don't have to take a snapshot in time.

DR. TEMPLE: That's sort of a slope, but okay.

DR. BRAEKMAN: Indeed, it tells you what's going to happen with the slope.

DR. GILMAN: Well, that's an assumption.

DR. BRAEKMAN: Next slide please.

This is like a methodology slide. What you do in PK/PD analysis, you come up with a model, like if you calculate the mean, you have a model, but this is a little bit more complicated because we are dealing with biological events here. Out of this set, based on a question there, that what we work with are the AALS scores, and we have a pharmacodynamic model. The pharmacodynamic model says that the AALS scores change with time according to a slope starting from an initial base entry level AALS score, which is the score that patients have when they enter the study.

So, this is really a disease model which is in accordance with what you heard today about the AALS score. So, it's a very reasonable, very simple thing to assume, that it happens like this.

Now, of course, there is no drug effect at this point. When we now assume a drug effect, we hypothesize that the slope changes as a function of the IGF-1 serum concentrations. That's the assumption. So, we call this a slope model. Again, from some slope analyses that you heard this morning, it's again a reasonable thing to

assume.

For the IGF-1 concentrations, we had two sets of models. One set of models used the observed individual serum concentrations. The other set of models used individual estimated values for these trough levels based on an optimal PK model where you also take covariates into account, you use body weight, age, binding protein, three C-min levels, and then the clearance and the endogenous synthesis rate that you can calculate from a PK analysis.

So, what do you put in there? Well, you put in there the AALS total scores versus time. You put in there what happens to the slope based on these concentrations. What you get out of the model is the actual slope, the base, their estimated values, their shape parameters for the concentration response curve.

So, some of you may be familiar with the term "nonlinear regression curve fitting," and that's actually what we are doing. If it means anything to you, it may just give you a better understanding of what we are trying to do.

This slide is a complicated slide, but I wanted

you to see the three graphs on one slide because they are very well connected. We have simplified this by purpose to give you an idea of what we have done and what the results are. What you see here -- this is still for study 1200 -- you see here estimated concentrations. In this particular graph here, you see the serum concentrations versus time for a typical patient, a patient that is 70 kilograms, 55 years old, and has a BP3, binding protein 3, level of 3,500 nanograms per ml because these are the covariates.

So, these are estimated when you dose. The 0 here is start of treatment. When you start dosing a patient instead of the endogenous level, it starts going up. We didn't really have data for this, but once you reach steady state after a couple of doses, you get the steady state levels that are assumed to be constant. There is a variability on that, but we took the variability out here to give you an idea. This is just one patient, not assuming any day-to-day variability.

So, that's what you get. You get these trough levels. You get peaks and troughs which we only worked with the trough levels, and this is in this case is an

estimated level based on the PK analysis. The same patient, if he would have had placebo, based on the placebo group, would have had levels that stayed constant, and it's constant for the 9 months of the study.

So, you have a fair comparison.

A question? Yes.

DR. COYLE: I'm a little bit confused, so just to get things a little bit clearer. What type of assay is being used to measure?

Secondly, you're measuring trough levels. Just in both studies were bloods routinely drawn and at what times on a monthly basis? And what database are we going to be looking at here? Because I'm a little bit confused.

DR. BRAEKMAN: This is a good question. We use all the concentrations that we had in study 1200 before randomization, at baseline after randomization of all patients, of all dose groups. These are the concentrations we measured. This is what we put into the model.

DR. COYLE: Well, when were these drawn in timing to dose? In other words, were these drawn --

DR. BRAEKMAN: They were monthly intervals.

Can we go back two slides?

DR. GILMAN: No. That's not the question.

DR. ADAMS: The question is if they had a shot at 6 o'clock the night before, did they get another shot before they got the level, or this is an hour after the shot or 12 hours after the shot? I think that's the question.

DR. BRAEKMAN: The protocol specification was that they came for their visit in the morning, and before they got the morning dose, they were taking a blood level. And there is some variability on that.

DR. GILMAN: Did they get the evening dose the same time or the previous day's dose the same time between subjects?

DR. BRAEKMAN: We don't know that.

DR. GILMAN: Somebody said yes.

DR. BRAEKMAN: It was a protocol specification and they were questioned about that, but they were not in a clinical site where this was monitored.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: We have broken you up and asked

1 questions.

2 You mentioned something about adjusting the

3 observed concentrations for something, and that's a little

4 mysterious to me because you measured it. What do you have

5 to adjust for? Why would you have to adjust for weight if

6 you actually have a measurement?

7 DR. BRAEKMAN: Well, we did it both ways. We

8 ran the PD model, as I said in a previous slide, with the

9 measured concentrations, and then we did a link from the PK

10 model through the PD model.

11 What you do in a PK model is you have a

12 function of the concentration in function of time with some

13 covariates, and in the population analysis there is an

14 inter-individual error and an intra-individual error or

15 residual error. The residual error also includes assay

16 error. If you make these estimates from the PK model, you

17 have more of an average over time for any single patient.

18 Does that answer your question? That's why

19 it's typically done.

20 DR. TEMPLE: Well, not quite. The

21 attractiveness of all this is that people get variable

blood levels, however they happen to do that. We probably don't know all the things that determine what their blood level is, but somehow, if you're fortunate, you'll see some relationship of outcome to those concentrations, however they were achieved. That's why this is attractive in the first place. So, adjusting the concentrations, unless you were to adjust them because of differences from the time of the injection or something like that, which would be plausible, still doesn't quite make sense to me, but I may just be missing the point.

DR. LEBER: Actually in fairness, I think we're going to try to address this, not the models, but something about the relationships of concentration and why concentration is important and how it's important in our presentation later.

My suggestion is it's their analysis.

DR. BRAEKMAN: The bottom line is we did it both ways and for most models, it doesn't make a difference. You still come up with a concentration effect relationship.

DR. GILMAN: But going back to Dr. Coyle's

question, how does the blood level vary with the time since the previous dose? If the previous dose was 8 hours earlier, will you get a different blood level than if a dose were 23 hours or 12 hours earlier or 11 hours earlier?

DR. BRAEKMAN: Within a patient, the blood level stays fairly constant over the time that we could measure.

DR. GILMAN: But you only measured it once.

DR. BRAEKMAN: Once per month.

DR. GILMAN: Once per month.

DR. BRAEKMAN: Over the 9 months, if we had 9-month data --

DR. GILMAN: Dr. Leber?

DR. LEBER: Can I ask a question? The first slide you showed showed how people did not attain their average blood level, talking about groups, until about 3 or 4 months after treatment. So, to say that their blood levels remain constant, I'd like to see the underlying data. Why don't you show the first slide?

DR. BRAEKMAN: It's actually the second slide, the blood levels, the second slide. I don't think we have

a slide with the individuals.

What's happening here actually, the blood levels go up.

DR. LEBER: Right.

DR. BRAEKMAN: So, it's a fair question to ask, do they stay constant. Well, our belief is if you look at the data, that as you go on, there is an appearance that the ones with the lowest blood levels drop out earlier, die, and that's why you have an increase. If you run the PK models for patients that you only have a couple of a numbers and other ones, when you put this all together in a population model, it shows you that there is not that much of a variability from day to day. Well, there is variability just like we have seen it.

DR. GILMAN: But we're not seeing any day-to-day --

DR. BRAEKMAN: No.

DR. GILMAN: We're seeing nothing day to day and we have nothing between 0 and 1 month. So, we don't know to what extent the blood level will vary --

DR. BRAEKMAN: Well, baseline --

DR. GILMAN: Let me finish. With the time from the previous dose of medication, nor do we know the day-to-day variability from these data or the time that it took to get to that level after 1 month. Or do you have those data?

DR. BRAEKMAN: Well, the baseline here is entry, is before start of dose.

DR. GREBOW: I'm Peter Grebow with Cephalon perhaps to help out on your question.

The half-life for IGF-1 is approximately 20 hours. We have single dose studies in normal volunteers showing that these individuals reach steady state blood levels by about 5 to 7 days. So, by 1 month, these individuals certainly have reached steady state levels.

You are looking at here, over the course of 9 months, different individuals as the course of the study goes on, as the patients attain either their dropout levels or through attrition.

Maybe also to get to Dr. Drachman's question of earlier, we did another analysis, which we don't have presented here, which is not a formal PK/PD analysis. The

reason for that is for a formal PK/PD analysis, you need to use all the patients.

If I can just complete the thought. In this study, we looked at the pre-dose slopes versus the post-dose slopes for only those individuals who had three points pre dose and post dose. This is a report that has been submitted. In that, there is a correlation between the IGF levels and the change in the slope.

DR. GILMAN: Can you tell us whether the increase in level over time represents the fallout of some of those who dropped out of the study?

DR. GREBOW: We have done some analyses that we have not yet shared with the agency where we show that as you have higher concentrations of the IGF-1, it appears that the patients will survive longer. So, you have a dropout occurring as a result of the IGF-1. It tends to be the people with the lower levels of the IGF-1 will drop out, but we have not confirmed that analysis yet. We're still working on that.

DR. GILMAN: Dr. Leber?

DR. LEBER: As we said in the mailing, the

1 issue of the concentration relationship is important into
2 the extent that one wants to examine beyond the simple
3 design of the studies about whether there's additional
4 evidence that might but not conclusively, but might speak
5 to the fact that Myotrophin did it rather than something
6 else. So, we're interested in finding a relationship
7 between a patient's concentration and their attained
8 outcome whatever it may be.
9 One of the problems is how do you represent the
10 attained concentration of a patient fairly because there is
11 scatter throughout time and you have this kind of group
12 effect which the firm is now telling for the first time is
13 due to the fact that there are losses, so that apparently
14 through time, their argument is that this is explained by
15 losing people with low concentration. Their argument is
16 based on the fact that in a volunteer study, in a single
17 dose, steady state should have been reached in 5 to 7 days
18 so that would be incompatible with this gradual escalation
19 unless it's due to differences.
20 Now, it's possible that the patients in the
21 study, for reasons we don't understand -- this isn't

1 something we've looked at -- don't attain steady state,
2 even though the single dose studies predicted it, for a
3 long time. I don't know what the data is and we haven't
4 seen it yet.
5 But as we said in the mailing, it's probably
6 premature, because we've seen so many different analyses,
7 to look at the models in a rational, fully comprehensible
8 way at this point. I think we're getting off.
9 The theory is -- and I think you've got to go
10 back to what the aim was -- to say if you could find a
11 prediction from concentration under the right circumstances
12 -- and John will address that -- then perhaps you had
13 additional evidence. But right now, I am at a loss to
14 understand how you can demonstrate that these
15 concentrations arise in this pattern the way they do.
16 For example, this may suggest one analysis I
17 had in mind. You could look at every individual patient's
18 time to what you would call plateau, if such a thing
19 exists, and then you could look at the distribution of time
20 to attaining that plateau. If the distribution of time
21 varied among individuals and there was a big spread, that

would be very different than if everyone is reaching their plateau immediately, and then of course, the differences might be due to the pattern of dropouts and losses.

But we don't even have that most fundamental of information yet to assess this, and that's why it's somewhat frustrating to have this discussion right now. We don't have all the facts.

DR. GILMAN: Dr. Kawas?

DR. KAWAS: A very quick question. I just need to make sure I understand what I'm looking at. The means and the standard errors that you have plotted are only in one direction?

DR. BRAEKMAN: They are the standard deviations in one direction so you could differentiate them from each other. It's just a visual type of thing otherwise the plot would not be very reasonable.

DR. KAWAS: I see. Thanks.

DR. BRAEKMAN: When we look at the data and explore the data, it is in each particular patient -- patients may be different from each other but in each individual patient, it appears that they reach steady

state, that the levels are relatively constant over the time that we have their data. I'm willing to address this in more detail at some other time, but that also comes out of the PK modeling. There is an error model in there. It's very complex. I don't want to take your time to talk about it at this point, but that's what the conclusion of that analysis is.

Let's go on to my slide. I didn't really go through the analysis yet and how you prove, how you demonstrate beyond chance that there is a concentration response relationship. So, let's continue with this.

This is just to demonstrate, taking all the variability away, which is explained in the model -- some of you may understand that it's a repeated measures ANOVA. It's a little bit more complicated. The error models in there are more representative for this biological processes, pharmacokinetics and pharmacodynamics. But when you take the errors away, you compare apples with apples, which is the same type of patient. When that patient would be in the placebo group, we would get these levels. The highest doses would get these levels. That's one thing you

get out of this.

In the analysis what you get -- I have told you about the slope parameter. It's an IC50. It's an inhibitory concentration of IGF-1 that decreases the slope at 50 percent, and that's the model we use. It's a saturable model that you all know from what has been used for decades for in vivo and in vitro dose-response and concentration-response relationships. It's again a very easy assumption to make, very simple, very acceptable.

Based on the shape parameters, that's how the IGF-1 trough level affects the slope. When you take a placebo level, you are here on that response curve. When you have the highest dose for this particular example of a patient, you are somewhere here. So, when you go from placebo to a certain concentration -- and you could put in there an observed concentration rather than a predicted or an estimated concentration -- you can do the models. You can do the models in both ways. You travel down that dose-response curve and, indeed, in the actual data it then is correlated with a change in slope between the placebo-treated patient and the highest dose patient.

Now, you could say, okay, you have all these data. You have the IGF-1 concentrations. You have the ALS score and now you have some mathematical equations. You put it all together. You do a nonlinear regression, and you're going to get something anyway.

There is actually a statistical test included in this model, and I tell you what that statistical test is. It's for this particular model, the slope model, for this particular type of correlation or type of function it is statistically significant between IGF-1 has an effect and not.

What we did and what's typically done, what you assume is that all the patients in the study, that there is no effect of concentration on the slope. If we put them all together -- and of course the middle dose is somewhere in the middle -- when you put them all together, you make the assumption that there is no effect of IGF-1 on the slope.

This would be comparable with the flat line of your IGF-1 trough concentrations. This is as a population, but every patient would be on his own slope and keeps on

moving on that slope with no change no matter what the concentration is.

You can calculate the probability that such a model explains the data, and then you do what I told you. You have a model that includes an influence of the concentration on the slope. And you start seeing what the influence is. Of course, for different concentrations, you have different slopes. But again you can calculate for that model what the probability is, that that model is a reasonable explanation, while in this case for this model, when you compare the probabilities and you do a statistical test, the model that includes an influence of the concentration on the slope is statistically significantly better beyond chance, beyond that this happens accidentally. It would be chance. It would be only 5 in 1,000 that it happens accidentally. So, this is basically the statistical test that demonstrates that there is a correlation.

Now, we have used other models. It turns out that you can make other assumptions of this curve. One of them was a straight line. You can use, instead of PK

1 predicted concentrations, PK estimated concentrations, the
2 individually observed concentrations. When you do this in
3 most of the models for study 1200, for most of the rational
4 models, we find a statistically significant influence of
5 the IGF-1 concentration on the slope.
6 What about study 1202? We did the same thing
7 for 1202, the same assumptions. The concentrations with a
8 function of time were not majorly different from 1200.
9 When you calculate the clearance, the endogenous synthesis
10 rate, all the PK shape parameters that give that
11 relationship between IGF and function of time, it's very
12 similar.
13 However, in most of the models, we could not in
14 our models link IGF-1 concentration to a change in slope in
15 the way I have explained it to you for study 1200. So,
16 again, this is really comparable with the classical
17 efficacy analysis.
18 So, in conclusion --
19 DR. TEMPLE: Can I ask a question?
20 DR. GILMAN: Yes, Dr. Temple?
21 DR. TEMPLE: For the non-modelers, do you have

some sort of visual representation of what the relationship between concentration and outcome is? If I understand what you do is you draw a theoretical --

DR. BRAEKMAN: This is not a theoretical. These were actually predictions for a patient where I gave you what the demographics are. We made a change.

DR. TEMPLE: Well, let me see if I understand. You drew a theoretical blood concentration line in the patient. You didn't actually measure that. You I guess assumed a 20-hour half-life and you said here's what happens. And then you drew the line for the .1 group. That wasn't theoretical. That was just the observed line. Then you drew a concentration relationship.

Now, that's not a conventional thing where you say, okay, here's the people who had this concentration and here's their slope and here's the people who had this concentration and here's their slope. We'd all understand that.

This is a line that you drew that represented what? The best fit, the thing reduced the difference between observed -- what was that exactly?

1 DR. BRAEKMAN: It is the best fit. Go back to
2 the model. You put in the model the AALS values versus
3 time and your IGF-1 concentrations are covariates. They
4 change the slope. You put this all in one model. It's a
5 population model. So, what you get out of the model are
6 the PK and PD parameters that tell you something about the
7 population. It doesn't necessarily tell you something
8 about an individual patient.
9 So, that's why I had to pick out one individual
10 patient for his demographics, for his characteristics in
11 the population model to get out how it looks like. It's
12 the only way how you can demonstrate.
13 DR. TEMPLE: Okay. Suppose you were to do
14 something crude and stupid. Maybe John is going to address
15 this. But suppose you use something sort of crude and
16 stupid and divide people up into --
17 DR. LEBER: Please. That's what's John going
18 to do.
19 (Laughter.)
20 DR. TEMPLE: -- into deciles. Okay? You took
21 the lowest 10 percent and then the next 10 percent and then

the next. You'd see a similar slope, the sort of thing anybody who's not a modeler could understand?

DR. BRAEKMAN: Yes.

DR. TEMPLE: But you didn't do that.

DR. BRAEKMAN: Right.

DR. TEMPLE: Because you do models.

DR. LEBER: We're going to try to illuminate this. We'll shed some light on it.

DR. GILMAN: A word from the sponsor please.

DR. GREBOW: Yes. I'm sorry. We have a slide that we will get a transparency made where again it's the data that I alluded to before. It's not a modeling. Again, it will show you the change in the slope versus blood concentration for those individuals who we had three points of pre and post slope showing a correlation in 1200 of that data.

DR. LEBER: One question about that. Does that include everybody in the study or only those on drug?

DR. GREBOW: That is only those -- again, this is why we will only look at -- we didn't present it as a primary because it's not PK/PD. It's not presented. But

1 what we looked at is the change in the blood concentration.
2 So, by definition, you're eliminating a good number of
3 placebo patients essentially because we're assuming --
4 we're looking at now the effect of the IGF-1 concentration,
5 the change in that concentration versus the change in the
6 slope for those individuals.
7 DR. LEBER: You were not quite clear about
8 whether it is restricted to the patients randomized to
9 treatment or included any placebo or .5 dose group people
10 in the same analysis.
11 DR. GREBOW: In this analysis -- and we need to
12 check it one more time -- it is that we subtracted out the
13 endogenous IGF-1 levels from the individual --
14 DR. LEBER: That's not the question I'm asking.
15 I'm asking the individuals on whom the analysis is
16 conducted, are they people who are in the .1 milligram
17 group or do they include all patients in the study,
18 assuming this was done on 1200, or are they combined
19 results across both studies?
20 DR. GREBOW: Dr. Dobbins?
21 DR. DOBBINS: Yes. Dr. Dobbins.

1 We performed a very simple -- asked a
2 relatively naive question and that is, separate from the
3 PK/PD aspects, we took patients with at least three pre-
4 slope values and at least three post-slope values,
5 subtracted them to get the change, and then looked at high
6 dose, low dose, and placebo and looked at the change in
7 average IGF concentration for a patient. So, each patient
8 contributed an average IGF concentration on the study and a
9 slope change. What we found was very simply a linear trend
10 on the high dose group which was significant at the 5
11 percent level, not significant for the low dose, and not
12 significant for the placebo.
13 DR. LEBER: The clarification, though, is that
14 this is a comparison of the slopes of the .1 concentration
15 versus the .05. It's a between-group comparison still even
16 though it's based on information on change of slope or is
17 it a comparison within the group randomized to .1 of their
18 slope concentration relationship.
19 DR. DOBBINS: Yes. It's within the patients
20 randomized to .1.
21 DR. GILMAN: To .1.

DR. TEMPLE: But you did that for each group. You also looked at --

DR. DOBBINS: Yes.

DR. TEMPLE: Okay.

DR. GILMAN: So, you did it for .1 and you did it for .05.

DR. TEMPLE: That doesn't seem complicated enough.

(Laughter.)

DR. DOBBINS: I think that's the beauty of it.

DR. GILMAN: While we're waiting for those data, Dr. Drachman has a question.

DR. DRACHMAN: I am missing the punch line here.

(Laughter.)

DR. DRACHMAN: The reason I'm missing it is that I expected that you were going to show us that there is considerable variability in the way in which the blood levels relate to the dose that they received and that in fact when you measured the blood levels of those on .05 or placebo or .1, that when you had higher blood levels, they

did much better than when you simply looked at whether they were on .1 or .05. I also expected that you were going to show us similar data from 1202.

Instead of that, what I'm hearing is that you are confirming fundamentally what we already knew, namely, when you look at .1 and you look at placebo, there's a difference.

Now, tell me what I've missed.

DR. GILMAN: You mean in 1200 only.

DR. DRACHMAN: In 1200 only. What am I missing that is being refined and amplified by a detailed analysis of the exact blood level for the individuals within each study?

DR. BRAEKMAN: What the previous analyses, the prespecified and the post hoc analyses, what they have shown you was a dose effect. What this shows you, that there is a concentration effect.

DR. DRACHMAN: Is it greater than or different from the dose effect?

DR. BRAEKMAN: That's a comparison that you cannot make.

DR. DRACHMAN: Then what's the point? Why should we bother with it. We already know the dose is -- that's what I'm missing.

DR. BRAEKMAN: It gives you confidence that the drug works.

DR. DRACHMAN: No, that the drug level corresponded to the dose.

DR. BRAEKMAN: Well, I don't know of any drug that does not work where you can demonstrate this beyond an accidental occurrence which is a chance of 5 in 1,000 for this analysis.

DR. DRACHMAN: What I'm really asking is are the failures of absorption? Are there differences in the pharmacokinetics? Are there certain individuals who got high doses and had low blood levels, low doses and had high blood levels? People who, because they were European, failed to absorb? I don't know what they were eating but something.

(Laughter.)

DR. DRACHMAN: But in any event, is there some explanation that hinges upon the blood level that doesn't

relate to the dose?

DR. BRAEKMAN: This is not a question that the analysis tries to answer. What this analysis tries to answer, if there is a correlation between concentration and effect on slope. In trying to analyze this, it uses error models. It also uses some correction based on the blood levels. When you go from dose to blood levels, there is some variability in there. When you go from blood levels to the effect, there's some variability in there. This is offered together in one analysis.

If you only look at dose and effect, you assume that there is only one type of error that you can really have grips on. So, PK is used as a way to explain the differences. But asking the particular question is a particular group of patients or patients that they got a higher dose, have lower levels, have a lower outcome, that's not the question that was answered.

DR. GILMAN: Can you explain why you did not see this effect in study 1202?

DR. BRAEKMAN: Well, I think all the same reasons that were given by the clinical presentation can

apply here. I just can tell you from the PK/PD perspective, when you try to analyze these models -- and I didn't go into a lot of detail, but there are intra and individual variability that's built into the model. That variability was very high in 1202 compared with 1200 to the point that the model could not really -- in certain models could not estimate what the shape parameters were.

DR. GILMAN: What was the variability? Drug level scores? What was the variability in 1202?

DR. BRAEKMAN: This is variability. If you look into the model, it is mainly the residual variability in the pharmacodynamic effect from month to month. Based on the outcome of some of the models that gave you an outcome for 1202, it looked like from month to month that there was a larger variability than what you have in 1200.

DR. GILMAN: Can you explain the reason for that?

DR. BRAEKMAN: I don't have any explanation for that.

DR. GILMAN: Dr. Dobbins has been standing patiently at the microphone for a bit.

DR. DOBBINS: Thank you. I just want to address the slide and a point of clarification. I misspoke a moment ago. It has been a while since this analysis was performed.

The graph that you see represents the predicted average change in ALS score slope from pre to post for the 164 patients in the study with at least three points for the 164 patients. So, it represents not only the high dose, but all patients with at least three points pre and post baseline.

On the horizontal axis, we see the change in average IGF serum concentration from baseline. It's a simple linear regression and the p value is .04.

DR. GENNINGS: Can you read the legend for us? I can't see it.

DR. DOBBINS: Yes. On the vertical axis you have the ALS score slope change from pre to post study, and on the horizontal axis the change in the average IGF serum concentration for a patient.

DR. GENNINGS: Which line is which?

DR. DOBBINS: Oh, I'm sorry. It's a predicted

mean change in slope with 95 percent confidence intervals.

DR. GILMAN: Dr. Leber?

DR. LEBER: There's a critical point that I want to underline. I asked the question before, whether in the slopes analysis, patients who were assigned to placebo were included within it.

The reason that becomes important to this analysis is we already know that by virtue of assignment to treatment, the groups differ in their ALS scores. Accordingly, you have to ask does the information in this tell you more than what you already know is a function of concentration or is this doing no more than reexpressing the fact that the groups differ by virtue of treatment assignment to the various doses.

We're going to address that, but that's why we are making such a point about whether placebo is included in this analysis.

DR. BRAEKMAN: Just to answer your question, Dr. Leber, in the PK/PD analysis, the placebo patients are included and the assumption is that if you have a high IGF-1 level, even if you are in the placebo group, that it does

not differ in effect from a level that's caused by dosing with Myotrophin.

DR. LEBER: But if we were doing this as a hierarchical model -- I mean, just think of how we usually look at what we do. This is a schematic by a consumer statistical information, not a producer of it. We start with something that says you can describe what went on in an experiment by taking the mean. Then we say, well, maybe the mean isn't good enough. Let's put a model that has the mean and some explanatory factor plus error in it.

Now, we've done that. Our explanatory factor here is treatment assignment by group. Now they come along and they say, well, let's add concentration rather than treatment assignment. Well, what happens if there's no difference between a model that explains the data well because of the combination of the mean and the effect of treatment assignment versus the mean and the effect of concentration? It's the same information reexpressed under another label.

So, what we want to know, having in some way taken account treatment assignment, which is the group

assignment, does knowledge of concentration within the group change information about what causes things? And there are different ways to approach this.

Part of the struggle that we're going to face today is recognizing that the way you organize these arguments and the way you think about this can affect what result you get. It turns out not to be as simple as we'd like it to be. I think that's our bottom line. John will get into it.

DR. GILMAN: Dr. Braekman, did you say that you may not get a difference in level between placebo and treated patients?

DR. BRAEKMAN: What I said was if for some reason, like the endogenous production of IGF-1, if a patient has higher endogenous levels of IGF-1 in this model, the assumption is that it still can have a beneficial effect on the slope. So, it does not really matter. The IGF-1 circulating concentration -- if it comes from your own production or you take Myotrophin and it increases the level to that same level, there is no assumption that there is a difference between a Myotrophin

IGF-1 molecule and a circulating level within the placebo patient.

DR. GILMAN: That's a discussion of the model. You're not implying that there were such findings.

DR. BRAEKMAN: I'm not implying that there are such findings. Correct.

DR. GILMAN: Are there such findings?

DR. BRAEKMAN: We didn't really address that question, but this is the assumption that goes into the model. Since this model has shown to be statistically better than a model where there is no influence of IGF-1, it is implied in the outcome.

DR. GILMAN: All right.

Dr. Temple?

DR. TEMPLE: Well, it's important to recognize what these things are and what they're not. We already know the outcome between 1200 and 1202 is different, and that continues to be the case even when you do these models. So, this is not going to help explain some magic imbalance or something that led to the outcome in 1202.

What it does -- and this is well laid out I

think in the document that was sent -- if you look within the group that was assigned to -- the results of any given trial could have been due to the drug effect or they could have been due to some distribution of patients that led to this outcome that was unrelated to the drug. That's what you always worry about. What this a chance effect?

By looking within the group that was assigned to Myotrophin and finding a relationship to concentration, whether you do it using modeling or something, you make some attempt towards saying this is a little stronger than I thought because, randomization aside, baseline characteristics aside, I got something that emerged that shouldn't have emerged unless there was a drug effect.

Now, the document points out there can be spurious relationships between concentration and outcome also, and if you don't randomize the concentration, you always worry about it. This is sort of a poor man's -- or poor person's -- concentration-response curve. If you were doing it properly, you'd randomize the different concentration levels and then we'd all be happy and there wouldn't be any questions about all this. But that's what

this is.

So, it can add some weight. That's why we're interested in it, but as you've already seen, it's not going to explain why 1202 didn't come out. That remains interesting and a major concern, obviously.

DR. GILMAN: Yes.

DR. BRAEKMAN: Can I just respond to this for a second? Very brief. This method was developed for mainly observational data. So, we take the observational data and put the model together. It's multifactorial. It's more representation of the real world, and then we have this kind of an outcome.

I agree with you completely. You could reach the same conclusion by randomizing patients to a certain level, but as you know, these studies are very difficult from a logistic point to do.

DR. GILMAN: But I think Dr. Temple's point is that we've not learned anything new or different about the comparison of 1200 to 1202. Your analysis, elegant though it may be, has not told us much about the difference between those two studies.

DR. BRAEKMAN: It has told you -- it has shown you that -- the previous analysis shows you that there is a dose response. This shows you that there is a concentration response.

DR. GILMAN: In 1200.

DR. BRAEKMAN: In 1200.

DR. GILMAN: But not in 1202.

DR. BRAEKMAN: Correct.

DR. TEMPLE: It could strengthen 1200 to some extent.

DR. GREBOW: Could I please help clarify?

DR. GILMAN: Please, go ahead.

DR. GREBOW: Because I think there's a lot of confusion of why this is presented, and let me try to explain the sponsor's intent. I think Dr. Temple sort of summarized that, but just from our point of view.

There's been a lot of talk I think from the clinical point of view. We've shown you what we think is excellent, robust data for 1200, the clinical data. There's still concern from individuals. Is that chance?

The PK/PD modeling or analysis simple without

any modeling is another way of looking at 1200 data alone and confirming that the element of chance of this study being a positive study has now diminished even further. You're looking at data where you're just looking at blood levels versus effect, regardless of the dose, and emphasizing the strength of the study. It's not the sponsor's intent to discuss 1202 of why it did work or didn't work as far as the PK/PD analysis.

DR. GILMAN: But your argument doesn't hold for 1202. There's our problem.

DR. GREBOW: But then again, you've seen the clinical data on 1202 also. So, it's the same issue with 1202. But it does confirm via another pathway that you use blood concentrations as a marker that the study actually was a positive study.

DR. GILMAN: Dr. Leber?

DR. LEBER: I think we want to clarify that this is a point in dispute. We agree the logic of the analysis, which actually we proposed in our analysis -- and I think other people came to it independently in our briefing -- is that if one within a treatment group could

find a relationship between exposure and response, as Dr. Temple just said, that would lend additional credibility to the argument that the treatment differences in that study were attributable to the treatment and not to chance, bias, or something else.

The sponsor has done an analysis that you see presented here which includes the placebo group. So, we're still in doubt about whether they have shown an effect of concentration per se or an effect that's due to the group differences that are linked to various concentrations by common sense. Clearly if exogenous IGF-1 causes plasma concentrations to go up and the .1 group is simply better by chance, you're going to get a correlation between plasma levels and response by virtue of the fact they were originally different anyway. So, we need to distinguish within the group whether there's a concentration gradient.

There may be an analysis which shows it which we haven't seen yet. We don't know. There may be analyses that don't show it. But right now we're in doubt, and that's all we want to say. The case is not proven.

DR. GILMAN: Does the sponsor want to respond

to that? That's a key point here.

DR. GREBOW: Yes, I think so in that there are analyses that was submitted in the appendix to the PK/PD report that showed that there was an effect within the 0.1 milligram per kilogram dose using the models that Dr. Braekman alluded to and also with models that we've had in discussions with representatives from the FDA.

I also want to turn this discussion around a little bit. Maybe it's another way of looking it. Maybe 1202 is the real study and 1200 isn't. If that were the case, what's the probability of actually seeing a blood concentration effect in 1200? Dr. Braekman, what is that number?

DR. BRAEKMAN: It's 5 in a 1,000. The p value was .005.

DR. GREBOW: So, that again is an issue that we should consider.

DR. BRAEKMAN: (Inaudible.)

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

DR. DRACHMAN: The problem that I have with that is were one to give high dose aspirin to the group

that got 0.1 in addition and measured the aspirin level in that group, clearly that would be different. We already know that the groups are different on the AALS measure. So, whether or not one demonstrates that as a group they had higher levels of IGF-1 doesn't change our thinking any more than it would if they were given aspirin as well and their aspirin levels were higher just as one example.

What I think I've heard said, everybody else has raised an issue of, is given variability within the .1, the .05, and the placebo group across groups, can one show an exceedingly high correlation between the blood levels and the outcome. And I'm waiting.

DR. GILMAN: Dr. Leber?

DR. LEBER: I wanted to make a point to make a distinction between the fact that there may be some analyses -- remember, analysis takes into account a model one builds of the data after the fact of how you want to model it. There may in fact be analyses that attain nominal statistical significance. P values might be small even, but that doesn't mean that the model applied to the data is an appropriate one.

1 That's one of the arguments we have. We
2 haven't specified any of this in advance. People are doing
3 post hoc explorations trying to find some patina, some
4 argument that will help persuade us one way or another
5 about what the data mean.
6 I don't want to give the impression that
7 someone couldn't produce an analysis. What we want to do
8 is look at the analyses in our presentation and ask are
9 they appropriate models, are they appropriate ways to look
10 at the evidence. And we'll try to do it without getting
11 into the models, but more getting into the data. I just
12 want to leave you with that thought.
13 DR. GILMAN: Do you want to respond to Dr.
14 Drachman's comment?
15 DR. WILLIAMS: Yes.
16 DR. GILMAN: Please identify yourself.
17 DR. WILLIAMS: I'm Dr. Lewis Williams from
18 Chiron.
19 I just wanted to be sure we didn't miss a
20 relatively straightforward point in your question. Excuse
21 me if I've oversimplified this.

But you asked the question I believe that if you look across the groups, placebo, .05, and .1, if you include all of those and look for a concentration effect on response, do you see one.

DR. DRACHMAN: No. One that is different from simply the dose they were given, greater than, more precise, zeroes in on it, shows that it is exactly or more exactly related to it.

DR. WILLIAMS: Well, the analysis, as Dr. Leber I believe pointed out, doesn't attempt to group them by their group, but simply looks at them by their concentration. So, it is a different way of looking at the data across the groups simply looking at the concentration.

For example, suppose someone had an IGF-1 producing tumor. You could end up in the high concentration group having never gotten Myotrophin.

And this analysis doesn't take into account the way patients took their drugs, whether they did or not, whether they were dosed appropriately, et cetera. It simply looks at concentration across the groups, as you suggested. So, it is a different way of looking at it.

We don't want to overblow it, but I just wanted to be sure that your question was answered.

DR. DRACHMAN: Right, and is it better than by group?

DR. BRAEKMAN: In this modeling approach, there is no comparison between -- if you stratify patients by dose, stratify them by concentration, there is no comparison between these two models. We did not do that and I don't know of a method, with the methodology that I have to my disposal, that can actually look for that.

The question we asked, was there across all the treatment groups a concentration-response relationship? And with the p value of .005, there is a significant correlation in 1200. That's the only question we answered with this.

DR. GILMAN: Well, no. You also answered the question of whether there's a similar effect in 1202, and there's not.

DR. BRAEKMAN: In 1202 we tried the same thing. And I have to remind you that in a lot of models it didn't work, but in a lot of models it did work. We are just very

conservative by saying here that it was much more difficult to come to the same conclusion in 1202. So, we are conservative. There are certain models that are rational and that seem to work. We don't want to make a big deal about this.

DR. GILMAN: It was more difficult to come to the same conclusion. You mean you did not find a relationship.

DR. BRAEKMAN: In most models, no, we did not.

DR. GILMAN: In any?

DR. BRAEKMAN: In some we did.

DR. GILMAN: I will not ask further.

(Laughter.)

DR. LEBER: I think in fairness what you're seeing is the difference between how modelers think and how people who make the usual inferential tests on clinical results think. What's going on is that the modeler has free rein with the data in hand to try to fit it to an explanation that is rational and reasonable. And they choose a model on the basis of how well it predicts or fits that data. So, they may be persuaded by one set of models

being a realistic way of examining or a rational way and not another. So, I think that you have a conflict in philosophy here that partly explains why they are persuaded in 1200 something exists or not.

I was answering or trying to address a different question, and that is not whether there's a concentration relationship across the groups. I'm saying there has to be given the order you have. Given the results of this, we know that group A had the best. That's .1. They got the highest dose of Myotrophin. So, even if A-ness versus nothingness accounts for the difference between those groups, it's a tautology having given them exogenous IGF-1 that they're going to have higher concentrations, and therefore there will be a regression of group concentration against the outcome.

DR. GILMAN: Of course.

DR. LEBER: It doesn't illuminate anything.

What we want to find is whether within one of these subgroups there's additional information that will allow us to say, yes, it makes sense that Myotrophin might have done it because within the group there is this sort of

vector of response that correlates with concentration exposure. There may even be some of that. We have to find out.

DR. GILMAN: Right. Well, but if they have a model that works for one study, one would hope that that model could be generalized and therefore would apply to the other study. But that's not the case, giving one less than great confidence in that model as a predictor of anything in these two studies. It doesn't explain 1202.

Dr. Hoberman and then Dr. Temple.

DR. HOBERMAN: Well, I have an overhead that might give you an idea about the raw data.

DR. GILMAN: Please, yes.

DR. HOBERMAN: This is sort of a presage of our presentation that Dr. Feeney will give.

DR. GILMAN: Hopefully we'll get to your presentation sometime.

(Laughter.)

DR. TEMPLE: No wonder we were confused before, David.

(Laughter.)

DR. HOBERMAN: This is a scatter plot that was constructed in the following way. What we did is simply take the data available on the database and fit in this case the change in slope. On the top you'll "CHSLOPE." So, in this case, it's a plot of the change in slope of people who were on the PK database. That means that this includes people not included in the primary analysis because we wanted to use all the data available.

Across the horizontal axis, this is the average concentration, effectively the average concentration, over time for each patient. So, each one of these symbols represents a patient. And the vertical axis represents the patient's slope in points per day, and the horizontal axis is their concentration.

The only distinction between these squares and the pluses is an artifact because, for the purposes of what I was doing, I wanted to separate people who had concentrations less than or greater than 300. But that's pretty much irrelevant to the point.

The point is that the phenomenon we're talking about, that is, the tautology that placebo patients will

1 tend to have lower concentrations and higher slopes simply
2 based on the randomization analysis, is illustrated by --
3 these values up here are basically the majority of these
4 patients that would induce the kind of straight line that
5 Dr. Dobbins showed you are basically placebo patients.
6 I want to distinguish between what the sponsor
7 has done and what we have done, that is, the presentation
8 you've just heard. We fit slopes just like they did in the
9 primary analysis with just these squares, lines. This is
10 not the same thing as modeling a population parameter.
11 However, the results should be fairly similar.
12 Now, what you do is if you take out these
13 patients, if you visualize it, you basically have a cloud
14 of patients. .05 patients tend to be in here. .10
15 patients tend to be in here. I think that this answers Dr.
16 Drachman's question about the variability of concentration
17 given that you have a high dose.
18 So, really the question we're talking about is
19 not what's happening down here because we know that that's
20 expected. What we're really interested in is when you see
21 this cloud of symbols here, right in here, is there a

straight line or is there any discernable relationship between concentration and slope.

Now, to the naked eye, it doesn't appear so. There may be analyses that claim to show it. In our presentation, we'll go into this in more detail.

DR. TEMPLE: David, you'd see a downward slope if there was an effect of concentration. Right?

DR. HOBERMAN: That's right.

DR. BRAEKMAN: Can I ask you a question? This is a change of slope and you said you wanted to use data for all patients. Now, some of the patients, the pre-dose slope had like maybe two, maybe some of them had even one point. How did you calculate the slope and how can you reliably estimate that kind of a slope with only a couple of months of data and in certain cases not a lot?

DR. HOBERMAN: Okay, that's fair. One thing I did was exclude all patients who had only one point, obviously. I did use patients with two points because I simply wanted to use all the patients. But I must say that if you use only the on-slope slide, which unfortunately I've not brought, you get the same pattern. There's really

very, very little qualitative difference in any inference in this data that I have seen that is based on the change in slope or the slope in study 1200.

DR. BRAEKMAN: When you would try to fit a line through these curves, the error model that you assume is a linear model.

DR. HOBERMAN: Oh, yes.

DR. BRAEKMAN: And you lump all the errors together from PK/PD, all kind of covariates.

DR. HOBERMAN: Well, no. I'm simply taking the ALS scores for each patient and fitting a straight line. When I do that, it is a reasonable, as a matter of fact, unbias supposedly -- if I were to take the mean of all those slopes, that would be an unbiased estimate of the population slopes.

DR. BRAEKMAN: Well, it's a very simple model. What a population PK/PD model does, it has an error structure about variability that has been proven for a lot of compounds in the meantime for the last 30 years to be more representative for the real world how clearance change, how there is an error model on the IC50, and all

these other shape parameters.

DR. HOBERMAN: Well, that's true, but on the other hand, in one of the reports that was submitted by the sponsor, they abandoned basically using -- not abandoned, but they were unable to get convergence in the programs if they used the observed concentrations and decided to use essentially the average concentration.

You're making an argument I think which is a little off the point, and I grant you that those models are very complicated. They introduce inter-subject and intra-subject variability that sounds very sophisticated, but it's not necessarily so that they give you a better picture of a population parameter than another model. Those are technical statistical issues which I don't think anybody wants to go into.

What we're concerned about is something that everybody can understand that makes common sense and has statistical validity on its own. But granted, it's not as sophisticated in the bells and whistles as PK/PD modeling.

DR. BRAEKMAN: Well, I'm sure we can discuss this and it could be a really intensive debate of which

model is the right one. I don't think that's the idea of this discussion.

DR. GILMAN: I agree.

Dr. Temple, do you still have a comment?

DR. TEMPLE: Only a very short one. The success of all of these efforts depends a little bit on an experiment of nature. As other people have said before, if all of the people who got the high dose had concentrations that were very close to each other, you could never distinguish between the assignment and the concentration. So, you would ultimately fail. So, the more scatter there is in the blood levels attained, the better shot you have at all this.

In answer to what Dr. Drachman was saying before, that's why this could represent, if it was successful and persuasive, a somewhat independent view. It's almost as if you had both a concentration controlled study and a placebo controlled study at the same time. The question is whether you have that, whether it's persuasive. You've already heard that there's a lot of difference in how these come out depending on what you do and what your

assumptions are.

DR. LEBER: Just as a matter of truth in what we're doing, there are other FDA analyses that exist, some of which, depending upon when they were done and what models they used, have actually produced evidence that somebody would suggest is compatible with the concentration relationship, but others that have not.

Now, I don't know to what extent anyone would want to look at them. I guess my judgment was that it's very arcane material, hard for the non-expert to understand. I just think we ought to put it on the record that we are not fully satisfied that we understand but there are analyses that produce discrepant or discordant results. And they're not all from this review team. We've got consultants throughout the agency, and if the committee wants it, we could ask them to be presented.

But I think the problem will be how do you choose among a set of disparate models that produce different results given our backgrounds and skills. I just wonder whether it will illuminate anything. I just want you to know they exist.

DR. TEMPLE: It could also be that that's something the committee will think is worth looking into later because we're plainly not finished with this aspect of it.

DR. BRAEKMAN: I just want to make one comment on both the last speakers. The models we used are simple. They are rational, and there was a scientific exchange between the two modelers, one of the FDA and one of Cephalon. The input that was given was really valuable in that we at the end end up with better and more rational models which show for 1200 that there was definite significant correlation.

DR. GILMAN: Dr. Hoberman?

DR. HOBERMAN: I have a very brief comment. One of the consequences of one of those models -- and I think this will come up after lunch -- is that the post-baseline concentration predicted your ALS score before you were ever treated. Now, if you think about that, you've got another problem because it is possible that the people who started out the best at baseline, before they were ever treated, were fated to get high concentrations. That is

one of the results of one of the statistically significant models that was submitted as a result of your conversations with our modeler. So, it raises some issues about the rationale of all of these models anyway.

DR. BRAEKMAN: Are you referring to the models from addendum 2 that we submitted?

DR. HOBERMAN: That's probably it, yes.

DR. LEBER: I think there's a clinical side to it that I'd just like to finish, and that is that we have always admitted, although this is a rational way to think about it, it's always possible -- and we said so in our mailing -- that the relationship between concentration and disease state is in the other direction. I can imagine or make up a number of models that would account for a concentration gradient predicted by disease state rather than the other way around. Correlations for that reason are treacherous. And we don't know. We just wanted to explore it. So, I don't think this is a definitive answer but something worth looking at.

DR. BRAEKMAN: I just want to address Dr. Hoberman's question. The levels before treatment starts

and the slope that you have there -- the ALS scores that you have there are not treated differently than when you start dosing. There is a model that allows variability. In the models, variability for these observations are allowed. And each patient that contributed measurements contributes to the information that the whole population then shows. So, the PK/PD model is one of the most unbiased models there is in the sense that you don't leave patients out, not even the ones that you have only one observation.

DR. GILMAN: Dr. Braekman, I don't think you ever summarized. You had a final slide up there, but I'm not sure whether you want to at this point or not. I think we've heard the arguments clearly. Do you want to conclude now, or have you said enough?

DR. BRAEKMAN: I think I made it very clear that for 1200 I think basically it's the middle observation or the middle conclusion where we think we have shown with a high probability in 1200 that there is a correlation, that there is a relationship between IGF-1 serum levels and response effect on slope, and that's beyond chance.

Thank you.

DR. GILMAN: May I ask the sponsor whether you have more presentations to come?

DR. GRANEY: We have an extremely brief safety presentation which extends into some survival and a risk benefit. I would anticipate that it's probably a total of 25 minutes.

DR. GILMAN: Well, it's about quarter of 1:00 now, and that would take us well past the 1 o'clock hour. I would suggest that we break for lunch, resume in one hour from now, quarter of 2:00.

(Whereupon, at 12:45 p.m., the committee was recessed, to reconvene at 1:45 p.m., this same day.)

AFTERNOON SESSION

(1:52 p.m.)

DR. GILMAN: Let me welcome everybody back so that we can continue reviewing Myotrophin.

Cephalon and Chiron are here and we're about to hear the end of their presentation. I've asked that all presenters now be as succinct as possible. I remind you again we have read all of the briefing materials. Please be brief.

DR. GRANEY: Thanks, Dr. Gilman.

This afternoon, after I briefly summarize safety and our survival experience, Dr. Bruce Scharschmidt will present the risk-benefit and Dr. Bob Miller will present an appreciation from a caregiver's point of view.

As you saw from your documents, safety is not an issue on which there is any disagreement. So, I'll present only a single slide to recap the elements of safety. The material is presented in detail in the briefing document.

The first element is that the general observation across the clinical program is that Myotrophin was well tolerated by patients with ALS. The adverse experiences, as you would expect, were largely those associated with ALS. We did have minor injection site complaints and we did see some of the previously described adverse events with IGF-1 or growth hormone. However, through all of these, discontinuation for adverse events was uncommon.

Symptoms of hypoglycemia, a concern that clinicians new to the area sometimes express, were rare.

Finally, we observed that deaths were associated with previously identified risk factors, age and FVC, and we'll consider that in the survival presentation.

As I mentioned this morning, we did extend the follow-up through July 31 of 1996 to gather more

information on our patients. All patients were followed up as of that date so that we do have information on whether they were alive or dead at that time. I'll review just a few points to keep in mind as we look across the survival experience.

75 percent of patients entered the open-label treatment of the total number that were randomized previously. Because in the open-label treatment phase all patients received Myotrophin for compassionate reasons, there is no true placebo group and the FDA's document notes this. In effect, patients who were identified as placebo-treated really differed from the Myotrophin-treated patients in that there was a 9-month delay before they started Myotrophin. So, there's not a great deal of difference in the drug treatment to produce an effect during survival.

Finally, throughout the presentation, you'll see that we do label patients based upon their original treatment.

This is the Kaplan-Meier unadjusted for North America, and it presents the survival experience for the

patients originally treated with Myotrophin and those originally treated with placebo. I apologize if the red does not show up well.

In this study, the median follow-up time for patients was 35 months and 195 of 266 patients died during the follow-up. The median survival for the Myotrophin group is 20 months. The median survival for the placebo group is 17 months. It may be hard to make out on the curve that you see on the screen, but no separation emerges until about 6 months and then it pretty much persists through the rest of the observation period.

We can look next at the comparable Kaplan-Meier curve for the European experience. Here the follow-up is briefer because you'll recall the study started later. The median is 27 months. 117 of 183 people died during the observation period, and the observation that you simply can't miss here is that early on there were more deaths in the Myotrophin than in the placebo group. As you'll see, we believe that significant differences in the distribution of patients at high risk for death does largely account for that difference.

As I noted, we found in our program that risk factors involved with death really reflected what was seen in the literature, and the two with the strongest effect were age and pulmonary function. These two Kaplan-Meiers were prepared by combining all patients in all treatment groups in both studies to try to get an overall picture of the impact of risk. In the first we examined impact of age and in the second pulmonary function measured as FVC as a percent of predicted.

In the first graph, patients are separated at age 55 which was approximately the median in the program. As you can see, there's a significant separation between the younger and the older patients. The same story occurs with the FVC division which is made at 80 percent, again approximately the median. The impact of age is 12 months at the point of median survival. The impact of FVC is 9 months, a fairly large difference when you consider the period over which the observations were made.

We can quickly look at the real impact of these factors if we just look at patients by their risk and in each of the studies. The lowest risk patients, the

youngest with the best pulmonary function, are listed on top, and the highest risk patients, the older patients with the poorest pulmonary function, on the bottom. As you can see, there was a large number of deaths in the bottom group. In fact, two-thirds of the deaths occurred in the 35 percent of patients who are represented in this particular risk group. So, that just gives you a picture of the impact of the risk, and I hope you will see how it can impact the outcome of the survival study.

This slide, which has a lot of numbers on it, basically presents the distribution of patients in a given risk group across the treatment groups in the North American. The group of interest, again because so many of the deaths occurred there, is the highest risk, older patients with a poorer pulmonary function. If we look across the treatment groups, they are relatively evenly balanced, as were the deaths early on in Myotrophin. In the North American study, there was really no great difference between the deaths in Myotrophin and placebo during the first 300 days.

We can look across those treatment groups just

1 to get a picture of what survival was by looking at a
2 Kaplan-Meier for each of them. Again, the lowest risk
3 patients are separated here, the youngest with the best
4 pulmonary function, the two intermediate groups, and the
5 high risk group. In fact, there is some degree of
6 separation for the curves in each of the groups.
7 Now, if I can have the next slide, the balance
8 that we saw relatively clearly in the North American trial
9 did not exist in the European trial. Going again to the
10 high risk patients and looking at the percent as they
11 distributed, there was a 3 to 1 ratio of the high risk
12 patients as compared to a 2 to 1 that would be expected
13 based on the 2 to 1 randomization, and there's a very
14 slight excess of the low risk patients in the placebo. So,
15 we did have this group of patients who accounted for a
16 disproportionate number of deaths over-represented, if you
17 would, in the Myotrophin-treated patients.
18 DR. TEMPLE: Could I ask a question before you
19 do that?
20 DR. GRANEY: Yes, please.
21 DR. TEMPLE: That's a very strange

presentation. It's an unbalanced randomization, 2 to 1.

DR. GRANEY: Yes.

DR. TEMPLE: Ordinarily you'd present the risk group as a fraction of the whole group like you'd present what fraction of the age less than 55, FVC greater than 80 is the placebo group. But you've done it as a percent of the total.

For example, if you do what I just said, and take the worst risk group at the bottom.

DR. GRANEY: Okay.

DR. TEMPLE: 25 percent of the placebo group is that.

DR. GRANEY: Yes.

DR. TEMPLE: And 33 percent of the Myotrophin group is that. Now, that's a direction but it's 33 versus 25, not 74 versus 26. Am I being clear on this? You expect two-thirds of everything to be in the Myotrophin group because that's two-thirds of the patients.

DR. GRANEY: Yes.

DR. TEMPLE: So, you start out with 67 percent.

DR. GRANEY: Yes.

1 DR. TEMPLE: You should. So, 73 percent is
2 neither here nor there. It's not very different from 67.
3 DR. GRANEY: Except for this group -- it is
4 true you'd expect two-thirds and one-third, looking at the
5 2 to 1 randomization.
6 The point is that -- and I didn't make it clear
7 -- the relatively high mortality rate of the patients in
8 this high risk group does make even this slight weighting
9 basically convert to a relatively high mortality rate in
10 the group.
11 DR. TEMPLE: Well, okay, but it's a slight
12 weighting. It's 33 percent versus 25 percent, not
13 something else.
14 DR. GRANEY: Yes. I acknowledge that. As I
15 said, the reason that we call attention to it is just the
16 markedly different overall mortality experience in that
17 group.
18 We pointed out we hope in a relatively
19 straightforward fashion --
20 DR. GILMAN: Excuse us one second, Dr. Graney.
21 Dr. Drachman?

DR. GRANEY: Yes, sir.

DR. DRACHMAN: Where are the Kaplan-Meiers for the 1202, just like the ones you showed us for the 1200?

DR. GRANEY: Do we have those available?

DR. GILMAN: Why don't you proceed and then come back to that?

DR. GRANEY: Yes, sir, I will. That's what I'll do.

As you can see, we clearly presented the data without the inferential statistics because it is a post hoc analysis. We certainly did conduct the post hoc analyses and did take an adjustment to look at what the effect is of these very powerful risk factors.

As you saw in the agency's document, there are some very important considerations that have to be made with those adjustments. It's true that when we adjust the North American study, based upon the risk factors that I showed you, the cuts at the median for age and for FVC, one does get a p value that's less than .05, but we agree with the observation which is in the agency's document that you have to be careful in interpreting this and that the

significance does show a fair amount of sensitivity to where the cut points are.

We think there are additional impacts in that as you move away from the median to make your cuts, individual cells become relatively small in number, so it's harder to get significance. But there's no questioning that this is a post hoc analysis and that the p value is relatively fragile.

That's the reason that we've chosen to show you the unadjusted analyses which show that what we believe to be the emergence of a suggestion of survival in the North American trial.

In the European trial, we did not see that. However, we did find significant maldistribution of risk, and when we conduct a simple analysis of observed versus expected deaths in the European trial where we just do a calculation as if the Myotrophin-treated patients behaved as the placebo patients in a given risk did, we find that the observed and expected deaths matched. Essentially the message is that when we give consideration to the risk factors, a concern over whether there might have been

excess deaths out of proportion to the risk is allayed.

You're asking for the individual ones.

DR. DRACHMAN: I want the same one that shows whether those who you say were higher at risk were in fact those who died earlier, just like in the other study.

DR. GRANEY: Oh, yes. We can show you. Yes. That would not be the Kaplan-Meier, but we have a table that shows that.

Yes, Dr. Dobbins?

DR. DOBBINS: I'm sorry. We're having a copy made at the moment. It inadvertently was not in the slide.

DR. GRANEY: Okay.

DR. GILMAN: Well, maybe we can get back to that then.

Could you conclude then, Dr. Graney, or could you finish?

DR. GRANEY: Yes, I will conclude and we'll bring the other slide up.

If I could have just my last slide back. We think there are two important points to take away after looking at the survival. We believe that the information

1 from the North American trial does suggest that Myotrophin
2 has a favorable effect on survival. We believe that in the
3 European trial, the analysis that we've done for the high
4 risk of death in patients with greater age and poorer
5 pulmonary function does allay any concern about Myotrophin
6 and probably does account for the imbalance in early deaths
7 that you saw in the Kaplan-Meier unadjusted for Europe.
8 DR. GILMAN: All right. Yes, Dr. Adams has a
9 question.
10 DR. ADAMS: In the primary design of the North
11 American trial, you stratified by baseline Appel scale 60
12 or less and 60 and above.
13 DR. GRANEY: Yes.
14 DR. ADAMS: Have you done an analysis similar
15 to this with age and vital capacity showing in maybe
16 quartiles or something the comparisons of the lower,
17 medium, and higher risk by baseline Appel scales to show
18 the same sort of effect on mortality?
19 DR. GRANEY: We do have a slide which shows a
20 division at the median for Appels, and can I have that
21 please?

DR. ADAMS: The question comes back to the question that I've been asking on several occasions, which is the placebo patients in the North American study possibly being sicker at the baseline.

DR. GRANEY: This is actually all patients and doesn't break them down by treatment group, so I don't think this slide will address your question. If I can restate your question then, you're asking if we have a display from the survival which looks at the placebo perhaps to show that the North American did not differ from the European placebo group in survival.

DR. ADAMS: Well, no. What I thought you were trying to say with this post hoc analysis is that you have decided that age and vital capacity are critical in looking at survival.

DR. GRANEY: Yes.

DR. ADAMS: I assume, because you had the baseline Appel scale as a stratification variable, you assumed that the baseline Appel scale equally is important as far as predicting survival and other bad things happening. Maybe I'm wrong.

Is there a relationship in survival with the baseline Appel scale?

DR. GRANEY: I don't believe that we have it with baseline Appel, but we do have it with slopes, do we not?

DR. DOBBINS: We have survival by pre-slope stratified at the median of greater than or less than or equal to 4.0, and we could show that.

DR. GRANEY: Great. If we can show that slide please. That would be the stratification by the pre-slope.

DR. DRACHMAN: The importance of the Kaplan-Meier divided by high and low risk is that you've shown and you've presented in the books we got the fact that in 1200 there was a greater risk for those over the age of 55 or with a low FVC. You then showed that there were more people, or relatively more people, with these risks in 1202, but did not show us the comparable Kaplan-Meiers. So, you're fundamentally saying things equal to equal things are equal to each other which works in geometry but maybe not here. So, I'm waiting to see those slides.

DR. GRANEY: Yes. We're trying to get those

for you, sir.

DR. GILMAN: They will have them.

In the meantime, other questions from the panel about safety or this trial?

(No response.)

DR. GILMAN: Let me ask you whether you have any concerns about diabetics receiving insulin receiving this agent.

DR. GRANEY: We do not have specific information on ALS patients with diabetes, but we have conducted in another program where we proposed to look at diabetic neuropathy, a study where we were able to make relatively simple modifications in insulin dose once patients started on the Myotrophin. I think it would have to be taken on a case-by-case basis, but in fact a very simple fractional adjustment of the baseline insulin therapy allowed the IGF-1 to be tolerated fairly well. That's a study that we just have gotten a report in on, but we don't have any indication of problems. IGF-1 apparently has a fairly stable effect, and there was no increase in the patients having either hyper or hypoglycemia, but the

insulin dose did have to be adjusted.

DR. GILMAN: Yes.

DR. WILLIAMS: Williams from Chiron.

I just wanted to be sure we understood your question, Dr. Drachman, and that is are you asking for a Kaplan-Meier in 1202 removing the high risk group?

DR. DRACHMAN: No.

DR. WILLIAMS: You want the individual subgroups. You want the subgroups. Is that correct?

DR. DRACHMAN: Yes, or even the --

DR. WILLIAMS: Or the high compared to low?

DR. DRACHMAN: Yes. High risk, yes, placebo, and treated. Right, exactly.

DR. WILLIAMS: Okay, and we have that.

DR. GRANEY: There are two slides, are there, Tom, which showed the 4?

DR. DOBBINS: Yes.

DR. GRANEY: Okay, so our groups are the youngest here. We have at the top, we have age 55 with an FVC greater than 80 percent. So, we have the lowest risk group here.

1 And it may not be possible for you to see,
2 there doesn't appear to be a great deal of separation out
3 to about 18 months, and then there is some separation with
4 perhaps better performance by the Myotrophin.
5 And then the other group that we would want
6 would be the oldest patients with the poorest pulmonary
7 function. That would be age greater than 55, an FVC less
8 than 80. I think these probably come pretty close to being
9 a wash.
10 I think that is our observation on this, that
11 probably the survival is an extension of the functional
12 improvements. We saw the functional improvements in North
13 American and saw the beginning of a survival effect. In
14 Europe, we didn't see the functional and we did not see an
15 emergence of the survival effect, but I don't think we saw
16 anything adverse to Myotrophin which matches with our
17 analysis that the risk factors accounted for the death
18 experience.
19 DR. GILMAN: Dr. Dobbins?
20 DR. DOBBINS: Yes, just one final point on the
21 matter. The sample sizes in the European study are a

little bit smaller. Particularly for the Kaplan-Meiers, particularly for the placebo group, you see the numbers are rather small because of the 2 to 1 randomization.

Another approach that we had for the European study is to ask the question of what impact the risk -- the prognostic imbalance had on the Kaplan-Meiers. By a method very similar to the stratified log rank, we performed an adjustment to the Kaplan-Meier that would draw the curve as you would expect it to look if there was balance in the prognostic groups.

VOICE: Could we see that figure please?

DR. DOBBINS: So, this is a Kaplan-Meier, adjusting the Kaplan-Meier estimates for the imbalance in the prognostic subgroups, very similar to what the stratified logrank would do.

DR. GRANEY: Again, rather than color, this has lines, and it looks like the curves are essentially superimposable out to 18 months, certainly to the median. Myotrophin does a little bit better there, but I don't think we'd want to make a great deal out of that.

DR. GILMAN: Dr. Graney, can you then conclude?

1 Have you finished?

2 DR. GRANEY: Yes, sir. Yes. The conclusion I

3 have is just the two points. In North American where we

4 had the functional effect, we saw what we believe is the

5 beginning of emergence of a survival effect. In Europe, we

6 did not have a functional effect. We certainly did not get

7 a survival benefit, but a review of the risk factors puts

8 to rest any concern that there's an adverse effect of

9 Myotrophin.

10 DR. GILMAN: Can we hear then from Dr. Miller?

11 And I ask you to be very brief.

12 DR. GRANEY: Actually Dr. Scharschmidt is going

13 to do a brief presentation on our risk-benefit. It is a

14 brief presentation.

15 DR. SCHARSCHMIDT: We have heard discussed a

16 lot of information today. I'll now review this information

17 in the context of risk benefit and in the process address

18 important points raised by Dr. Leber in his opening

19 comments and outlined in the FDA briefing document.

20 First, let's consider the clinical context.

21 ALS is severely debilitating and uniformly fatal. Every

patient with ALS faces not only death but the prospect of being awake and paralyzed and dependent on life support prior to death. The median survival of ALS patients is about 3 years. That's worse than the survival of patients with HIV infection, worse than the survival of patients with cancer, and about the time required to plan and execute a clinical trial.

There is no approved drug therapy which slows loss of muscle strength and function. Thus, the unmet clinical need is great.

Now, these considerations regarding ALS have regulatory, as well as a clinical interpretation. The ALS was designated by FDA in 1988 as a severely debilitating and life-threatening disease. While the statutory requirements for efficacy and safety apply to all drugs, risk-benefit analysis is central to the decision regarding marketing approval of drugs intended to treat such diseases, particularly when there is no alternative therapy. These regulations provide the FDA considerable discretion in its consideration of drugs such as Myotrophin.

1 The regulations also recognize that approval
2 for such drugs may be granted in the face of outstanding
3 questions regarding their benefit and optimal use and
4 further stipulate that the FDA can require the sponsors to
5 address such questions in the context of a phase IV or
6 post-marketing, post-approval study.
7 At its meeting last June, several panel members
8 raised questions which the sponsors concur are important.
9 These include the effect of Myotrophin on survival, the
10 effect of Myotrophin on patients with slowly progressing
11 disease, its effect in different concentrations or its
12 effect in combination with other agents.
13 The sponsors are committed to addressing these
14 questions in the context of the post-approval study and
15 have been in active discussion regarding its design with
16 the members of the division, with the sponsor of riluzole,
17 and with a special working group of the World Federation of
18 Neurology. The protocol shown here is the product of that
19 effort. It has been reviewed with the division and several
20 members of the WFN working group who participated in its
21 design are here today, including Dr. Robert Miller. Both

we and our collaborators believe this protocol will provide valuable new information regarding the optimal management of patients with ALS.

Now, granted that questions remain. Let's consider risk-benefit in the context of what we already know.

Treatment with Myotrophin is not associated with significant risk. Patient discontinuations were infrequent. Deaths related to ALS and its complications and symptoms of hypoglycemia were rare. Thus, analysis of all adverse events, with particular attention to those we might reasonably expect given what we know about the biology of this molecule, indicate the treatment is not associated with clinically significant risk.

Now, this view is shared by the FDA which states in its briefing document that the risks associated with daily injections of Myotrophin would be entirely acceptable, provided of course that Myotrophin has a beneficial effect on the signs, symptoms, course, or outcome of ALS.

Now, with that, let's consider benefit. We've

heard a lot of complex discussion today regarding the efficacy analyses, including after-the-fact analyses focusing on subgroups. At the end of the day, the simplest and most straightforward approach, the one least subject to bias, is the protocol-specified analysis. Let me just now remind you of what those analyses showed.

Conclusions regarding efficacy are based on the North American trial. Benefit was registered by the Appel scale which is a measurement by the clinician of the morbidity of ALS. Benefit was corroborated by the SIP which registered morbidity as viewed by the patient. Myotrophin injection was well tolerated and extended follow-up of patients in the North American trial suggests a survival benefit.

Now, the findings of the North American study are summarized here. Each of the physician-based measurements, the Appel slope, the change from baseline, and the Appel score, the time to protocol-specified termination criteria registered benefit. The SIP score which measures the effect from the standpoint of the patient also registered benefit, and extended follow-up was

suggestive of a survival benefit.

Now, what are we to make of these findings? In its briefing memorandum and again in our discussion today, the FDA has raised the critical issue. There's always a possibility that the observed outcome of a study is not due to the treatments assigned but to some confounding factor or factors either known or unknown.

So, is it possible that the positive findings of the North American study resulted from some problem in patient selection or randomization? This is a critical question for the panel. It is certainly one the sponsors asked themselves before submitting the NDA.

Please consider the following points.

A beneficial effect was registered in two different measures which assessed morbidity from two different standpoints: the standpoint of the patient, the standpoint of the clinician.

Statistical significance was achieved for all efficacy variables for both study measures.

The p value is 0.01 for the primary efficacy variable comparing high dose and placebo. Now, the Appel

slope is not only the primary efficacy variable, it's also the one least influenced by study dropouts.

A dose-related pattern of response was seen for all efficacy variables for both study measures, and this dose-response relationship was corroborated by a blood level-response relationship.

Now, we would submit that chance seems unlikely to account for these findings. Indeed, we find it hard to come to the opposite conclusion, namely that all these findings can be readily explained by chance alone. To the extent that poorly understood variables may have contributed to outcome, they appear more applicable to the European than the North American study.

We know, for example, that site-to-site variation in the Appel slopes was more than twice as great in the European study as in the North American study. Site-to-site variation by itself can be controlled for, but this suggests the presence of other factors, poorly understood and therefore difficult to control for, related to the design, execution of the study, or the biology of the disease which accounts for the difference in findings.

1 Now, with that, let's consider the European
2 trial. The European study did not achieve statistical
3 significance. However, as shown in this side-by-side
4 display, the results were directionally consistent with
5 respect to all but one efficacy variable. A positive
6 treatment effect was seen in 5 of the 8 European sites and
7 12 of the 16 trial sites overall.
8 We would submit that the findings of the
9 European trial did not negate those of the North American
10 trial. We would further offer that the findings of these
11 two trials viewed together offer persuasive evidence of
12 efficacy.
13 Now, this discussion of benefit has focused to
14 now on statistical significance. In closing, let's
15 consider the clinical significance.
16 The FDA briefing document raises this important
17 issue in its statement that the North American study
18 provides evidence suggesting a modest symptomatic effect.
19 So, what does a 26 percent decrease in the Appel slope mean
20 for the patient with ALS?
21 Well, for patients with ALS, the relationship

between the Appel slope and time is like the relationship between speed and distance. One drives 26 percent slower, takes 35 percent longer to travel any given distance.

This display depicts the impact of higher dose treatment and the time to clinical milestones in the North American study. The North American study, recall, included patients with Appel scores ranging from 40 to 115, and this corresponds to a period of relative self-sufficiency and/or mobility.

Now, because high dose treatment produced a 26 percent decrease in the Appel slope and because Appel slopes were linear, Myotrophin-treated patients experienced an average increase of 35 percent in the time to milestones which were embedded in the Appel score.

Now, what are these Appel and clinical milestones which patients traversed during the course of the study? They include the inability to speak clearly, the inability to eat solid food, the inability to dress oneself, the inability to climb stairs, or the inability to walk unassisted. Thus, the period of relative self-sufficiency and mobility which precedes terminal disease

was increased by 35 percent.

The clinical significance of these findings were corroborated by the SIP. Therefore, the effect of treatment in the North American study was clinically significant viewed both by the clinician and as perceived by the patients themselves.

Now, in its briefing document, the FDA has offered the following challenge to the panel. Whatever its views of the evidence were in June of 1996, the committee is urged to set them aside and examine all the evidence now available afresh. The sponsors appreciate that statement, and based on the evidence, we would submit that Myotrophin treatment offers clinically meaningful benefit with minimal risk to patients with ALS, a life-threatening and severely debilitating disease. This is why we are here today and this is the issue we ask the panel to consider in making its judgment.

Now, in closing, the sponsors wish to thank both the members of the panel and the FDA for its attention. We also wish to thank the investigators and the patients whose participation in these clinical trials made

today's presentation possible.

DR. GILMAN: Thank you.

Can we have a very brief comment then from Dr. Miller?

DR. MILLER: Thank you, Dr. Gilman. I do promise to make it short and sweet.

I was asked to provide a clinician's perspective to all of the data that you've heard here before, and I would like to say that the comments that I would like to make are my own, not that of Cephalon. I was not an investigator in this study, but I am the director of a large NDA ALS center in San Francisco where we see somewhere between 250 and 300 patients with ALS per year, and I've been involved in clinical trials for about a decade and in the care and management of patients with ALS for that time. As such, I have several observations that I would like to make.

The first is that this is a safe drug, and we've heard no dispute about that. I want to make that point loud and clear.

And the second point is that as a clinician and

as a clinician investigator, I find the data in study 1201 to be extremely convincing.

DR. GILMAN: I think you mean 1200.

(Laughter.)

DR. MILLER: Sorry. 1200. Thank you. Did I say 1201?

DR. GILMAN: You said 1201.

DR. MILLER: I made up my own trial.

(Laughter.)

DR. GILMAN: I thought you were hedging your bets.

(Laughter.)

DR. MILLER: I really wanted to talk about my own investigations.

(Laughter.)

DR. MILLER: Study 1200 has an internal consistency that points up not only the high degree of significance of the high dose result on that primary outcome measure, but also the statistical significance in virtually every secondary measure.

I've been involved with a large number of

trials in ALS and there have been no clinical trials that have come close to this degree of strength and robustness of evidence and this degree of internal consistency. So, I find this clinical study extremely convincing.

This data has matured between last June when we were here and heard this and the present time. I've had a chance to see all of this data myself and gone through it in detail, and I am convinced about it.

With respect to 1202, I am satisfied for some of the explanations that I've heard about the reasons that this was not a positive study.

Now, having said that about what I consider to be convincing evidence, let me talk about whether this is functionally meaningful and clinically significant data because that question has arisen now several times today.

We've heard that for the primary outcome measure, we've got a 26 percent slowing of the rate of the disease. Putting the brakes on the relentless progression of ALS of the order of magnitude of 26 percent in a 9-month trial, that means 3 extra months. That's what we've just heard. 26 percent slowing means a 3-month slowing of the

loss of function.

Now, we don't have a handle on ALS that's all that precise, but when our measures, the AALS, and patient perceptions, the SIP, the quality of life, independently administered give comparable results about the delay in the loss of function and the delay in the erosion of quality of life, I have to take notice.

26 percent is very close to the beneficial effect of plasma exchange or intravenous immunoglobulin in the slope of recovery for a patient with Guillain-Barre syndrome. It's about 25 percent there. That same figure has been borne out in multiple trials and it has been accepted by all countries as standard treatment now. And some of the treatments for multiple sclerosis have an order of magnitude that's similar to 25-30 percent. TPA, right in the same ball park.

For a disease like ALS, which from my perspective is one of the most dread diseases that we have to deal with, slowing the loss of function and slowing the loss of quality of life by that order of magnitude is extremely important and highly meaningful from a clinical

perspective.

Where should we go from here? We should move toward clinical combination studies. That's what has made the difference in cancer and that's what has made the difference in AIDS. It was not the single agent. It was the combination of agents that has begun to make a difference in these other diseases and I believe it will make a difference here.

We have the protocol for the combination trial nearly finalized and ready to go. I urge you, ladies and gentlemen of the panel, to allow us to get on with these important studies and to approve Myotrophin.

Thank you.

DR. GILMAN: Dr. Miller, before you leave, can I just ask a question? You said that you are satisfied for the explanation given for the lack of positive effects in study 1202. Can you explain?

DR. MILLER: Dr. Gilman, I don't want to get into a lot of the statistical issues there, but I do believe that the imbalance in terms of the risk distribution and also the 2 to 1 randomization and the

generally smaller numbers are some of the factors, the difference in care patterns in the country too. For me those are some of the explanations.

DR. GILMAN: Dr. Drachman?

DR. DRACHMAN: Would you explain why approval of Myotrophin would alter whether or not a trial of Rilutek with Myotrophin would be carried out?

DR. MILLER: Well, I don't have a definitive answer in that regard because we do not yet have the complete go-ahead from either company. When both drugs are on the same footing and we're in the post-approval situation, I think we will stand a better chance of getting this off the ground. In the pre-approval situation, that has been difficult.

DR. DRACHMAN: But this is not a regulatory thing. This is a company issue. Is that right?

DR. WILLIAMS: Yes. It is an important question and one we spent a lot of time thinking about and discussing. The question of combination therapy is a different question than the question of the study of Myotrophin alone that we've talked about today.

It's also a challenging issue for the companies in a disease that is a relatively -- basically it's an orphan disease in a relatively small population compared to other diseases -- to consider another phase III trial. This is a challenging situation for us to be able to do that.

Secondly, in an environment in which there is an approved drug, having an arm that's a placebo-controlled arm adds a degree of complexity to the trial that would be possible technically, but it would make it more complex and hence in our opinion larger.

Finally, given the importance of performing a trial that has statistical significance and the importance of measuring the endpoints in a complex disease in which the measurements are not like measuring blood pressure or MRI or some highly quantitative, single objective test, we feel that a small trial in a short time is not in the best interest of studying this disease, that another phase III trial, for example, would be a significant period of time and a large population.

So, for these reasons, in our view a phase IV

trial in which we actually look at combinations, in which we have significant size, and we address the issues of the best mode of treating the disease is the best path forward.

DR. GILMAN: Any other questions from that panel for Dr. Miller? Dr. Temple?

DR. TEMPLE: No. It was for the previous speaker. There was one part I didn't understand. What's the difference between the presence or absence of a placebo group? I don't think anybody thought in a combination study comparing the combination with each of the two components, they needed a placebo group because superiority of the combination to each of its components would speak for itself.

DR. WILLIAMS: Yes.

DR. TEMPLE: So, neither phase III -- I mean, I understand perfectly well why you'd rather it be a phase IV study. What's placebo got to do with it?

DR. WILLIAMS: Right, I agree with you.

In some discussions with the FDA previously, there has been an issue of can we do a smaller phase III trial or how long does it take. I think all of us are

concerned about how large the trial would be and how long it would take, and the issue of another therapy out there adds a degree of complexity. That means the trial is larger and longer, et cetera. That's simply the issue.

We've heard today about a trial that's of the size you've heard about without that confounding complexity, and so in our opinion to account for that complexity, we'd have to do even a more extensive trial.

So, it's not a yes or no answer. It's an all or none. It's not saying that one couldn't do such a trial. It simply adds to the complexity. So, we don't want to oversimplify the situation to say, oh, we can do another small phase III trial and answer some of the issues that are here. That's the point.

DR. GILMAN: Dr. Zivin has a question.

DR. ZIVIN: Last June we approved this drug for a treatment IND. I would like to know what has been done in terms of additional research based on that treatment IND.

DR. GRANEY: Dr. Zivin, I think I can answer that. The treatment IND does not really lend itself to

1 collecting information because the patients are brought
2 into the trial through a lottery, and basically any
3 practicing neurologist can enter his patients. The
4 patients are not in a setting or don't have the homogeneity
5 that we would need to gather meaningful clinical
6 information.
7 To date in the lottery, we have 450 patients
8 who've been selected. Drug has been shipped to 205 of
9 them. It has been a relatively brief period of time that
10 it has been in force, so we don't have a lot of
11 information, but there don't seem to be any safety
12 problems.
13 But we did talk with the agency after our
14 meeting last year about the potential for gathering
15 information from the treatment IND. Our strong and we
16 believe sincere feeling was that, given especially the
17 difficulties that were so clear in 1200 and 1202 and the
18 need not to restrict it to specific centers, that we could
19 not collect information that would really be meaningful
20 from the treatment IND in a research mode.
21 DR. GILMAN: Dr. Graney, please stay at the

microphone. There's an additional question for you from Dr. Adams.

DR. ADAMS: In Dr. Feeney's document, page 1 of tab D, the statement saying a third trial of Myotrophin in ALS is in progress in Japan. That trial is a randomized, double-blind, placebo-controlled parallel trial comparing .1 milligram per kilo per day to placebo. The expected completion date is in 1997. Do you have a report on the progress of this trial and when it will be available? And then maybe the after-question is, why we should act now with this trial not being completed?

DR. GRANEY: Yes, I can. As Dr. Feeney noted the trial is on the surface very similar in design to protocol 1200. It does have some characteristics to it that are unique to Japan. The study is being conducted in 30 centers for a total of about 180 patients which gives a very small number of patients per center. The observation from past experience is that that does make efficacy interpretation very difficult.

We're particularly concerned because of the Appel. We know from our own experience that extensive

1 training and in-service is needed. That's one aspect of it
2 that we don't really think that the Japanese trial has a
3 high likelihood with coming back with the useful efficacy
4 information.
5 In terms of the progress of the trial, it
6 actually belongs to not even an affiliate but a licensee of
7 our drug who are conducting the study on their own in Kyowa
8 Hakko. In fact, it does not appear now that enrollment
9 will complete until 1998 and then there will be some period
10 of six or so months beyond that before we would have an
11 analysis.
12 But I think from a clinical research point of
13 view, the most cogent observation is that it has been at
14 least my experience that this type of complex trial in
15 Japan does have difficulty demonstrating efficacy and that
16 this area has some specific difficulties to it that we
17 think the Japanese study does not meet.
18 DR. GILMAN: I'm puzzled why you're engaging in
19 the trial if you have these concerns about how it will be
20 done.
21 DR. GRANEY: Well, it is really a commercial

matter. The Japanese company is a licensee, has full rights to carry out a research program in Japan. We advised them and, indeed, if you look at the trial on the surface, they modeled the trial after our protocol 1200, but we do not give them directions. We could not, for instance, insist upon the same degree of initial training and in-service that goes on with the Appel. All we can do is function in an advisory method. As the FDA folks probably know, the enrollment in it has picked up, slowed down, picked up, and slowed down.

Just looking at it as a viable clinical research operation, we believe that it will provide useful safety information. In fact, we do get and have reported the safety information from the trial. The blinded death rate, the type and number of adverse experiences is certainly similar to what we've seen in the U.S.

But we do think it's unlikely that useful information will come from that when we hold it up against how complex it is to evaluate ALS.

DR. WILLIAMS: Your question is a good one. Just to be really clear about it, it's not our trial and

has not been part of our regulatory plan to seek approval. So, I agree with you, we wouldn't do the trial --

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

DR. DRACHMAN: Has there been an interim analysis done of it?

DR. GRANEY: There has not been. There is an ongoing safety review by a physician or committee of physicians in Japan -- and I don't know exactly what the number is -- who look at it for safety factors just the way that there might be a safety committee looking after a program in the United States. But there has been no interim analysis, and with our brief contact, the Japanese company has indicated that they are not interested in doing one. We cannot compel them or require them to do that.

DR. GILMAN: Dr. Leber?

DR. LEBER: I was just curious because the terminology is a little vague. When you say it would not provide useful information, would you tell me what you mean?

DR. GRANEY: Well, I think that ALS is one of

-- I should say the complex evaluation of ALS is one of the environments where if the trial is not conducted in a rigorous fashion, if the instruments that are being used are not rigorously QAed, what is more likely to come back is a lot of noise, which would obscure the efficacy. I think it's almost comparable to what you see in congestive heart failure trials where when the population was learning to do them, there were a lot of trials that weren't positive. I think part of it is actually using the scales, using them efficiently, handling patients correctly during the trial.

DR. LEBER: So, you're really saying you expect this trial to fail.

DR. GRANEY: Yes. In terms of coming back with a positive, we think it would be a random result that would come back.

DR. WILLIAMS: Again, there are a couple of specific answers to your question, Dr. Leber. The Japanese trial has a small number of subjects per site, and that's an issue to us. And secondly, parameters like some of the

parameters we've used have cultural attributes in the administration of some of these instruments, and we're concerned about that.

DR. LEBER: So, you expect it to fail.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: I have a similar question. The trials are described as very complex, but the only complexity is whether you can expect people to get roughly the same Appel score from the same patient. At least one of the things you submitted suggested that perhaps this is in trained people. The test/retest is very good actually within a point or two. So, I guess you're saying that you need some special training to achieve that.

On the other hand, there are some other observations that suggest it may not be that impossible. The distribution of Appel scores in the U.S. and European studies, despite very different environments, was pretty right on, suggesting that somehow if people are entered into a screening period at one point and then followed for three weeks, bingo, they end up with the same distribution.

So, I don't know. The constant reference to it

as complex seems to me it means that the changes you expect are small relative to the value, and that's always the problem when the changes are relatively small. It's hard to show things.

But this is an area where a relatively simple endpoint trial would seem very suitable and that wouldn't be complex at all. The critical endpoint here is probably easy to define. We can define it as wheelchair-bound or death or any of those things. It's an area that's quite suitable to very simple design. You know, you have to do it.

DR. GILMAN: Ms. Phillips?

MS. PHILLIPS: I'd like to know why so few patients received the drug through the treatment IND.

DR. GRANEY: Well, as I mentioned earlier, the number of patients who have now been selected in the lottery is 450. That increased from 200.

To be very frank, there is an issue of the cost involved. The support of the lottery -- we actually have a very large operation going on with a contract research organization who provides a sort of disinterested

1 management of this for us. Although it seems like a small
2 program, it really is quite expensive, especially on a per-
3 patient basis. We spent a considerable amount of time
4 making the decision to pick the first number and then add.
5 But in terms of the delay, why all 450 patients
6 have not had drug shipped yet, at least a fraction of that
7 delay is due to operational elements. It did take some
8 time to get set up for the lottery, and then because it is
9 an investigational program, most university centers -- and
10 indeed most patients are at the university centers -- do
11 treat this as a study and it's required to go through the
12 study and institutional review boards. So, that threw a
13 block of several months into the operational elements.
14 So, we do feel that we have made the effort to
15 increase the number now. We've taken a very hard look at
16 components in the system that can let us get the drug to
17 patients faster once they're selected in the lottery, and
18 as I mentioned, we have shipped drug to 205 patients. We
19 would like the number to be more certainly.
20 I see Dr. Baldino at the other microphone.
21 DR. BALDINO: Mr. Chairman, just one note of

clarification on this. If you remember when we came before you in June, we stated that we only had a small amount of inventory and at that time, even though the demand was great for the treatment IND, we only had material to supply 200 patients, and we did that.

Subsequent to this, the manufacturing facility at Chiron has been inspected for the treatment IND and approved as such, and as soon as that approval was obtained, we've expanded the selection to an additional 250 patients I believe since that time. So, it was really a supply issue originally despite the demand.

DR. GILMAN: Dr. Zivin?

DR. ZIVIN: I guess I'm increasingly puzzled. We spent a good deal of effort, as you did you, in evaluating this drug program for a treatment IND last summer, and I'm puzzled as to why it is that we went through all that effort if you didn't plan to use the data or increase the data or to do anything more for the patients.

DR. WILLIAMS: If I can understand your question, you're wondering why we're not using the

treatment IND to provide data to support approval. Is that your question?

DR. ZIVIN: Yes. The point is we went through this exercise last June.

DR. WILLIAMS: Right.

DR. ZIVIN: I don't understand, if you then went on with essentially the same information that you had at that time and have now come to us for an NDA at this point, why it is you didn't do that at that time and dispense with this extra step.

DR. WILLIAMS: Well, of course, we're following our discussions with the FDA and the FDA's recommendations on the purposes of these two meetings which were different.

But I'd like to just make one point. I think Dr. Leber wants to say something, but that point is that to use enrollment in a treatment IND as a mechanism for gathering information in this setting is difficult because there's a lottery for entry into the treatment IND. So, there's not the entry criteria that we have for the study. For this number of patients, we didn't feel that it provides us an opportunity to generate additional data.

We'd love to be able to do those two things at the same time, but it's a lottery process to get into the treatment IND.

DR. GILMAN: We understand that a treatment IND is not a means of conducting a double-blind, placebo-controlled trial. It's for safety and we understand that.

Dr. Leber?

DR. LEBER: Yes. I think Dr. Temple may have another view, but it's certainly true that if you look at the treatment IND, it's a protocol that's intended to allow patients access early on for a transient period to a drug that has promise, a drug which is yet to be fully evaluated for purposes of an NDA. So, to turn around at this point and argue that they haven't made more of that data, I think is a bit unfair. I don't usually like to rise to the defense of people who I think are able to defend themselves, but in this particular case, I think the law is pretty clear that that's not a requirement.

That doesn't mean that someone couldn't have done a large, simple study with randomization which I would have loved to have seen because it would have accomplished

the same, the lottery, except you would have been lotterized to an opportunity to get the drug and lotterized to an opportunity not to get it, and it would have provided some of the structure of the design. But in fairness, we asked them to do the treatment IND. They would have one a lot earlier hadn't it been for the play of 1202.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: Well, I agree with all that. There's certainly no requirement that a treatment IND be used to gain information. However, there's no requirement that it not be, although it always works out that way.

There have been a number of attempts to think about how large, simple trial methodology could be incorporated into an treatment IND, and perhaps we should have pressed this thought more than we did. But the fact that the drug has to be given out by a lottery is a perfect situation in which you could actually learn something because in fact not everybody who wants the drug can get it because it's not there. So, it would have been possible. It takes imagination. Again, maybe we didn't press it enough.

It would be possible to identify people who get the drug right now and others who get it only when there's more so that you would have a potential simple trial with a very hard endpoint and one could do those things. It's not often thought of.

I'm not being critical at all of their not having done that. Very few treatment INDs have ever done that, but it's the sort of thing that can't be contemplated. One wouldn't want to think that either.

DR. BALDINO: I'd like to comment on Dr. Temple's remarks.

First of all, a treatment IND in this disease was administered through a lottery and it's administered randomly through a lottery. I think what we've learned today, by looking at the studies that we've performed -- and as the panel has readily said, you've had two chances now to review both of these studies carefully. These are complex factors that influence this disease.

One of the questions the panel raised a moment ago is why haven't we initiated another bigger study. Well, to be perfectly honest with you, we've just come to

grips working with a lot of neurologists who specialize in ALS with the differences between these studies and some of those prognostic factors that have such a profound influence.

We pointed to two today, FVC and age, that change the survival outcome dramatically. A study that does not take those into account I think would be an investment misspent. It has to be carefully planned and carefully accounted for.

The proposed study we have, the combination study, is a result of one year's effort with the experts in the field, a few discussions with the agency that have been helpful. Only now do we feel that we have enough control of this -- enough understanding of this disease and how these patients progress for us to do a study to have some meaning.

I can't imagine, with all deference to Dr. Temple's comments, how we can stratify for these prognostic factors and all the other standards of care that need to be controlled in a treatment IND environment. We thought about it. It's very difficult.

1 And last of all, if I could just finish my last
2 thought, many people -- and some of you may have
3 participated in these studies over the years -- have tried
4 to do a small, focused clinical trial in this disease.
5 It's something we would have dearly loved to do. We can't
6 figure out how to do it. Everyone who has tried to do a
7 short study in this disease has failed. We saw a few this
8 year. We saw even a few bigger studies this year that have
9 failed.
10 Our view was, if you're going to look at this
11 disease, you have to do it comprehensively and completely
12 taking all these factors into account and that's what we
13 have proposed.
14 DR. GILMAN: Dr. Temple?
15 DR. TEMPLE: Well, I just can't resist the
16 opportunity to advertise more for low tech trials. I'm
17 really not being too critical. These have not reached the
18 ears of neurologists for the most part, but they have
19 reached the ears of the cardiovascular community. You do
20 not have to stratify or account for every variable in a
21 trial. You have to have enough patients so that they come

out even.

If you're talking about things like age, a trial of reasonable sample size will give you an age distribution. If you look at the large cardiovascular trials that are done, age is similar in the two groups to two decimal places. That's a matter of numbers. You will get a comparably aged population because age is a common factor. If there's some very obscure, rare factor, that might not distribute properly, but age and pulmonary function and those things will be distributed in a large trial.

If you believe, as you obviously do since you made the case, that functional benefit will eventually translate to survival benefit, it's a very excellent setting actually to use a trial with simpler data collection and look at hard endpoints that everybody can believe in and detect. It's a very suitable environment for that and a treatment IND is not an impossible setting to do it in. You don't have to be skilled to know whether people are alive or dead. That's not center-dependent. It's not analyst-dependent. In fact, even if you get the

baseline scores not quite right, you don't even have to collect the baseline scores.

These methodologies have been well worked out in the cardiovascular arena. They are very good at detecting 25 percent differences. That's what all of the thrombolytic trials have done. And they don't sweat the baseline very much because the baseline comes out even when you have 30,000 patients, and they come out even when you have 500 too.

(Laughter.)

DR. TEMPLE: They come out very close when you have 400 or 500. So, it's really something that should not be abandoned before it's thought about.

DR. GILMAN: I believe we should move on now. We are ready for the FDA's presentation. It is almost 3 o'clock, and I would urge the FDA to be as succinct as possible. We have thoroughly read these documents. Dr. Feeney?

DR. FEENEY: The ordinary standard for approving a new drug in this country is the demonstration of effectiveness based on at least two controlled trials.

1 In the case of Myotrophin, there are two controlled trials,
2 but one of them is negative. By the ordinary standard
3 then, Myotrophin should not be approved.
4 It has been contended that in severe life-
5 threatening diseases like ALS strong evidence of an
6 important effect in a single study can warrant the approval
7 of a new drug. For example, an effect on mortality or
8 irreversible morbidity might warrant approval with only one
9 study. But the results of study 1200 are not strong,
10 either not quite reaching statistical significance on the
11 protocol-specified analysis here or just barely reaching
12 statistical significance on the FDA's analysis.
13 Let's look at study 1202 first. The protocol-
14 specified analysis was negative. Covariate adjustments did
15 not help that at all, and all of the secondary analyses
16 were negative.
17 The change in slope analysis is not in the
18 protocol. We talked about it a little bit earlier today.
19 We believe that it accounts for most of the information on
20 all of the patients accrued during the conduct of the
21 study, study 1202 here again. Basically each patient who

has at least three post-baseline Appel scores has a slope fitted and then that is compared to their pre-randomization slope and then the distributions are compared here. These are cumulative distributions and a shift to the left would be a favorable shift. But really the point here is that these curves are totally superimposable. There's no trend here in any direction at all.

These are Kaplan-Meier curves for the two treatment groups in study 1202. This is a time to combined endpoint that includes death, trach, Appel, or FVC. I think what you can see here is that again the curves are superimposable with no obvious trends, no directional consistency going on here.

These are the Kaplan-Meier curves for extended survival. As you already heard, within the first 9 months of double-blind treatment, there was the excess of deaths on Myotrophin. The company has put forward the imbalances on FVC and age, and we acknowledge those, the way they did that. We tried to go back and look at the primary outcome variable here, the Appel slopes, the Appel scores, adjusting on those same covariates, and still we're never

able to produce a positive analysis on the Appel scores using those same covariates of age and FVC.

So, with study 1202 already casting doubts on any result achieved in study 1200, let's look at the strength of study 1200.

The protocol-specified analysis achieved a p value of .055. Our analysis got the p value of .05. Therefore, we would ordinarily accept this as one of two studies supporting an NDA. The question is, is this study strong enough to stand on its own in the face of the negative results of study 1202?

This slides shows the Kaplan-Meier curves for the two treatment groups, high dose Myotrophin and placebo, in study 1200 for the open extended survival. One of the ways for study 1200 to stand alone would be to provide an unquestionable effect on survival.

The first point here, the open extension may not be the ideal way to follow people over time because after 9 months, everybody is on the same treatment. We acknowledge that.

The second point, the high dose Myotrophin and

placebo curves are not statistically significantly different with a p value of 0.21.

The third point, there's the conflicting evidence coming out of study 1202.

This is the sponsor's own slide posing the question, could the results of study 1202 actually be chance occurrences? We think that the answer is yes. You've already heard from Dr. Leber that bias and chance can account for between-group differences just as much as a treatment effect.

Now, if you look at the first two points here, they basically reiterate the same point, the multiplicity of endpoints. There is a multiplicity of endpoints in study 1200. The problem is that this multiplicity doesn't speak at all to what causes the difference between the two groups. It doesn't speak to whether it's the treatment effect, bias, or chance at all.

The third point here, .01. We think this is an improper p value coming from an improper analysis. Maybe our statistician, Dr. Hoberman, can talk about that a little later.

But the important thing isn't the size of the p value. What's important is the reproducibility of results independently in two studies, and we all know that that kind of consistency just doesn't exist in this development project here.

Then the other point is the dose-related pattern of responses for all efficacy variables. What this is referring to is an ordering of three treatment groups. You've already heard that we accept that there's a difference between the high dose group and placebo. If you think about that, the third group has to fall either between the two groups or to the other side of the placebo group. So, there's a 50 percent chance that it will fall to either side and you'll end up with that ordering.

The fifth point here is the PK/PD analyses, and I'm going to go to some overheads here. We have basically two points that I want to develop. The first you have actually already heard. In trying to model any of the PK data/PD data in study 1200, we believe that you really can't look across all three treatment groups without basically reproducing the results of the trial. And you've

heard reasons already and there can be more discussion about that later.

The thing I want to develop now is just kind of a relationship that we've identified really only recently, and we think it may really create some problems in trying to sort through the PK/PD modeling in study 1200. So, let me just kind of run through that for a few seconds here.

We talked about this before. This is showing concentration of IGF-1, and this is showing the visits by month. 1 here is baseline. I know most of you can't see that. The first thing is baseline, and then this would be visit 1, visit 2, visit 3, and so on.

Now, you heard earlier today that this time to steady state concentration in study 1200 in the high dose Myotrophin patients is driven by the dropouts that occur early on. I want to tell you that that's just not true because what you're looking at here is only patients who completed the entire 9 months. So, in completers it takes 3 to 4 months to achieve steady state concentrations.

Now, the next thing I want to do is just ask you a question. To test your understanding of these

trials, ask yourself what patients had the highest Appel slopes in study 1200. I'll give you the answer unless somebody else wants to volunteer it. It's the cohorts of patients who endpointed early. We could actually show you that, but take my word for it. The patients who endpoint early have the highest slopes. It's just the way it is.

Now, if you look at this, you see another relationship between somebody who could potentially endpoint early, and that is if somebody endpoints at visit 2 or visit 3, they have not been in the trial long enough to achieve steady state concentration. They will endpoint with a low concentration.

So, you have two relationships: early endpoint/low concentration, and then the second correlation is early endpoint/steep slope. Put it all together, you get low concentration/steep slope. It's an artificial relationship that comes out of the study design.

If you go to the next overhead now, what you're looking at here is a very simple-minded scatter plot of on-study slope versus average concentration achieved in the trial 1200, and all of these points represent all of the

patients in the high dose Myotrophin group. Each point is a patient.

Now, if you look carefully, it looks like there is a relationship between concentration and on-study slope here. You could probably draw lines cutting across, something like that, or maybe even a little steeper coming down like that.

Now, I'd like you to imagine if you could take this cohort of high dose patients and somehow look up here and tell which patients endpointed before reaching the visit 8 or visit 9, if you could do that, you would end up with the next overhead.

The next overhead represents the same patients, but the patients who were in for 8 or 9 visits are represented by squares, and any patients who did not stay in long enough to get to visit 8 are represented by little crosses. What you see is that that relationship we were looking at, that imaginary line coming across here, is driven by all of the early endpointers who had low concentration and high slope. You see there's a little cluster of them here, and then there's all of them up here.

They're the ones that are driving them. If you take them out and just looked at the distribution of the boxes, you would just see kind of a circular shotgun.

So, I really think that trying to model this data is going to be misleading. We didn't really realize this. Everybody at the FDA was trying to model this data for the last month or so. Maybe there is a way to get around this, but I don't think there is and if anybody knows of a way, I'd be surprised.

DR. DRACHMAN: Why would a drug with a 20-hour half-life take 3 or 4 months to reach a maximum level?

DR. FEENEY: You could probably imagine lots of mechanisms, given the biology of IGF-1. One that I've heard proposed is the induction of the binding proteins, some change in clearance over time, different feedback circuits. I don't know. I don't know.

DR. GILMAN: Yes, a response from the sponsor?

DR. WILLIAMS: Also, we don't have a hard and fast answer to that, but the biology of IGF-1, we agree with you, could explain this. For example, IGF-1 is known to interact with a number of binding proteins, and we don't

know what happens in this case, whether those get induced. It's not simply the free concentration of IGF-1 that's relevant here. So, I think we should be careful about attaching too much significance on these kinds of levels.

Again, I think the clinical argument is the one we're here to represent today, and the binding proteins and the other complexities make it difficult to understand these kinetics. I agree with that.

DR. DRACHMAN: So, should we ignore them?

DR. GILMAN: That undercuts your previous model, though.

DR. WILLIAMS: I'm the last guy who wants to get into a discussion about the model.

(Laughter.)

DR. WILLIAMS: But the model, as I understand it, accounts for the data without asking the question how you got there. It accounts for the fact that the changes are the ones that you see. It's an empirical model. If you'd like, I'd much rather have someone else discuss the model.

(Laughter.)

DR. GILMAN: Dr. Leber?

DR. LEBER: Well, I thought we tried to address the possibility before, Dr. Drachman, about why there could be discrepancy. Remember, I believe -- and correct me if I'm wrong -- that the half-life of 20 hours came from a single dose study done in normal volunteers. This is not the same setting and what you observe once after a single dose may not reflect all the events that could happen thereafter. It's one of the possible risks of extrapolation. We don't even know what we mean by half-life here.

DR. GREBOW: A couple things maybe to address that. One is I'm puzzled by your figure because we haven't seen these figures before, the first one where you gave the plasma concentrations on the individuals, your first slide, Dr. Feeney, on plasma concentrations.

DR. FEENEY: Yes. We'll put that back up. The concentrations over time?

DR. GREBOW: Yes.

This looks very similar to the slide that we have with our mean values at each time point.

DR. FEENEY: These are mean values for the patients who completed the study.

DR. GREBOW: All of them. So you went back into our database and pulled out all the patients --

DR. FEENEY: Yes. We wanted to see what happened to mean concentrations over time for a cohort of patients that completed. We didn't want the means to be driven by any funny relationship between dropouts or early endpoints, and this is what we got.

DR. GREBOW: We haven't really had a chance to look at that data per se, but with respect to the half-lives, we've done a single-dose study in ALS patients. The half-lives of those patients are comparable to what we saw in normal volunteers, again a single-dose study.

Based on the single-dose modeling that we've done in normal volunteers and projected half-life and clearance, the trough levels that we see are very close to what we would expect to see in normal volunteers.

We have to really look at this data further to have a better explanation of the data. What we've seen in some of our plots is looking at the individuals, that

they're fairly constant once we go through one month.

DR. FEENEY: Well, actually I have to say that I went back and looked at one of the original PK reports that came in for study 1200 submitted by Cephalon and it actually addresses this phenomenon of time to steady state.

DR. GREBOW: I'm sorry. What is that -- maybe we could clarify. This is one --

DR. TEMPLE: The y axis doesn't go to 0. You should notice that.

DR. GILMAN: Wait, please. One person at a time.

DR. GREBOW: This is total IGF-1 concentrations that you've plotted here?

DR. FEENEY: Yes.

DR. GREBOW: And the base levels are --

DR. FEENEY: Baseline level is at the 1.

DR. GREBOW: And this is all patients.

DR. FEENEY: It's the completers --

DR. GREBOW: Regardless of the dose.

DR. FEENEY: High dose group. It's completers, high dose group, study 1200.

DR. GILMAN: Eliminating the dropouts.

Dr. Leber, then Dr. Temple.

DR. LEBER: The reason this is done is because we couldn't figure out, whether it was in volunteers or in patients, why a drug which had 5 to 7 days to steady state would show what appeared to be accumulation. One explanation, a rational one that you offered this morning, was the possibility that the number of individuals whose means are being mapped changed systematically over time, with those who have very low concentrations dropping out because of one reason or another.

This seems to be the definitive rejection of that argument at least for those who completed the study, who got to 8 or 9 months, and who took Myotrophin throughout. This is their individual -- this is like an analysis of covariance which has people throughout. And this is the mapping of their concentrations.

Now, we're not offering an explanation of why it's true. What we're interested in is the fact that because it appears to be true empirically it undercuts any arguments about what you can really get out of

concentration vis-a-vis the apparent slope. We think it makes it more complicated.

John just invited you to consider the possibilities of coming up with a model that explains this. We don't know yet whether the models you've done do take this into account, but on the basis of the presentations made, I guess we're sort of at a point of agnosticism about it. We don't know how to deal with it.

DR. BRAEKMAN: A couple of points I wanted to make.

DR. GILMAN: Please, before you speak, Dr. Temple had a comment.

DR. TEMPLE: I only wanted to point out for people who can't see the numbers on the left that this is not as steep as it looks because the lowest concentration there is I think 200, if I'm seeing it correctly.

DR. HOBERMAN: That's right.

DR. TEMPLE: So, it's not a complete y axis, just so people know that it's not sort of almost 0.

DR. FEENEY: Yes. The axis goes from 200 up to 600.

DR. GILMAN: All right, Dr. Braekman?

DR. BRAEKMAN: One question. The 1 on your time scale, is that before dosing?

DR. FEENEY: That's baseline.

DR. BRAEKMAN: That's baseline.

DR. FEENEY: Yes.

DR. BRAEKMAN: So, if you look at this curve, it's only the first 3 months. If you take these first 3 months out of it, you're pretty much at a steady state, what you call steady state.

My second point I want to make, you can take any cohort of patients and try to explain why you see these patterns. Again, I don't want to make a big deal about the PK/PD modeling again, but all patients in part of it, and we look at very gross patterns. In the PK modeling we took into account the BP3, the binding protein 3, levels. If you look at the means over the 9 months, they are fairly constant. They are different more between patients than in time. If you do the PK/PD modeling, and over time changes something in BP3, it's part of the modeling. It's a global approach and that doesn't take this into account.

The main thing I want to say is that if you take a cohort with trough levels, you have to realize in this trial -- and we are very impressed by ourselves that we could come up with a correlation, could even come up with a pharmacokinetic explanation by only measuring trough levels. It's a very severe limitation of what you can do with only trough levels. There is a lot of variability on there, and if you take a cohort, you can actually see that random errors start to appear at certain times more than at other times, and that could be very well the explanation for this.

DR. GILMAN: Dr. Hoberman, then Dr. Leber.

DR. HOBERMAN: I'd just like to come back to Dr. Feeney's major point. Regardless of what mechanism produced this, what we're left with is the data. The data is what's produced. The data is what is modeled.

There's no wishing away the fact that trough levels in a very significant early terminating cohort were low and having high slopes. What that does is basically I think eliminate the possibility of getting meaningful models out of this data. You can make up any explanation

you want, but you can't put in some explanation that is going to turn that data into something that shows a concentration effect.

DR. BRAEKMAN: I have a question about the points on there. You don't show standard deviation. Did you actually test if these early points are statistically significantly different from the later points?

DR. FEENEY: Dave, do you know the answer?

DR. HOBERMAN: No. We only wanted to profile to see whether there was a monotonic increase with a relatively slow increase.

DR. FEENEY: Let me add one other bit of information that may be relevant to this. After seeing this pattern, I talked with our preclinical people, and it's my understanding that in animal models this phenomenon of taking 3 to 5 months to achieve steady state is seen also.

DR. GILMAN: Dr. Leber, then Dr. Dobbins.

DR. LEBER: Yes. I think I made the point earlier. I want to repeat it because I think rather than argue about what accounts for this, we can address it

directly. We need a rule for identifying when a patient reaches a plateau of plasma concentration based on trough, and then we can look at the distribution of time for all patients to that particular criterion. And that will give you a picture of what the median time to that point is, and then there's no longer a fight. If everybody really reaches it within a month or 2 months, which is what the single-dose kinetics suggest should have happened, then that's one thing. If it doesn't, we can't explain it but it's there.

DR. RUTTER: My name is Rutter. I'm from Chiron. I'll just make a couple of points.

Certainly I don't want to get into an argument on PK/PD either, but what I do want to do is to emphasize a few aspects about the biology of IGF-1 which is consistent with a couple of points.

Certainly we're not espousing the point of view that ALS is a deficiency disease for IGF-1 and therefore that there should be a direct correlation somehow of IGF-1 levels and ALS. ALS has a separate etiology and there are various good reasons to suspect that that etiology does not

involve IGF-1 as a fundamental, primary causal situation.

Second of all, with respect to the biology of action of IGF-1, I want to just amplify a little bit the point that I'm sure all of you know to some degree, and that is that there are seven binding proteins each of which binds IGF-1 and essentially keeps it from effectively binding the receptor and its action on cells. So, there are eight equilibria that are involved with free IGF-1 and each of its binding proteins and its receptor.

Patients can have different levels of receptor, as is indicated between normal and ALS patients, and they as individuals have different levels of the binding proteins.

Now, what has been measured here is the total IGF-1 concentration in the sera which is basically a function of the binding protein levels. If you add IGF-1 alone in such a way that it doesn't bind the binding proteins, it has a very short half-life of a few minutes just like insulin has a short half-life.

So, what is happening, when you begin to measure these rather longer-term effects, is they are

effects essentially on binding proteins which keeps the total level high, and obviously that affects the free IGF-1 level that can bind the receptor.

So, how does that translate into these models? For sure, there are patients that one would expect that wouldn't be driven solely by IGF-1 concentration. For sure that's the case. If you really want to do a study on available IGF-1, of course you have to take a single patient as its control and then follow that patient throughout.

So, I'd say on the one hand I'm fully agreeing I think with the position of the FDA in the sense that this is a complex situation and PK/PD analyses are somewhat complex.

However, let me just point out that in the aggregate you do get this relationship for whatever it's worth on a population base, that after treatment over a period of time, there is a correlation that can exist between the ALS score and the concentration which, after all, has this long component.

So, think of the disease as an independent

etiology upon which this hormone can act over a period of time. I think that's one way to look at it.

DR. GILMAN: Dr. Dobbins?

DR. DOBBINS: Yes. That's essentially my point regarding that. The analysis that I described earlier with the three post and the three pre-measurements that the patient had essentially would exclude patients who had been on the study less than 3 months.

I'm not sure that in the context of the progression of the disease in measuring something very delicate such as a blood level-response relationship in something that changes very gradually why we would expect to see that occur very quickly, certainly within the first month or two. I think that's a high expectation.

What we would look to see is in the patients who remained on the treatment over a longer period of time who have had a chance to achieve a blood level and then have had a chance for the drug to take effect in slowing the progression of disease over a long period of time, we'd have an opportunity to see it.

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

DR. DRACHMAN: This is a saturation issue. Does one see that those on the lower dose either reach this level more slowly or move at a different rate? In other words, do you have these data for the .05 folks?

DR. FEENEY: We don't have the data on completers. This morning you saw the means over time for everybody in study 1200. The sponsor has that.

DR. WILLIAMS: We have a slide.

DR. GILMAN: Perhaps you could pull the slide. Dr. Leber has a comment then.

DR. LEBER: I just wanted to step back a minute and say once again why we got involved in this. We have no expectation that a firm presenting an NDA for a drug will show that there is a relationship between the exposure and the response. They didn't do that. It would be nice if they can.

We entered into this not because we sought to model or understand the actual mechanisms by which serum concentrations are maintained, but because we hoped it was an avenue to address this uncertainty about causation. So, there's no fault if you don't find it.

1 The firm came forward with an analysis to
2 suggest that, yes, there is something in the concentration-
3 slope relationship which would compel you to believe that
4 the results of study 1200 are in fact attributable to the
5 action of Myotrophin. All we're doing at this point is
6 addressing our doubts about whether they found such a
7 relationship and saying that because of the pattern of
8 censoring and time, whether it can be predicted by a model,
9 really serves the purpose that we asked them to us.
10 So, I don't think there's much dispute about
11 this being complex. The question is what value does
12 concentration-slope relationship serve, and for the goal we
13 had, I guess we'd argue that it has not been demonstrated,
14 that is for showing that the effects in study 1200 are due
15 to Myotrophin.
16 DR. GILMAN: All right. Can we move along
17 then? Dr. Braekman, yes?
18 DR. BRAEKMAN: Just two simple points, very
19 short.
20 We didn't say anything about causation.
21 DR. GILMAN: You said something about

correlation.

DR. BRAEKMAN: Correlation.

DR. GILMAN: Not causation.

DR. BRAEKMAN: It's a different thing.

DR. GILMAN: We got that.

DR. BRAEKMAN: If you put the slide back on, you can very easily see what the error bars are on the first months, and what we are talking about is variability, and singling out points and trying to read something into is very difficult.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: That doesn't seem entirely fair. In fact, the curves are very similar. It's just that one is for everybody and one is for completers. By looking at completers, you remove the possibility that you've simply been censoring the people who were low and that's why you went up. That does not explain why you see the same curve in a completer group. You're not censoring anybody. So, who knows why it takes that long to get to steady state. Nobody can figure that out, but if the fact is it does, then that's got to be taken into account in the model

1 somehow or make you wonder if you know what's going on.
2 DR. GILMAN: Yes. That's a good point.
3 Let's move along. Dr. Feeney?
4 DR. FEENEY: That's pretty much the last point
5 I wanted to make.
6 Basically, in conclusion, we don't take the
7 position that Myotrophin doesn't work but we don't take the
8 position that it works either. We just think that there's
9 not enough evidence to decide one way or the other at this
10 point. For that reason, we think it would be hard to
11 approve this NDA.
12 DR. GILMAN: All right. Thank you, Dr. Feeney.
13 Are there questions for the FDA from the panel?
14 Dr. Temple?
15 DR. TEMPLE: I just need to make something
16 clear in case you don't already know it.
17 What you've heard is the views of the review
18 team. If we had reached a settle conclusion as an agency
19 or as an office, we wouldn't be bringing it to you. We're
20 bringing it to you because there are still things to think
21 about. You've heard the pros and cons and you've heard

1 presentations from different points of view about why one
2 might lean one way or the other. I'm sure you already knew
3 that, but I just want to be explicit about it.
4 DR. GILMAN: Next on the agenda is for
5 committee discussion. It has been a long day and I'm
6 pretty worried about the length of time this meeting is
7 going to go on. So, I'm going to take the executive
8 privilege of not having a break. Please leave as you need
9 to leave this afternoon, but let's push on.
10 We still have some 21 people who want to speak
11 to us, both patients and others, and I'm going to ask that
12 they be very brief.
13 Now, for the committee discussion, let me lead
14 off just with a few provocative comments. We've been asked
15 today to answer several questions, three in fact. The
16 first is, does NDA number 20-654 provide evidence for more
17 than one adequate and well-controlled clinical
18 investigation supporting the conclusion that Myotrophin is
19 an effective treatment for ALS?
20 I think I will simply take the privilege of
21 presenting my own point of view and then see if the

committee wants to respond to this and see where we are with this.

Thus far we have heard a good deal of information about one study, study 1200. It has shown significance. We are told that the significance is not strong and I think we need to discuss that point initially and then go on to study 1202. So, I wonder if anybody on the panel wants to discuss that first issue, getting to point 1.

DR. GENNINGS: I have a question. Do we know about the consistency of the results across the centers in the North American study?

DR. BALDINO: We have that slide to show you. We might as well put both studies, the one with Europe and the U.S. together.

DR. SCHARSCHMIDT: This is a slide which depicts the site-by-site results for the North American study, and we're looking at the total scores slope for each site. The red is the placebo and the yellow is I think the high dose Myotrophin.

DR. GENNINGS: So, there's one center that

looks a whole lot better than the rest.

DR. TEMPLE: One looks a lot worse.

DR. GILMAN: Dr. Temple, we can't hear you. Please.

DR. TEMPLE: I'm sorry. One looks worse. One goes the wrong way, but if you were going from left to right, center 1 shows a good size difference and center 3 -- or I guess that says 4. I can't read it from here. So, the first, third, and fourth are directionally consistent. One goes the wrong way and the others are sort of close.

I guess I wouldn't have said there was only one that looked good, unless you wanted to say that the fourth one over is a pretty big deal.

DR. GENNINGS: That's what I was talking about.

DR. TEMPLE: Yes, okay.

DR. GILMAN: Yes.

DR. SCHARSCHMIDT: There's one center which is out of line in terms of not showing a treatment effect among the seven.

Does that answer the question or were there more issues?

DR. DRACHMAN: What was the smallest number of patients in any site?

DR. GILMAN: Can the sponsor answer that question?

DR. GRANEY: The smallest number of patients at any site in the United States was 23.

DR. GILMAN: Is there any more discussion about study 1200? Dr. Kawas?

DR. KAWAS: I just want to refocus back to your question since everyone else has refocused this group today.

(Laughter.)

DR. KAWAS: I think that we have one study and only one study that in fact does suggest that there is a safe and effective response to this drug. That's the way I felt with the previous shows of data and all the information that I've heard today has not changed my opinion on that.

Although the modeling is very interesting and I understand the kinetics and I understand all the other data presented by the FDA, although the biological issues are

interesting, the fact is that we need to decide this based on the results of clinical trials. There were two trials and one of them is positive, and I'm convinced of that positiveness. But the second trial is not and I would like to see more information to convince me of causality. When we consider causality, we want consistency of response or strength of response, and consistency is usually gotten by a second study.

I think in this case the sponsors tried to give us other ways to find data that supports this consistency by looking at the levels, which was interesting but at least for me was not adequate. So, in answer to the question, I think that we only have one study right now that suggests a response to drug.

DR. GILMAN: Yes. I wanted at this point more to discuss your thoughts rather than get to conclusions. We can hold our conclusions till the very end, but I think we need to see whether the committee believes that there is enough evidence presented before us to answer these three questions. To discuss where you are with this would be perfectly all right.

Any other issues about study 1200?

(No response.)

DR. GILMAN: Well, study 1202 does not provide very much confidence, and I don't think there's much doubt about that, indicating that there is a beneficial effect. The study was clearly negative. I do have concerns about adding the two studies together because of the points made by the FDA, namely that the effect of one study may carry the second study along. I would instead prefer to look at study 1202 by itself, and there we find no significance.

Again, let me ask whether members of the panel want to discuss 1202 further. Dr. Adams?

DR. ADAMS: Well, it's my understanding the sponsor does not have a great deal of confidence in 1202, and I guess I would like to know why 1202 should not be considered to be equal to 1200 as far as design, conduct, and overall analysis of the results.

Now, I realize we have these two post hoc analyses with vital capacity and age being the stratification, but I for one am not sure why I should ignore 1202 which is a negative trial.

DR. GILMAN: Would the sponsor like to reply?

DR. SCHARSCHMIDT: Just as I'm sure the panel is wrestling with the issue of 1200 versus 1202, we spent a lot of time thinking about it ourselves. There are some things which appear don't explain the difference between the two trials, for example, the blood levels of IGF-1 are not different between the two trials.

We know that there are some things which are different. We pointed out some design issues, which I won't reiterate. I could perhaps mention the challenges of trying to apply the SIP in a multi-cultural environment.

We note that there are standards of care which are different between the two trial sites. We see that as reflected by the use of concomitant medications.

We've discussed the randomization of patients with advanced age or low FVC. That by itself does not explain the difference.

I think importantly, when normalized for individual variation in the Appel slopes, what we see in the European trial both pre and post randomization is twice the site-to-site variability in the European trial as the

North American trial. I made the point earlier that that could be corrected for by itself statistically, but it suggests that there are other factors that we don't fully understand related to perhaps the biology, the design, or the execution of the study which created a background against which a signal was harder to see in the European study.

So, the examination of the two trials has helped us in two respects. One, we think that by comparison the 1200 study is one we have more confidence in. Second, examination of the two has helped identify risk factors such as age, FVC, variation and progression of the disease, which are clearly important to stratify for, in the proposed approval study.

DR. GILMAN: Dr. Khachaturian?

DR. KHACHATURIAN: Have you done any analysis in the 1202 where there are subgroups in which you get better results? Are there subsets of the patients where the results --

DR. SCHARSCHMIDT: Yes. We have done subgroup analyses. These were exploratory, after-the-fact analyses.

Some of these were discussed with members of the panel last year.

When the patients with more severe disease, as defined either by the higher Appel scores or the more rapidly progressing disease, are analyzed, we see that actually in both trials the results are most evident in patients who have the higher Appel slopes. We didn't focus on that today because we really focused on prespecified analyses. But that has really been very important in our thinking regarding the two trials and the issues that we would need to address going forward.

DR. GILMAN: We had a lot of concern about those post hoc analyses since they were, I guess, data-dredging is the word.

Yes, Dr. Drachman?

DR. DRACHMAN: Did your trainers train the European folks? Did your monitors monitor those studies? Were they subject to the comparisons of the Appel scale use?

DR. SCHARSCHMIDT: Dr. Graney, can you answer that question regarding the training of the Appel?

DR. GRANEY: There is no clear dichotomy between the management and the follow-up in Europe. The training was conducted by staff from Baylor for both of the studies. There was assistance by CROs in both North America and in Europe. That's a potential source of some difference. A small company like Cephalon doesn't really have enough of its own staff to do every site. So, that's certainly a possibility but it's one that we can't really assess. Looking at it on the face of it, we did not see the difference in that.

DR. ADAMS: Are there data from other research projects that show that SIP is done differently in Europe than it is done in North America? Because one of the issues alluded to was that maybe it is. Are there, not necessarily ALS studies, other clinical trials that what is considered an SIP change in Europe is not necessarily North America or vice versa?

DR. SCHARSCHMIDT: Perhaps I could just comment generally on the SIP. It's a different instrument to use cross-culturally. Even when used in the UK, which is English speaking, it has required cultural translation and

revalidation.

In the European trial, there were some validated SIPs available for some sites and not for others. So, for example, for the Belgian site, the Dutch instrument was translated and used at the site in Leuven. So, the use of the SIP in a multi-cultural environment is a challenging undertaking, and in fact we're not aware of precedent for it having been used before in a therapeutic trial like this.

DR. GILMAN: Dr. Hoberman?

DR. HOBERMAN: This is an isolated point but it was something that came up in the data that I just found intriguing. I'm not saying that this invalidates the use of this particular instrument.

But I happen to notice that in the patient that improved the most from baseline in the .10 milligram group, that person left the trial early.

Now, is there some indication that somebody who might improve on a quality of life scale is somehow deteriorating clinically fast? Could there be a dysjunction between what the SIP measures and what's

1 happening clinically?

2 DR. SCHARSCHMIDT: Well, let me answer the

3 question a little more generally to see if the SIP and the

4 Appel were capturing the same patients. Essentially all

5 the patients who had Appel scores recorded also had SIP

6 scores recorded. So, the two instruments captured the same

7 group of patients throughout the trial. So, there may have

8 been isolated individuals who weren't captured by both, but

9 that was an exception rather than the rule.

10 DR. GILMAN: Well, but you're answering the

11 question as if the Appel scale were a clear indicator of

12 patient response and patient well-being and so on. I'm not

13 sure that your response answers the question posed.

14 DR. SCHARSCHMIDT: If I understood Dr.

15 Hoberman's question, it was there was a patient who

16 appeared to register improvement on the SIP score who

17 exited the trial early.

18 DR. HOBERMAN: Yes. I'm just wondering whether

19 it's possible that -- well, Dr. Leber has just answered my

20 question.

21 DR. SCHARSCHMIDT: I can't speculate.

DR. LEBER: Because there's a parallelism to this, if I may suggest, between the global in Alzheimer's and the ADAS-COG scores. We use them for different purposes, but it's certainly possible someone could have an improvement in muscle strength and at the same time there's some other event that would drive the SIP because the SIP is not demand specific. It doesn't deal with ALS so much as the sum of things that may go on that govern how one feels.

So, it's possible it's discordant although we don't think that that's too important from my perspective because what we want to find is whether the treatment is responsible for the difference between the groups in a beneficial way. I still believe that it isn't so important until after the fact when you concluded the drug has an effect that's beneficial that you have to go in and parse out exactly what it's affecting.

We approved tacrine, for example, on an ADAS-COG total score changes on the ADAS-COG portion, and later on people began to think that possibly it was affecting vigilance and attention more than anything else, something

that isn't so well rated in that scale and indirectly affected other things.

But I think the first question would be, is the drug responsible for a benefit? And then the issue is what is the benefit.

But I like to know precisely, but I still think the big question is, what's the benefit that you can be certain the drug has caused? That's the answer we want to know. So, what do you think it's caused by?

DR. SCHARSCHMIDT: While we're on the SIP, let me just spend one additional minute about how the two measures relate. They can be thought of probably as intersecting vin diagrams. There are 136 questions in the SIP, of which probably half or perhaps a little less than half address physical issues, physical function, which is also registered by the Appel but from different vantage points. The remaining questions on the SIP address issues not touched on by the Appel, such as mood, activities, shopping, do I continue to go out with friends, do I work. So, in that respect, they're both interlocked and separate measures, which really assess the same issue but from two

very importantly different vantage points.

DR. GILMAN: All right. Yes, Dr. Temple?

DR. TEMPLE: Just one point. In a certain sense, there's nothing really to explain about the SIP. The comments made by Dr. Scharschmidt and others that in 1200 why you see a certain consistency between findings on the SIP and findings on the Appel and maybe even a lean on survival, that just says those patients were doing better. These are potentially measures of essentially the same thing with different mechanisms.

Well, you turn to 1202 and on all of those same mechanisms, there's not a lot of difference. Well, that's not exactly surprising if they're measuring fundamentally the same thing.

So, it doesn't really require an extra explanation about the SIP. It just points out again that the results were fundamentally different for reasons we don't understand very well.

DR. GILMAN: All right. Well, I think there's only one remaining issue for us to discuss and that is the strength of the 1200 trial, what these data actually mean,

which would get to items 2 and 3 of the questions that are posed for us.

The statistics show bare significance, if I could put it in those terms, .055 with the sponsor's study and .05 with the FDA study.

DR. WILLIAMS: I'm sorry. In the high dose Myotrophin group, the p value was .01.

DR. GILMAN: Well, there's some debate about that.

Dr. Hoberman?

DR. HOBERMAN: Yes. There's an explanation for that. Please bear with me a little.

When the first trial came in, the protocol said that there will be a pooled analysis and if the pooled analysis is significant at the .05 level, then there will be pairwise analyses of the active treatment groups to placebo. It did not say what would happen if the pooled analysis was not significant. It didn't say what would happen.

So, I saw the .056. It was generated with a computer algorithm searching for covariates which I thought

was inappropriate and the sponsor has known for some time the FDA has thought is inappropriate.

In addition, if you separate out the treatment groups and just do an analysis of variance without covariates, to answer the question are the groups different in any way whatsoever between them, the p value was .10.

In order to be as faithful as I could with the document, I went back to the original protocol. What I just told you came out of an amendment. I went back to the original protocol that mentioned Dunnett's test. Now, Dunnett's test is simply a procedure which allows for the fact that you are testing two separate treatment groups against control, and so you have two chances to get a statistically significant difference.

Now, I performed that analysis and found that the .10 milligram group made it right on the border. So, what happens is that the way to report that is by the Dunnett's test, the p value for .10 milligrams is in fact .05.

Now, what the sponsor is contending is that, well, even though it was .06 for their pooled analysis,

1 they went ahead anyway, tested .1 against placebo with a
2 covariate analysis, which I didn't think was appropriate.
3 So, at the very end of the game, the decision
4 was made that there was enough evidence to declare this
5 study statistically significant at the .05 level, but we do
6 not believe that .01 is the true p value for that study.
7 DR. GILMAN: Does the sponsor want to respond
8 to that?
9 (No response.)
10 DR. GILMAN: If not, then we will proceed.
11 Yes?
12 DR. LEBER: You may all recall there was
13 extensive discussion of this at the June meeting.
14 DR. GILMAN: We do.
15 DR. DOBBINS: I simply want to make the point
16 that the sponsors disagree with that assessment.
17 DR. GILMAN: We understand that.
18 (Laughter.)
19 DR. GILMAN: Dr. Temple?
20 DR. TEMPLE: Could you state the nature of the
21 disagreement further, though? The initial planned analysis

for the overall study was the combined groups, which gave you a value of somewhere between .05 and .056. So, that carries --

DR. DOBBINS: By a protocol-specified covariate analysis reviewed and approved by the agency prior to the unblinding of the 1200 study.

DR. HOBERMAN: Let me correct that.

DR. TEMPLE: But the primary analysis was for the combined groups. Right?

DR. DOBBINS: Yes.

DR. HOBERMAN: Yes, but let me correct that. It is not true to say -- let's put it this way. It's partially true to say that -- well, no, it's not true to say --

(Laughter.)

DR. HOBERMAN: -- that the FDA approved that analysis. It's not as though we're a registering agency that stamps analyses and says it's certified. What in fact happened was that I was the second one put on this project. The first person put on this project apparently did not object to this analysis.

DR. TEMPLE: But even if you don't object to the analysis, am I correct in my understanding that what was intended to be the first endpoint was significant at about .05 by the analysis you did.

DR. HOBERMAN: Yes.

DR. TEMPLE: The argument is about having done that and moving on to how the higher dose --

DR. HOBERMAN: That's correct, but it was done with a covariate analysis that I don't think was appropriate.

DR. TEMPLE: I'm merely making the point that whatever your belief system about these two things, we're talking about the initial analysis being significant at or about .05 at best. That's not a very low p value any way you describe it.

DR. HOBERMAN: Right. If you allow what was in the protocol, that's what you --

DR. TEMPLE: Okay. Having done all that -- and you were using the original analysis -- you reached the conclusion also that the primary analysis or what you thought the primary analysis should be was at about .05

also. Now, anybody can see, I think, that if the analysis of the whole comes out sort of marginal, most of that action is due to the higher dose group. So, I'm not sure how far one has to duel statistically.

DR. HOBERMAN: I certainly hope we don't. It's a statistically significant study.

DR. TEMPLE: Yes, but the idea that it's way out there --

DR. HOBERMAN: No.

DR. TEMPLE: -- I think we do not agree.

DR. GILMAN: All right. Other discussion about the strength of 1200?

(No response.)

DR. GILMAN: If not, unless there is other discussion the committee wants to engage in before we hear from the people who want to testify before us, let me ask the sponsor, have you anything further that you want to tell us? Have you had a complete airing of all of your data, all of your points?

DR. GRANEY: Yes, we have, Dr. Gilman. Thank you.

DR. GILMAN: Thank you, Dr. Graney.

And the FDA?

DR. TEMPLE: I just want to ask you a question. The sponsor put forth various reasons for you to believe that the study that was supportive is sort of bigger than usual. Now, are you going to discuss those later as you get to the questions?

DR. GILMAN: Yes.

DR. TEMPLE: Or is this the last discussion we've had of any of those things?

DR. GILMAN: This is the discussion that we're going to have of these items. We can certainly discuss them when we come to discussing the answers to the three questions that have been put before us, but I thought this is the time when we need to get the issues out, not indicate that we've decided but rather to indicate what our concerns are, what our questions are, where we stand with this.

DR. TEMPLE: Okay, just to make the point why we're interested. As the document that we provided said, usually we expect independent replication, independent

substantiation of studies. But the sponsor is entitled to make the argument that there are reasons for you to believe the study that was favorable should bear more weight. I just want to be sure you consider those reasons and tell us what you think of them. Maybe your vote would tell us all by itself, but we'd like you to be fairly explicit on some of those things. But you don't have to do it now. You can do it later.

DR. GILMAN: I think it's best for us to state our conclusions at the very end. I think this is the time for us to discuss any concerns that we have about them if we don't understand the data, don't understand the arguments. This is the time to get that on the table. If everybody is content that they understand the arguments, then we needn't discuss that further at this time.

DR. WILLIAMS: You asked if the sponsor had one final statement.

DR. GILMAN: Yes.

DR. WILLIAMS: So, I'd just like to make our position clear. We really appreciate all of the comments made and we agree in some part with the FDA and we also

agree on some of the confusing aspects of this.

Our discussion today and our point of view is based on the fact that if you view the data in aggregate, that we've come to the conclusion, and we think there is enough evidence to come to the conclusion, that IGF-1 has a clinically beneficial effect, that Myotrophin has a clinically beneficial effect in ALS.

We put that in the context of a disease that has no other treatment for morbidity, and we agree that there's uncertainty here. We can see that as well as anybody, but we agree that we think that the best way to address that uncertainty is in a post-approval environment.

We're faced with the prospect of thinking about doing another trial, and for us at this point in time, we just can't commit to another phase III trial. This would have to be something that we'd have to go back and reexamine and look in the context of all the priorities of the many diseases that are on our agenda. We are committed to, if possible, move ahead with this disease and we're quite interested in finding those answers.

So, our arguments are based primarily on the

aggregate data, on clinical endpoints, on the fact that we think there's a clinically beneficial effect of Myotrophin, acknowledging the uncertainties.

Thanks.

DR. GILMAN: Thank you.

Dr. Khachaturian?

DR. KHACHATURIAN: You talked about the aggregate of the two studies. You have two studies, one of which has quite marginal significance statistically. The other one does not.

Then the argument was made about the risk-benefit analysis with most of the focus on the study done in this country. If you were to make a risk-benefit analysis on the 1202, what would be your statement? How would you analyze, if you had just that one, that data to work with? Could you give an assessment how you would --

DR. BALDINO: I think looking at 1202, the European study in its own right --

DR. KHACHATURIAN: Just by itself.

DR. BALDINO: Just by itself? I think the sponsor's position would be the element of risk is the same

as that in 1200. I think one aspect of both studies that has been reproduced is the safety aspect. I think the agency agrees with this position. We have reproduced -- we have two pivotal studies underscoring the safety of the drug in this disease.

As far as the --

DR. KHACHATURIAN: Safety is not the issue.

DR. BALDINO: From the efficacy point of view, I have to say it's uncertain in 1202. I don't think it has met the standard of proof alone that we think 1200 has made.

Listening to the comments here, which are very good comments, of course, but you have to look at ALS relative to what has been achieved in this disease to date. I think that's really important. This is not depression. This is not schizophrenia. This is not Alzheimer's disease where drugs have been approved that have established standards for analysis, standards for comparability. This is a disease where for the first time we're seeing the chance of looking at a drug that alters the progression.

There are uncertainties, as we said all along.

We agree with what everyone said here today, but we think given how bad this disease is and given how little we know about it, as we learn together going forward, we think the 1200 study is important to consider in that context.

DR. KHACHATURIAN: I'm trying to be convinced. If the results in Europe were due to chance, that there were all kinds of extenuating circumstances why you didn't get efficacy, I am developing the thought that the efficacy gotten with the 1200 could be equally by chance. How would you convince me?

DR. BALDINO: Well, we've been trying to do that all day I think.

(Laughter.)

DR. BALDINO: But a short answer here is on its face the results of 1202 are directionally correct and because they did not reach statistical significance by definition then could have occurred by chance.

DR. KHACHATURIAN: I'm not swayed by the statistics. I want to get the clinical impression, in what way the patient is going to benefit.

DR. BALDINO: If 1202 was the only study out

there, you couldn't make the determination that the results, even though they're in the correct direction, did not occur by chance. In fact, it would be highly probable until you have some other basis for that.

What 1200 gives you is the fact that every endpoint reached statistical significance. There's a range of p values we've discussed, and the importance of those I don't think we need to further discuss. Internally consistent, dose-related, every endpoint, even the post hoc analyses of survival, although not significant as a primary analysis, was also dose related. I know very few, if any, examples of consistent dose-related effects across a number of endpoints measured independently by physicians and patients that would argue that that could occur by chance.

Now, that's not proving causality of course. A long way to go before we get there. But it's hard to imagine that that's the case. If 1202 went in the opposite direction and you repeatedly chose placebo over drug, I think it would be a harder case to make, but it didn't.

DR. GILMAN: Any other comments? Dr. Drachman?

DR. DRACHMAN: We spent a day last June looking

over very similar data. Could you list for us what data you regard -- and we came to the conclusion that we really didn't see the evidence strongly enough or roughly that. Could you list those data that we should look at now? I know you've been through it and we have too, but which data should we take into account that should change the balance of our view? List them. I don't want to hear them all over again. We've all heard them, but list those items that you regard as the ones that change the balance.

DR. BALDINO: This was from Dr. Graney's presentation. A few points here. One is on the clinical side, the extended survival experience. We came to you last time with barely 18 months survival in the North American study and I believe considerably less in the European study, 12 or 14 months. I don't know exactly. We've had now time to collect and extend that database to beyond 3 years and 2 years for the European study. I think that was important in a lot of regards, and I don't want to go through all the data but it did point out that with a 3-year extended database in the North American study, whatever effect there is there, it is persistent and it

1 remained for that entire period of time.

2 The nice thing about the European study, it

3 allowed us to go back in and evaluate these imbalances and

4 really convince ourselves and I believe others, the agency

5 included, that it probably accounted for the early placebo

6 effect on the European study.

7 The risk factors were a big deal for us and a

8 big deal to show to you today. We were perplexed, as you

9 were, with what the factors were that could possibly

10 account for the dramatic differences in results between

11 1200 and 1202. Before we went ahead and thought about

12 another study and not only the investment alone, but the

13 design of that study, we really needed to understand the

14 role of those prognostic factors. And, yes, there have

15 been a few papers touching on them over the years.

16 This was a very comprehensive study in this

17 disease and there were two of them to look at these

18 prognostic factors. I think we learned a lot from them,

19 and I think it explains at least in part -- certainly not

20 all, but in part -- the differences in protocol 1202.

21 The concentration dependence of this effect I

1 think is also something new to share today, and that was
2 obviously this agreement -- we're seeing slides from the
3 agency that we haven't seen before. We don't know what
4 that is yet, and they're seeing things that they're in the
5 process of evaluating. I think the story certainly isn't
6 closed on that.
7 But it is interesting that there are several
8 models in 1200 that do point, at least suggest, a
9 concentration dependence of the effect, which takes it one
10 step beyond the dose-related effect. It needs to be
11 proven. It's not quite there yet, but it was interesting
12 enough to share with the panel.
13 In addition, we still investigate Myotrophin on
14 a preclinical basis. We never had the opportunity to share
15 that with the panel before. Some of the new data presented
16 today argue for utility and other indications as well, and
17 we thought you should have that in the context of your
18 decision today.
19 DR. WILLIAMS: The other thing that has changed
20 since last time -- excuse me -- is that in the interim,
21 unfortunately, there has been the failure of another large

1 trial and that's just the reality.

2 DR. LEBER: One technical correction just to

3 emphasize. The risk factor adjustment in 1202 was applied

4 to the issue of the primary analysis, the change from

5 baseline on the ALS score, and it did not affect -- it

6 still did not achieve significance. So, the correction

7 didn't fix that study. It may have perhaps explained some

8 of the deaths.

9 DR. TEMPLE: Yes. It did do one thing. There

10 was a somewhat disconcerting, anyway, excessive death in

11 the 1202 study in the treated group, and I think we're

12 reasonably satisfied that that's now --

13 DR. LEBER: Well, again it's a fairly

14 philosophical question because these particular covariates

15 and cut scores are not the only possible adjustments that

16 could be applied to the data. Those cut scores are, as we

17 said in our mailing, highly sensitive to what effects you

18 have. And finally, there is the array of attributes not

19 measured that are not in the analysis. So, adjustment is a

20 tricky thing.

21 DR. TEMPLE: But, Paul, I think we have said to

the sponsor that we are considerably reassured by that analysis with respect to the possibility it was actually doing harm in the 1202 study.

DR. LEBER: I don't think -- we said we didn't think we had a safety problem.

DR. TEMPLE: Okay. That's a difference from last time.

DR. LEBER: I just wanted to clarify what the punch line is, I mean, what's happened in 1202.

DR. GILMAN: Dr. Drachman?

DR. DRACHMAN: If my ears serve me, I heard you say there was failure of another large study. Do you want to modify that a little bit?

DR. WILLIAMS: I'm sorry. I mean, there was a failure of the BDNF trial which was a large trial which would have been an alternative treatment in this disease. That's one of the changes since last time in the environment.

DR. GILMAN: Will the FDA, Dr. Leber, Dr. Hoberman, Dr. Feeney, comment on the statement that extended survival experience is a new piece of information

that the sponsor says is convincing?

DR. LEBER: Well, it's certainly new in the sense that they collected information not available last year that went through July, as we met in June. The differences between the 0.1 randomized group and the placebo group exist and persist, and we'll be the first to admit, if someone was designing a survival analysis to look at the effects of the drug, you would not do it with a group randomized to placebo after a short delay of a few months that was then put onto the active treatment because under the assumption that Myotrophin works, that would underestimate the effect. But listen carefully. If Myotrophin is not responsible for the between-group difference, it makes not one whit of difference.

This is something that comes up all the time. It's very tricky. When you think about an experiment, do you think about it under the null hypothesis that no treatment effect has been shown and under the null that difference doesn't mean anything because it can't be attributed to the action of the drug? Under the alternative, it all makes a lot of sense that you've

underestimated the treatment effect. So, a lot of it determines how you view that data.

So, I don 't think that that can tell you very much. If the group differences in 1200 are due to Myotrophin, then it all hangs together, makes a lot of sense. Our question is -- and it's driven in part by 1202, in fact largely by 1202 because we don't have other trials to deal with -- that it didn't.

Remember the quote I had from Ronald Fisher this morning? It isn't that we expect the p values to come out right all the time. It's expected, when you know something, that you're able to reproducibly show it. I guess call me a Doubting Thomas, but I just don't see that independent source of independent substantiation.

DR. GILMAN: Dr. Hoberman?

DR. HOBERMAN: I think Dr. Leber has said all that needs to be said about the survival from my point of view. I'd just like to comment on what Dr. Baldino said about the strength of the evidence that these measures all came out the same in a dose-related fashion. I've put together two things that Dr. Feeney touched on.

Number one, the ALS endpoints are all functions of each other. So, if you see a result in slopes -- Dr. Temple mentioned this too -- you're probably going to see it on time to 20 endpoint, you're probably going to see it on time to ALS. As a matter of fact, a lot of it is the same information, because I went back and checked.

As far as the SIP is concerned, you might expect that to go along with it.

The issue about the dose-related thing, this really can be exaggerated and you have to think carefully about it. If you come from the point of view that you've done the trial and you look at the data and you see that .1 really does well, then there's a tendency of mind to say, well, gee, I guess it works and it really makes sense that it works because .05 went along with it. That's coming at it from one point of view.

But what we like to do is to look at it dispassionately and ask what would be the chances of this order under certain circumstances. That's where this issue about seeing the .1 there and having a 50 percent chance, if the drug doesn't work -- if the drug doesn't work, you'd

still have a 50 percent chance of seeing the .05 between placebo and the drug.

You can take that one step further -- and I'm not going to go into details about it -- but you can look at it not only from the point of view of the order, but in terms of the statistical significance. Now, the fact is that .1 milligrams was found statistically significant. If you ask the question if the drug doesn't work in the presence of a statistically significant result in the .10 milligram group -- so you have a good result on .10 milligram, but in fact the drug doesn't work -- the chances are 75 percent that you would see the .05 between 0 and .10.

So, if you think about it from the point of view of what could occur by chance, given a good result on .10 milligram, the case about the dose response is certainly not as impressive as it sounds. If you come from the point of view of, gee, .10 made it, gee, that looks like it works, then it certainly makes sense that .05 works.

DR. TEMPLE: Just before you leave that,

however, thinking prospectively, which is different -- you've said, okay, if I already know that .1 did well --

DR. HOBERMAN: Absolutely.

DR. TEMPLE: Thinking prospectively, the chance that they'll order themselves that way is lower.

DR. HOBERMAN: It's one-sixth.

DR. TEMPLE: It's about one-sixth.

DR. HOBERMAN: Right.

DR. TEMPLE: So, again that makes the fact that they ordered themselves that way means something but maybe not so much. Right?

DR. GILMAN: That's the question.

DR. HOBERMAN: Look at all clinical trials with three groups.

DR. TEMPLE: Well, one-sixth is a pretty fair -- that's a pretty large --

DR. HOBERMAN: Well, that would make our job much easier 17 percent of the time.

DR. TEMPLE: But again, though, I guess to me what's going on is there are little things that might make you think somewhat more of that result, and that's one of

them. The question is whether it makes you think that much more of it or not. But it's not that it's --

DR. LEBER: This is typical but I think it's also true that you ought to try to distinguish what things would intuitively and psychologically make you believe something is stronger evidence and what kind of things would still have that psychological effect and yet be misleading. I mean, give mother nature a chance. You know, she'll mislead you. There are a lot of things that are intuitively felt that are absolutely wrong. So, I think one of the things we're trying to do is separate what is appealing psychologically from what really makes sense taken a hard look at it.

This is a difficult disease to do it in because I think there isn't a person here who, convinced that the drug was effective, wouldn't want it approved. I mean, that would be insane. I think the doubtingness comes from the fact that we think there's equal harm from approving a drug that doesn't work and raising false hope.

DR. GILMAN: All right. Any further discussion about these three questions we've been asked to address?

(No response.)

DR. GILMAN: Hearing none, then I will turn to the Executive Secretary for instructions to the speakers.

MS. McGOODWIN: I want to thank the people who are coming to speak at the open public hearing for their patience in waiting to address this committee.

As you get up to speak, we're going to ask if you would identify yourself and the organization you represent. If you would identify any financial interests you might have and whether your appearance today was supported by an organization. If you have no financial interests to report, why, just please tell us. Thank you.

DR. GILMAN: Let me ask also that all the presenters be extremely brief. We have 21 people who wish to speak. We can allocate about an hour to this set of testimonies, but please be very brief and succinct.

Many on the panel are neurologists. We understand the nature of amyotrophic lateral sclerosis. We appreciate what a serious and dreadful disease it is, and we are here to make judgments based upon the data we hear primarily, also on our experience and our compassion for

people with this disorder.

So, let's start with James Brady II from Louisville, Kentucky.

MR. BRADY: Thank you, sir.

In response to the statements here on my podium, I'm Jim Brady. I'm the father of a patient. I have no financial interest in the organization or the proceedings, but a lot of emotional interest.

So, good afternoon. It has been a long day. Lots of charts. Mine are all right here.

I'm happy to be here but I'm real glad that you're here because you represent that precious commodity, hope, to some very special people.

I'm no expert on neuromuscular disease or all of its ramification. I don't have an M.D. or an L.L.D. or a CEO after my name, but I've got a D-A-D because my daughter Erin Brady Worsham is sitting over there in the corner, and her husband Cory is here someplace and their son Daniel.

In her pre-ALS life, Erin was an actress and a singer and an artist, but for the last two and a half years

she's been in a different business. She and Cory are in the hope business, which simply means beginning each day and living it to its absolute fullest, and then you hope for a miracle tomorrow.

Speaking of miracles, the 2-year-old Daniel that they brought with them today is a miracle because after more than 8 years of hoping for a child, Erin conceived Daniel, as nearly as her doctor could calculate, approximately 1 day following her ALS diagnosis and she bore him normally nearly a year into her illness.

Like all the other dads in this room, when one of my kids came to me with a problem, you tried to find the right button to push, the right lever to pull, the right words. So, when Erin was diagnosed in September of 1994, I tried to revisit the magic of my buttons and my levers and my words, but this time nothing worked.

While I searched for the right button to push, she lost the use of her toes and her feet and her legs. While I searched for the right lever, she lost her fingers, her hands, and her arms. And while I groped for the right words, her words became slurred.

Finally,it became numbingly apparent that Erin's dad was eyeball to eyeball with the most insidious, relentless, cruel, and frightening opponent he had ever faced in the world of business, on the playing field, or in war.

But I learned during Erin's nearly three years of day-by-day and hour-by-hour battle there's one thing that ALS can't do. ALS can't conquer hope and hope, I submit to you is that sturdy engine that drives all the thousands of Erin Brady Worsham's of this world through their long days and nights.

And something else I've learned. In ALS patients, hope is different from your hope or your hope from my hope. An ALS patient doesn't look for something to get them from this week to next week or even from today to three days from today. An ALS patient looks for something to get them from this morning to this afternoon, from 11:00 a.m. to 4:00 p.m. and then from sunset to night to sunrise tomorrow which, if they make it, signals the start of another day they've been granted in which to pursue their struggle for hope.

It seems to me that the resilience of our marvelous human spirit demands that there be hope. Always there must be hope. And today with this promising new drug we've heard discussed in such great detail today, Myotrophin, closer than ever to reality, for my daughter and tens of thousands like her, hope can become more easily sustainable.

I must admit to you that during most of my growing-up years and well into my so-called adulthood, I've been an unabashed fan of John Wayne. No matter how bleak things looked for the besieged fort, the encircled wagon train, or the platoon cut off behind enemy lines, you just knew at the last possible moment hope would triumph and that distant bugle would sound and the Duke and the cavalry would pour over the hill and save the day. Right?

Well, if I can leave just one thought with you today, it is this. If that faint puff of dust out there on the horizon just might be John Wayne and the cavalry at full gallup behind some distant hill, shouldn't we -- mustn't we -- do everything in our power to get them into this fight?

A vote for Myotrophin is a vote for hope.

Thank you, Mr. Chairman. God bless you.

DR. GILMAN: Thank you, Mr. Brady.

Christina Clark?

(Applause.)

DR. GILMAN: Christina Clark.

MS. CLARK: Yes, thank you. Thank you, Dr. Gilman.

My name is Christina Clark and I thank you for the opportunity to say a few words. I'm here today with my husband Emory and our son Peter, age 34. We are from Michigan. My husband and I live in Metamora, Michigan. Peter lives in Houston, Texas. I have no financial interest in the outcome of this hearing.

I come before you first and foremost as a mother. I have recently served two elected terms as county commissioner and continue to work in our community primarily on environmental and health care issues. I'm on the board of the Detroit Chapter of the Alzheimer's Association and am currently its public policy chairman.

My purpose here is to speak from the heart for

my family and as a member of the ALS community, particularly the 400 identified ALS sufferers in Michigan, and the many others yet unknown to us. Ours is an expanding family, including now veterans of the Gulf War.

Dr. Gilman, I bring today a letter from Michigan Senator Spencer Abraham and a letter from Congressman Dale Kildee which I would ask you to accept at this time, and a statement from the ALS Society of Michigan asking you to make Myotrophin available to all on an open and fair basis.

In January this year, Peter was diagnosed with ALS at Baylor University. After a year of battling neuromuscular symptoms, including surgery for spinal compression, Peter presented himself at Baylor for two days of testing. We left the hospital together. Peter with a new plastic bag in his hand, and as we crossed the parking lot to his car, he reached in and pulled out first some printed material and then a buttonhook. After all that, this is what I got? A buttonhook, he said. Yes, a buttonhook and a death sentence. That was then.

Today Peter is one of the luckier ALS

sufferers, much luckier. Because of compassionate use approval, Peter has been on Myotrophin for a couple of weeks, his name having been recently drawn in the last lottery from the registered pool.

But, Dr. Gilman, where can there be true compassion when so many are still excluded? How can we continue to receive the gifts of great courage day to day from all of those who wake daily to this degenerative illness and not return to them the gift of hope which is yours to give today?

On the second day of testing at Baylor University, Peter was visited by an occupational therapist who asked him to try out, among other aids, four foam rubber cylinders of different shapes to be put over pens and pencils for easier writing. As Peter tried each one, his inventive mind became engaged. He worked the angles of writing with a concentration of a new discovery and the look of expectation. And as his head bent lower with each effort and his tongue went into his cheek and he started chewing on it, I saw then my little boy creating his life with his Tonka toys.

And then the sudden realization of the true situation he was in swept over him and his face froze in sadness. He put down the pencil, he got up, thanked the occupational therapist, and walked away.

I picked up the paper on which he had written four times, I have a dream, I have a dream, I have a dream, I have a dream. Give back to Peter his dream of life and by your actions today give back the dream of life to the thousands of people who are with us today, present with us in the spirit of their courage and in the hope of your decision.

Thank you.

DR. GILMAN: Thank you, Mrs. Clark.

(Applause.)

DR. GILMAN: Diane Winokur?

MS. WINOKUR: I appreciate the opportunity of speaking to you today. I have no financial interest in Myotrophin.

My name is Diane Winokur. I am from San Francisco and I too am an ALS mother. My son Douglas was diagnosed with ALS last summer when he was 34 years old.

Douglas was an ambitious, energetic, athletic young man. He's a manager for an investment money management firm. He is married and they had started looking for their first house.

His avocation and passion has always been for theater and film, acting, directing and writing. As a teenager, he studied and performed with the San Francisco repertory company ACT. He also appeared in national television programs produced by our public television station.

Now Doug cannot speak.

Douglas loves sports, watching and participating. We're a tennis family and ever since our three boys were very little, there have been hard-fought family matches with their dad partnering with Doug against the older two.

Now Doug cannot even raise his right arm.

Doug loved backpacking and hiking. He and two friends took a year off from college to prepare for and to hike the Pacific Crest Trail from the California-Mexico border to the Washington-Canada border, the entire length

of the American west coast.

Now Douglas has great difficulty walking from room to room.

In the months since diagnosis of ALS, Doug has lost 50 pounds and eating is an increasingly difficult process with constant danger of choking. Last month he had a feeding tube inserted so that he can receive nutrition artificially. His lung capacity is down below 25 percent of normal and he will probably need artificial ventilation.

He is now 35 years old and he looks like an old man.

If Myotrophin had been cleared for general distribution when you evaluated it last year, Doug might still be able to speak. He might still be able to eat. He might still be able to breathe.

I have come across a copy of an FDC Report on Myotrophin dated June 14, 1996 which says: "Approval of the treatment IND would increase FDA's leverage should it decide to demand another trial for approval of the agent." It goes on to say: "With the product available through the expanded access procedure, the agency will be shielded from

charges that it is preventing patients from using a potential breakthrough product."

If this is the FDA's position, it is flawed. Just the opposite is true. The FDA does remain vulnerable to those charges. A few hundred patients receiving the product certainly is not expanded access. The impact on ALS patients, on my son, of this distorted interpretation of the purposes of the program is incalculable.

If you have determined that ALS is safe enough and efficacious enough for 200 people to take, why is it not safe enough and efficacious enough for 1,000 people or 10,000 or 50,000?

In a recent New York Times article on the new generation of treatments for cancer, biotechnology industry executives were quoted as saying that they are reaping the benefits of a liberalization of regulatory policy at the FDA that permits the approval of new drugs for life-threatening diseases with fewer, smaller, and less conclusive clinical trials.

It continues by pointing out that the fast track approval process has been a particular boon to small

biotechnology companies that have felt they could not afford the multi-hospital, multi-year clinical trials intended to prove that new cancer therapies prolong life.

This same consideration is especially critical to companies developing therapies for ALS. Your actions therefore affect not only the future of Myotrophin, but also the future of other therapies so desperately needed.

Why should the FDA appear to be acting with more compassion for AIDS victims and cancer victims than for ALS victims? Is it because many ALS victims cannot speak for themselves and so do not represent a potent political force?

Let me assure you that their parents, their spouses, their children, their siblings, and their friends are prepared to step up to the plate and bat for them.

Douglas is being cared for by Dr. Robert Miller, whom you heard from earlier this afternoon. Dr. Miller, as you know, is a recognized expert on ALS and thoroughly familiar with the Myotrophin trials. The decision of whether Doug should have Myotrophin should be between him and his physician.

Rilutek and Myotrophin are all we have right now. The nature of this most cruel of all illnesses is that deterioration is ongoing. Every day brings some lessening of function. We have lost a year now. For people whose projected life span at time of diagnosis could be two years, you have used half their remaining lifetime. We cannot wait any longer. Please approve Myotrophin today.

Thank you.

(Applause.)

DR. GILMAN: Thank you, Ms. Winokur.

Dr. Anthony Windebank?

DR. WINDEBANK: Thank you very much for having the opportunity to speak.

I'm Dr. Anthony Windebank. I'm a professor of neurology and Director of the Mayo ALS Center at Mayo Clinic. I was asked to speak by the National Organization for Rare Diseases, and I don't have any financial conflicts of interest.

My credentials for speaking today are that I care for about 300 to 400 ALS patients on a yearly basis

1 directing our center, and I've been involved in the design
2 and completion of about 18 to 20 trials of neuromuscular
3 disease, which many of you of course are familiar with
4 here, over the last 20 years.
5 What I would like to do is very briefly -- and
6 I will be extremely brief -- tell you that I have carefully
7 evaluated the data from the 1200 trial. I have had the
8 opportunity to do that, and I will try and answer the
9 questions that have been set before the panel.
10 Number one, no, there are not two trials.
11 There's a single trial.
12 The second question, is this a robust result?
13 I find the results very robust, that there is an effect
14 that is in favor of treatment in the 1200 trial without
15 significant risk. I've been involved in many clinical
16 trials and I've heard repeatedly today that .05 is a
17 borderline result. That may be true in the laboratory, but
18 in clinical trials of neuromuscular disease, .05 is a very
19 robust demonstration of significance when you're looking at
20 global scores in neuromuscular disease.
21 There has been a lot of discussion of why this

might have happened by accident, and certainly that is theoretically true. There's a 1 in 20 chance that it might have happened by accident, but I haven't heard any data presented by any of the reviewers or anybody who's looked at this in detail -- and I haven't seen anything -- to suggest why that might have happened by accident. There are many reasons why a trial like 1202 can have a negative result by accident. It's much easier to get a negative result or find the lack of efficacy by accident than to get a positive result.

I think the Appel score is a direct measure of loss of function which reflects the irreversible loss of motor neurons, so it is measuring the disease process in the irreversible loss of motor neurons, which is the significant morbidity in this disease.

Finally, what I would say is that as a treating neurologist, as I mentioned, with about 300 to 400 patients in our center, I have entered almost 200 patients into the Myotrophin lottery. Now, what is that saying? It means that I believe that the drug is effective and it is clinically useful for my patients that I'm treating with

ALS, and I'm very grateful that over 20 of them have now been involved or enrolled in the study.

The third question is addressed to the panel and I can't answer that, but I think the evidence before me, if I were sitting on the panel, would be to vote in favor of approval.

DR. GILMAN: Thank you, Dr. Windebank.

(Applause.)

DR. GILMAN: Kyle Hahn?

MS. FRANK: This is Kyle Hahn. He is an ALS patient and he has no financial interest.

I'm going to read his comments for him.

My name is Kyle George Hahn. I'm 38 years old. I was hit with ALS over two years ago. Before this disease wrought havoc and destruction on my life, I was a professional musician. I played lead guitar and keyboards in one of the most popular bands in the Cincinnati area. We were booked seven nights a week. I wrote music, managed the band, designed stage productions, and moved heavy equipment.

Now all I have left is the music that I still

write that is an isolated prisoner in my mind, as I cannot hold my guitar, play the keyboards, or even write a note of music on a piece of paper.

This disease has robbed me of my livelihood, my love, and my passion. It's a pirate that has pillaged my body and plundered my soul.

I was an active individual even outside of my profession. I used to go fly fishing with my dog Brandy. Now I can barely pet her. My fishing rods hang lonely on the wall with flies and tackle gear, their only companions in this solitary confinement.

I raced my bicycle in amateur road races, but now my bike sits in the attic gathering dust and reflecting only the memories of my victories and defeats on the road.

ALS has hit me in stages.

Before I began receiving Myotrophin three months ago, I was in a downward spiral. I coughed over every bite of food. Swallowing had become very difficult. Just a couple of Sundays ago I was able to eat an entire platter of fried oysters without a single problem. I love fried oysters. Bringing back just a simple joy like that

is enough for me to continue on this treatment.

Many of the improvements I've experienced since being on Myotrophin may seem like small, insignificant things to a healthy person, but they are great and wondrous achievements for an individual who has had to suffer the extreme and painful loss of muscular activity due to ALS.

Now I can raise my arms so that I can touch my eyebrows. I can turn my head from side to side. I can roll myself over in bed and get comfortable without the assistance of anyone. All these trivialities are things I have not been capable of doing for over a year.

I am not on a feeding tube. However, I've gained 11 pounds -- 13 really -- in the past three months. This is a great indication to me that Myotrophin is doing exactly what it is supposed to do. I think Myotrophin has in the very least halted the debilitating progression of this illness. We need to get to the bottom of ALS as it has gone on too long without a cure, even hope for some respite.

They tell me this disease will kill me within five years, but I don't believe that has to happen and with

your approval of Myotrophin, it will give many of us a fighting chance to prove it.

Thank you for your time.

(Applause.)

DR. GILMAN: Thank you.

Janis Dorfman?

MR. DORFMAN: This is my wife, Janis Dorfman. She was diagnosed three and a half years ago with ALS in December of 1993. She was here last year to address this distinguished committee. However, this year she's back again unable to talk.

Technology and an admirable spirit has enabled Janis to painstakingly write her statement and present it to you today. We hope you'll listen to each word intently, for the emotion and passion will be seen on her face and not heard in her voice.

Two years ago when Cephalon first announced safety and efficacy for its drug Myotrophin, I began to have faith and hope, hope that early access to Myotrophin would slow progression of this hideous disease for every victim being robbed of life.

My hope was quickly replaced by rules and regulations requiring replication of this first study. Yet, life for people with ALS cannot be replicated. This gold standard to which every study must adhere is actually depriving us of our gold years. During the year this second study was being conducted, I regressed from being able to function independently, even though (unintelligible) to require some type of custodial care and still I wait and still ALS patients continue to die along with their future.

You must consider quality of life issues and life expectancy when making your decision. I'm here today, four years after disease onset, in the late stages of muscle involvement and still I wait. If I had Myotrophin when I began my campaign, I would be talking to you now.

The ALS community is not participating in the demonstration outside these doors today because we are paralyzed and silenced. Until a cure is found, our only hope is the combination of drugs approved because they have demonstrated safety and efficacy. Do not question whether the results are robust enough. For a family living with

this, even any slowing of progression is more than what is available today. It also keeps alive the hope that a cure could be found during this gift of time.

The agency has been responsive when public health and safety is compromised. Threats hiding on supermarket shelves are removed within hours to protect against illness and death. Yet, those of us already suffering from a fatal illness must wait years. We are being protected to death.

I am asking that you recommend approval of Myotrophin this afternoon and let the agency convene immediately to act on your positive position. I expect the sponsor to move forward with integrity and with timeliness so that this drug is available to benefit every ALS patient without delay. I don't want this Sunday, Mother's Day, to be the one my children remember as the last with their mom.

DR. GILMAN: Thank you.

MR. DORFMAN: Thank you.

(Applause.)

DR. GILMAN: Mark Levison?

MR. LEVISON: My name is Mark Levison.

(Unintelligible.)

MS. SCHWARTZ: Today is the beginning of new hope for people with ALS, including myself. I come here today to ask you for your recommendations for the approval of a drug which I believe will be the start of a new beginning for people suffering with ALS.

I have had ALS since February 1990 and I have been in pain for the muscle atrophy and cramps which are a common, everyday occurrence in my life. I continue to use my muscles so I will not lose them, and maybe this is why I have so much pain.

Having ALS is very hard on the patient, but it is even harder on the caregiver. To see someone whom you love being struck by this unforgiving disease is very hard.

A drug like Myotrophin is not a cure but it is something that will give us hope and maybe grow some of the nerves back until we are unable to find the cure.

I ask you what would you pay to see a family member graduate from college or a grandson or a granddaughter be born or maybe just to go away to see a ball game? What would you pay for your life to be a little

easier?

We live each day with hope. I have served my country well in Vietnam and I've always tried to be an upstanding citizen within my community. I ask you, my fellow Americans, for the release of a drug on the market to help me and other ALS patients. Today you can make the difference for the future of ALS.

In the last five years, we have come a long way for the answer to this disease. I'm sure, if you approve this drug, we'll be taking a big step in the right direction. If Lou Gehrig were here today, he would say, let's find the answer for it's been too long.

I would like to thank you for your time and your consideration. Always remember as a team we can make the difference and we are all in this together. ALS has no friends. It just wants to kill. We have to strike out ALS now. Thank you.

DR. GILMAN: Thank you.

(Applause.)

DR. GILMAN: Jim McKeever?

MR. McKEEVER: My name is James J. McKeever.

I'm a patent attorney. I have a doctorate in chemistry and I have worked for both Merck and Pfizer and I am quite familiar with the Food and Drug Administration procedures.

I was captain of the track team in both high school and college, and today I can't walk.

I was an Air Force pilot in the Korean War, and I still can't walk today.

I rode a motor cycle for 30 years. Today I can't walk.

I skied in the Austrian Alps for 30 years. I'm still not walking.

I feel that anything that we can get to relieve or help cure a disease should be distributed to the needy as soon as possible.

One of the distinguished members of the committee panel said why should we approve Myotrophin today. You're looking at the reason because I'm luckier than most of the ones you've seen. I still have my hands and my fingers, and I can still speak and I can still eat. Now, how long that's going to last, I don't know, but if I have Myotrophin -- as you've heard with the people who have

had it on the trials, it has made their lifestyle much better.

And as far as that 1202 that was carried out in Europe, you have to remember that the people in Europe smoke like it's going out of style.

(Laughter.)

MR. McKEEVER: So, I would say if there were morbidity trials, you better check their lungs not their legs.

(Laughter and applause.)

MR. McKEEVER: So, I ask you -- I have season tickets for the Giants. I want to be able to cheer for them. So, get me Myotrophin.

Thank you.

(Applause.)

DR. GILMAN: Thank you.

Erin Brady Worsham?

MR. WORSHAM: My name is Cory Worsham. I'm Erin's husband. She doesn't speak clearly, so I'm going to read her statement for her. And we're from Nashville, Tennessee.

My name is Erin Brady Worsham and I was diagnosed with ALS on September 7, 1994. On September 8, after six years of trying, I became pregnant. I never thought to hear the word, but to my son Daniel my name is Mama. I believe in miracles because I live with one.

Before I knew I was pregnant, I'm ashamed to say my outlook was not so positive. When my doctor told me that eventually I would lose the ability to breathe, my response was, let's hope I get hit by a Mack truck before then.

Well, three months later I discovered I was pregnant, and suddenly I was so full of life it was hard to remember I was dying. Who could think of death when every day I felt the baby grow and move inside me? With the baby grew the hope that I might be a real mother to my child.

Giving birth to Daniel was the last time I felt in control of my body. He arrived by natural child birth and I have no doubt for some of my muscles it was the last hurrah. But what a glorious way to go.

Daniel has electrified our lives. Watching him grow and looking at the world through his curious eyes has

helped pushed this ALS bogeyman back into the shadows of my mind. But he won't stay there. Every time I say goodbye to another muscle, he is there raising the specter of death before me.

The terrifying thing about ALS is that it's not terrifying at all. It's like a delicious sleep. It creeps up over your body and tells you to stop struggling. It would be so much easier to just rest.

Three years ago, these proceedings would have meant nothing to me. I was healthy. I didn't need you or this drug. Even after I was diagnosed and heard about the new drug Rilutek, I was not impressed with its results. What was three months to me? I was still too healthy, and I'm afraid that good health breeds invincibility.

But then I met my son and fell in love. Now I had the whole world to lose and three months began to look like a lifetime.

When Rilutek became available, I took it, and now along comes Myotrophin with its modest slowdown in the progression of the symptoms of the disease. Modest. What does that mean? What a staid, unemotional sounding word

for such an incredible gift, for any slowdown is surely that, a gift of time.

I find myself faced with a deathbed conversion of sorts if there's any chance that because can give me more time with my family. I very much need your recommendation to grant me access. I am not accustomed to placing my trust in a drug, for I believe my hope lies with God, but it's like that old joke where the man is trapped on his roof in a flood. First one boat and then another boat and finally a helicopter comes by and offers to take the man to safety, but the man says, no, the Lord will save me. I believe the Lord will save me. Well, the man eventually drowns and he goes to heaven. When he sees God, he says, Lord, what happened? I believed you would save me. And God says, I sent two boats and a helicopter.

(Laughter.)

MR. WORSHAM: Well, Myotrophin may not be a boat or a helicopter. It may just be a sandbag that will hold the flood back a little longer and give me a little more time to leave my son with some memories of his mother.

Thank you.

(Applause.)

DR. GILMAN: Dr. Theodore Munsat?

DR. MUNSAT: My name is Dr. Ted Munsat. I'm Professor of Neurology and Pharmacology at Tufts in Boston, and I'm here at my own initiative. I paid my own travel and room expenses. I don't invest in any biotech company. I consider that much too risky for investment.

(Laughter.)

DR. MUNSAT: I wanted to come down today to express my view as a lifelong researcher in ALS. I spent most of my professional, as has Tony Windebank who spoke before me and Bob Miller who spoke previously, thinking about ALS, running a large ALS program.

We and others -- and you'll hear from Ben Brooks soon and Barry Festoff -- have spent hours if not days and weeks discussing ALS trials, what to measure, how to measure it, how to assess it, what kind of statistical techniques, what kind of trial design is most effective for what particular situation. What I would ask you on the panel to do is to listen to the testimony of those of us who have spent this amount of time over the years in

treating ALS. I think you'll hear a consistent theme.

We believe that Myotrophin should be approved not because of compassionate interests and not because we deal with patients and their families every day, but because the science is sound. We believe that there is internal consistency in the 1200 study, that there is a dose response, that there is modest efficacy, and we believe we know why the 1202 didn't show positive results. I would echo Tony's remarks that it's much easier, because of the way trials are designed, to show an effective drug to be ineffective than the other way around.

We strongly support the approval of Myotrophin because of scientific reasons. We want to move ahead. I think there's a general feeling that we've got a certain momentum and that we want to move into polypharmaceutical trials as quickly as we can. We need to work what we have. We're at the dawn I think of effective pharmacotherapy for ALS.

I believe if Myotrophin is approved that it will be a big impetus for us to finally achieve what we're all looking for and that is a form of polypharmaceutical

therapy that will truly have an effect that can be recognized by both patients and doctors. And we may not be too far away from that.

Thank you very much.

DR. GILMAN: Thank you.

(Applause.)

DR. GILMAN: Fred Kanzler?

MR. MEHL: Good afternoon, ladies and gentlemen. My name is Karl Mehl. I'm here with my very good friend, Fred. We are both very proudly members of the ALS Association, Philadelphia Chapter, and neither of us have any financial interest in this hearing.

I've been asked by Fred to again read his statement.

My name is Fred Kanzler. I live in Mount Holly, New Jersey, and without misleading you, I am happy to say I am back, unlike many of my friends and fellow ALS patients who did not have the benefit of treatment with Myotrophin. Because of Myotrophin, one month ago yesterday I turned one year older. I was able to celebrate the 49th anniversary of my 21st birthday in the circle of my

friends --

(Laughter.)

MR. MEHL: You've got to think about these.

(Laughter.)

MR. MEHL: -- former colleagues and, last but not least, my family. Because of Myotrophin, I was fortunate enough this past December to see my oldest granddaughter celebrate her ninth birthday and my youngest her second on the 21st of April.

In four days, my wife Ann will celebrate her 39th birthday for the 21st time.

(Laughter.)

MR. MEHL: Since June of last year, I was able to secure and finish two environmental consulting assignments from my former employer.

The other exciting news is that I'm still alive. In fact, if I'm not in a hurry, I still walk. Sidewalks and other walkways that are fitted with railings, I can walk without the aid of crutches or a walker. The only reason I use the wheelchair is that people savor the opportunity to push me around, particularly my wife.

On a more serious note, and just to refresh your memories, I was diagnosed by Dr. David Lee of Mount Holly on June 25th, 1991 with sporadic ALS. I have attached to my statement the statement read at the June meeting.

After an evaluation lasting about seven months by Dr. Howard Natter and based upon the deterioration of my overall strength indicated in the FL score, I was accepted on April 8th, 1993 to participate in a double-blind study for Myotrophin. Even though my extrapolated Appel curve indicated my expiration date as June 1994, I am not misleading you again when I joyously say, fooled you, thanks to Myotrophin. If that's not proof for efficacy for this medication, I don't know what is.

Obviously statistics may argue that I'm a one-point statistic. In a regressive analysis plotting Y equal dose, versus X equal life span, my data point may be way out to the right somewhere. However, we also know how confidence intervals behave when plotted around the mean in a regression plot. In any event, I'm here and I'm thankful for that.

Before I even knew about the ALS Association, I started a workout regimen in September of 1991. I had to do something to prove to myself that I'm not over the hill. Throughout the past six and a half years, my workout consists of cardiovascular activity on a stationary bike as warmup. With my exercise on modular weights, I try to maintain as much strength in my arms, biceps and triceps, and legs, thighs, calves, and hips as possible. I also do situps, tiptoe exercise, free walk with the guidance of a railing, and limb stretches.

After my retirement at the end of April 1993 and weather permitting, I have tried to maintain a six-day per week workout schedule. The elapsed time for my workouts amount to an hour and a half to an hour and three-quarters a day.

My main gauge to indicate wellness is the miles traveled on the stationary bike. To avoid any bias, I've used the same bike for two and three-quarters years.

(Laughter.)

MR. MEHL: The old bikes were changed at that point.

The daily average of miles since the beginning of this year up to April 26th is 5.6 miles, with an uphill workload of 80 to 110 watts and downhill 45 to 75 watts. For comparison, in 1993 I would average 6.1 miles.

I stated at the June hearing the injections, with the exception of the first few weeks after the start of the study, never posed a problem to me. As I also indicated in my June testimony, the atrophy of my muscles essentially ceased several weeks after the start of the study, so did the vesiculations. In fact, after several months into the study, the muscle tone returned, obviously not to the degree as I had when I was swimming in the South Jersey Masters Competition in the mid-1980's.

Both Dr. Lee and Dr. Natter are surprised about the continued strength in my limbs. The normally expected atrophy in my hands and feet associated with the usual deformation of these parts is essentially absent.

To my disappointment, my legs show a larger degree of spasticity than my arms. In fact, if my legs were to have the same quick response as my arms, I would be able to walk much more secure.

Just for fun at my February visit to Dr. Lee, he challenged me to a game of arm wrestling. He called for a truce after he saw I was on my way to winning. To be fair, he's only 5'7" or 8" and weighs about 160 pounds. However, he's an excellent golfer.

That is not to say that I am as strong as a healthy person. In fact, if I fall, I cannot pull myself up. I need the help from people capable to lift 188 pounds gross weight. There were instances when I had to crawl to the nearest stairway.

My bulbar problems progressed rather slow. However, I do have to watch how I swallow. At times the saliva goes into the wrong pipe causing a coughing spell. I can still eat regular food. As a result of the atrophy setting in at the vocal chord, the speech is certainly weaker and grows weaker by day's end. The loss of my ability to speak is basically my greatest fear I have to learn to live with because the people who know me well know I like to talk.

I noticed an additional bonus after about six months into study. I would comment here for Fred saying

this was not mentioned in the entire hearing today. There was hair growing in areas where I had lost it, even though it was only fuzz.

(Laughter.)

MR. MEHL: I also noticed more hair on my hands, arms, legs and torso. As my hands became more clumsy, the frequency of cuts during shaving increased. However, I noticed that my blood would clot much faster when compared to the time prior to my use of Myotrophin.

I am very proud to have been a partner in the research to find an answer to the treatment of ALS. I thank all the people from Cephalon who gave me the opportunity to lengthen my life by at least three years. It is my prayer and hope that the distinguished ladies and gentlemen of the advisory panel find in their heart, based on the presentations advanced today, the ability to make this drug available to all ALS patients.

The continued denial of Myotrophin to wives or husbands, to mothers or fathers of young children, or for that matter, to any diagnosed patient is in my opinion no longer warranted. I've seen too many people die

unnecessarily despite the fact that there is another drug besides Rilutek that would help them to live much longer.

Again, it is my opinion that the efficacy of Myotrophin has been demonstrated during the years of the phase III study period.

Those of us who spent May 8, 1945 in Europe remember today as VE Day. Ladies and gentlemen, let's let May 8, 1997, the day we spend together here in this room, go down in history as VM, Victory Myotrophin, Day and perhaps also as D-Day on the way to VALS Day.

I thank you for giving me the opportunity to present my views on this matter.

(Applause.)

DR. GILMAN: Thank you.

Dr. Barry Festoff?

DR. FESTOFF: Thank you, Mr. Chairman, colleagues on the panel, and ladies and gentlemen. I'm a professor of neurology at the University of Kansas and the VA Medical Center in Kansas City, and like Drs. Munsat, Brooks, and Windebank, I've been involved in ALS clinical and basic research in my case for over 20 years.

I'm pleased to have been involved in the entrance of ALS to modern clinical trial design but only 10 years ago, and 20 years ago I did a review on the then existing publications on clinical trials in ALS, over 300 of these, and not a single one was positive. Certainly in the intervening years, we have had much less activity in terms of positive trials in ALS than in other comparable conditions.

Ten years ago I chaired the first multi-center trial of a recombinant molecule in ALS, the human growth hormone study, and that was a negative study. But my colleagues, at the conclusion of that trial, suggested that IGF-1 should be considered.

In addition to the preclinical data that Dr. Jeff Vaught presented, it's important for the panel to note that there is a vast literature on ALS and its relationship to carbohydrate metabolism and intolerance. My colleagues and I showed that ALS patients were insensitive and in fact resistant to insulin and, on that basis, predicted that IGF-1 would not lower blood sugar levels.

What we need clarification of today -- and I

1 think in terms of my review of the data of the 1200 and the
2 1202 studies -- is that what we are dealing with is not
3 symptomatic improvement. It is also not modest. We are
4 talking about the progression of symptoms in this disease
5 that leads inexorably to death. No other agent in the
6 history of this disease has ever even suggested such a
7 benefit.
8 Like you, colleagues on the panel, I am
9 impressed with the data of 1200. I am gratified by the
10 powerful demonstration of such efficacy in this trial. In
11 fact, in a smaller double-blind study that I have had the
12 privilege of conducting as a grantee of Cephalon and a
13 consultant to Cephalon, I have two patients that have
14 received over 1,000 injections of IGF-1 since April of 1994
15 and these two patients are the only surviving patients in
16 this double-blind trial and were randomized to treatment
17 that we just broke the code on this week.
18 Like you, members of the panel, I am
19 disappointed that 1202 did not have this power. We have
20 heard a number of explanations for this possibility, and I
21 like my colleagues in this field accept those explanations

as plausible for why 1202 did not show the power.

However, I must reemphasize that the failure of 1202 does not negate the power and efficacy of 1200. And to underscore these results as being the first in history to convincingly show an agent capable of altering and slowing down progression, we have to remember that this is not symptomatic and this is not modest.

And like you, I conclude that much more information based on these exciting data and new opportunities are needed and believe that these results and information will yield additional results and information, and that after approval, studies as we have heard about today in terms of combination trials are clearly to follow very quickly.

I thank you for this opportunity.

DR. GILMAN: Thank you, Dr. Festoff.

(Applause.)

DR. GILMAN: Valerie Babisky?

MS. BABISKY: Mr. Chairman and members of the advisory committee, thank you for allowing me to address you today. My name is Valerie Babisky and I am the Vice

President of Patient Services for the ALS Association, and I have no financial connection to Cephalon.

As the Vice President of Patient Services for the ALS Association, I am here today as an advocate and the voice of the many ALS patients and their families throughout the U.S. who could not be here.

During this last year, the Patient Services Department of the ALS Association has averaged 2,000 calls each month, with the most frequently asked question being about drug development. We attempt to address the many questions from newly diagnosed patients. Sometimes the questions come from their family members or friends. We more frequently hear from patients who have been living with this diagnosis for a while. They have become fairly well educated about this disease and daily we hear the concerns about the lack of treatment options.

At the ALS Association, we have also noted that patients hear and comment about the progress being made in the treatment of other deadly diseases such as HIV and many cancers. Patients with ALS ask why they are not getting the same attention. I am an R.N. who has worked within

oncology for many years, and I have seen that we, the health care community, have to change our expectations about treatment for cancer over the 30 years that I have been an R.N.

Just as in oncology, ALS patients and the health care community had hoped for the one magic drug that would cure ALS. There may never be one individual drug which will provide the cure. So, is it not unrealistic for ALS patients to ask for treatment regimens or combinations of drugs or choices of drugs?

I understand a lot of patients wrote directly to the FDA. Some sent their letters to me to carry, and I brought a bag today of letters and signed petitions representing those thousands of ALS patients who were unable to attend this meeting. In these letters and petitions, these well-informed patients are asking you, the members of the advisory committee, to recommend the approval of Myotrophin.

The committee has already agreed that this drug is safe enough for you to unanimously vote for the approval of the Myotrophin expanded access program. You have also

seen the data supports that Myotrophin is effective in slowing the progression of the disease. This is very important to the ALS patients because this drug maintains their quality of life.

I ask you please to vote for the recommendation of approval of Myotrophin to allow ALS patients the opportunity to treatment choices. Thank you.

(Applause.)

DR. GILMAN: Shelby Oppenheimer?

MS. OPPENHEIMER: Distinguished panelists, thank you for allowing me to tell you my story. My name is Shelby Oppenheimer. I'm from New Hope, Pennsylvania, and I have no financial interests in Myotrophin.

For so long my life has been a fairy tale. As the daughter of Gloria and Jerry Wasserman and the sister of Brian Wasserman, I grew up in a loving and nurturing family, the kind of family that laughed together over supper. I've also been fortunate enough to have the same best friend since I was 3.

As I neared my college graduation, my family and I went to celebrate. There we were served by an old

high school friend and flame who was starting a business when he wasn't waiting tables. Jeff's presentation of the day's specials must have swept me off my feet because two years later we were married.

Two years after Jeff and I were married, that company he and a friend had started in their basement was now large enough to attract the attention of an even larger company. Soon after, they purchased his company and we relocated to Bucks County, Pennsylvania. The plan was to buy a house in the suburbs and start a family. Jeff and I decided that we had enough love to share with somewhere between four and six children.

But as we were about to embark on this beautiful and fulfilling life's mission, an old yiddish expression unfortunately became relevant to my story. Der Mensch traft und Gott laft. We plan and God laughs.

On the same day we discovered and put a deposit on our dream home, in the call we made to my parents to share this exciting news, we learned that my mother had been diagnosed with stage IV cancer. I sat at her bedside for weeks while she fought and lost a brief and brutal bout

with lung cancer.

As I watched my mother die, I thought nothing could be worse. Only now can I appreciate that through this horrible struggle, she knew that thousands of researchers and billions of dollars had beaten forms of her disease, were making progress on others, and because of this, she had hope that maybe, just maybe, she would be the beneficiary of all of these resources. Sadly that didn't happen for her, but that hope gave her comfort and kept her strong.

Since then I've learned that daughters don't ever fully recover from losing their mothers. I did not feel emotionally up to carrying and caring for a child just then, but soon, very soon.

And when I began to feel strong enough mentally, there was this matter of a pinched nerve that my family doctor had recommended I see a specialist for when we relocated in our new area. And from that moment, my discovery that I have amyotrophic lateral sclerosis is probably not much different from that of other patients. The terrifying, surreal process of elimination had left

only one devastating possibility. At age 28 I was diagnosed with a terminal illness.

Because of ALS, there are many things that will never happen. When I lost strength in my left arm, I could no longer pick up the children I loved so much when I was able to teach preschool. Many household tasks are too much for me now. Don't get me wrong. I don't miss doing the laundry, but I do miss the ability to do it.

Because of ALS, I may never have children of my own. However, Erin Brady Worsham is quite an inspiration. What I fear most is never hearing the words, "Mommy, I love you."

Although I devote myself to living each day for itself and not wasting them away consumed by what may be, somehow I can't help but worrying about which muscle will fail me next and how much longer I will be ambulatory. Instead of weekend plans, grocery lists, which preschool for my children, I can't help but be angry that I must think about slowly fading away physically and being completely aware of it mentally. I cry at the thought of not being able to tell my husband that I love him and I

weep at the thought of my father burying another child. It's not fair and I will do anything in my power to keep these things from coming true, and I've come here today to ask you to help me.

There's no single form of ALS, familial, sporadic, bulbar, limb onset. It's not surprising that treatments can affect patients differently. All I ask for is the choice, the option to see if Myotrophin will slow my progression and buy me valuable time. It seems every week new discoveries are made about Alzheimer's, Parkinson's, multiple sclerosis, ALS. Sunshine is finally finding its way past the veil. Each ray sheds new light on the darkness. Myotrophin is not a cure but it is hope, hope for me for more time, hope for more time to find a cure, hope that I will some day resume my fairy tale.

I'm tougher than I look and I'll do what it takes to win this and I'm asking you to do the same. Thank you.

(Applause.)

DR. GILMAN: Thank you.

Deborah Gelinas.

DR. GELINAS: My name is Dr. Deborah Gelinas, and I have been one of the principal investigators in the 1200 study. 45 of the patients whose data you've seen today have been my patients.

My allegiance, however, is not to Cephalon. My allegiance is to my patients. I have 250 to 300 of them per year. They're my age or they're younger now that I get older, and they have the same hopes and the same families and the same professions and the same dreams as I have.

I have very little to offer them. I offer them support. I offer them crutches. I offer them assistive devices. I uniformly offer them Rilutek and I am thrilled that I have that to offer them. And beyond that, I have little to offer.

My children come to visit at the clinic often, and they think I'm a psychiatrist. The reason why they think I'm a psychiatrist is because they see that I'm talking a lot and I'm constantly trying to reassure and give emotional support, and they don't see that I'm doing anything that they think of as real medicine.

I'm finding that in the field of ALS you just

can't stay distant. I'm finding that I become very intimately involved with my patients and I start to care for them very much. I'm finding that I go to their homes when they can no longer come to my clinic. I go to their funerals when they die. I visit with their families after they die. I write letters to their children and I write letters to their spouses and to their parents.

I think that this committee has heard a lot about the science of medicine. I don't think this committee has heard very much today about the art of medicine. I think that there's a lot we don't know in medicine. I think that there's a lot we don't know about treatment, a lot we don't know about chronic disease, and a lot we don't know about the need for patients to have hope and about the benefit that even modest treatments can bring.

I can tell you that my patients on Rilutek do better than my patients who cannot afford Rilutek, and I can tell you that I have patients who are on Myotrophin and that they're doing better than other patients.

I have one young man in particular who was my

very first patient who was enrolled in the Myotrophin study back in 1993. At that time he was in his early 20s. He was a policeman. He lived a very active life and he had a young girlfriend in with him. I didn't even want to like him because I knew he wasn't going to live long and I knew that the whole thing was just too heartbreaking.

I followed him for the nine months of the study and at the end of the study, I didn't need to see him as frequently. And, frankly, it was an emotional blessing because it was so painful to see this nice, young man and his nice fiancee, who became his wife, and she became pregnant and they had a baby and sent me the picture. As time progressed, I would have haunting thoughts of whatever happened to them but it was almost easier not to know.

Then he made a follow-up appointment because it was time for one more physical in order to get on a second extension trial of Myotrophin. I was dreading it and I was depressed because I knew he had a baby and I was afraid that he was just going to be at death's door and that it was going to be another loss.

He walked in to the appointment. He walked in.

He was still holding onto the baby's diaper bag, although had a hard time doing it. He was still talking, and he was still okay. He wasn't working anymore, but he was still functioning at a level that was sufficient for him.

I've seen him subsequently now many times, and it has now been over three years. The last time I saw him was about one month ago and his little boy is now a toddler and was running all over the place, destroying the office.

My patient told me that when he was first diagnosed, if someone had told him he was going to get to be like this, meaning that he was going to need his wife's hand on his belt in order to walk, and that he was going to have minimal use of is arms to the point where he really couldn't feed himself independently anymore, that he would not have wanted it. He would have preferred to die. And he said that just goes to show how stupid I was because I love my life. I love my family. I love my son. I love every single day. And I have to say that if Myotrophin can keep me like this longer, it's really, really okay. I can live like this. I like it like this.

I think that what you all have to remember here

is that you have a chance to make a vote which will give this opportunity to many more patients. I know how I would vote in your place. Thank you.

(Applause.)

DR. GILMAN: Thank you, Dr. Gelinas.

Ralph Kuncl, Dr. Kuncl?

DR. KUNCL: Good afternoon. My name is Ralph Kuncl. I'm a professor of neurology at Johns Hopkins School of Medicine and I have no financial interest in the sponsor today. I'm here completely on my own.

I've focused on ALS most of my career, and I was a contributor to some of the preclinical experiments you saw presented today. But I come wearing many hats. As a clinical trialist in ALS in six prior trials, I am convinced today by the wealth of corroborative data here. There are many functional outcomes within one trial indicating efficacy. This absolutely flies in the face of dozens of negative trials before.

I worry a little bit that the panel might be expecting too much perfection in a trial in this particular disease.

As a pharmacologist, I'm most convinced by the internal consistency, and this is especially clear to me in the dose responsiveness. This is far more convincing and overshadows any concern about bias. And I've certainly never seen a safer drug.

As a pathologist, I'm most convinced by the potent preclinical effect, especially in spinal cord slices showing very dramatic survival effects on motor neurons.

But as a treating neurologist, let me put my own face on this. A patient of mine, Solomon Nicholson, is a young and wonderfully creative computer scientist and programmer who invented strategic programs for government and industry worth many millions. He's had ALS for more than two years and now has very limited use of his hands. Nevertheless, he works about 15 hours per day coding in machine language by poking keys with a stick. He's losing function but he would gladly trade the lower half of his body for 15 or 20 Appel scale points. He cannot participate in any current experimental trial.

He asks me what is to be gained by living a few months longer by taking Rilutek if it does not change the

quality of his life. That question always gives me pause.

Would I like to treat him with Myotrophin? You bet I would. For that matter, would I like to treat any of you on the panel if you were my patient with ALS? I'm not a stock buyer, but I am a bet maker and I'd be willing to bet that 8 out of 9 of you would prefer treatment with Myotrophin.

Would I like to be involved in a phase IV combination trial? We all would and for that reason, I'd ask you to approve it today.

Thank you.

(Applause.)

DR. GILMAN: Thank you.

Benjamin Brooks?

DR. BROOKS: Thank you, Mr. Chairman. I'm Benjamin Brooks, Professor of Neurology and Chief of the Madison VA Medical Center in Madison, Wisconsin, and Director of the Muscular Dystrophy/ALS Clinic at the University of Wisconsin Hospital and Clinics.

Like Dr. Windebank and some of the others, we come from an area where ALS is slightly more common per

capita, and it's a big problem for us.

But I'd like us to think like Bill Cosby. When you look at a cup, if it's half full, is it half full whether you're filling it or whether you're emptying it? What I want the committee to consider today is in actuality the cup is three-quarters full. You have two studies which show that safety is okay, and one of two studies that shows efficacy is okay. As a practicing clinician treating ALS patients, that would be compelling data for us.

Now, the development of drugs in ALS is a fragile alliance between scientists, doctors, and patients. The scientists want to understand the pathogenesis like Ralph has presented and presented good data supporting the rationale for this. The doctors want to decrease morbidity and mortality, and we found evidence today that that is occurring. And patients want to laugh a little longer, write a little longer, eat a little longer, survive a little longer.

What we heard today -- I just want to crystalize it in your mind -- is that with respect to one study, there's a 26 percent difference compared to placebo

in slopes or from baseline. In a separate independent evaluation, the SIP, there was a 45 percent difference and no problems with respect to safety that we've heard about.

I think we have to go back to William Osler's counseling to us that the art of medicine is making a correct decision on inadequate evidence, and I would ask you to vote for approval.

(Applause.)

DR. GILMAN: Thank you, Dr. Brooks.

Dr. Jubelt?

DR. JUBELT: I'm Burk Jubelt, Professor and Chairman of Neurology at the State University of New York, Health Science Center in Syracuse, and I've been caring for ALS patients for approximately 20 years. I have no financial interest in Cephalon.

As a physician/scientist who has been involved in other than Myotrophin clinical trials for ALS and for other neuromuscular diseases, I've had the opportunity to independently review the evidence that's being presented to support the NDA for approval of Myotrophin in ALS.

Study 1200, the North American controlled

trial, clearly demonstrates a statistically significant effect of Myotrophin at a dose of .1 milligram per kilogram per day as compared to placebo on the rate of clinical disease progression measured by the rate change in the slope of the Appel ALS score which is a measure in the change of disease morbidity.

Thus, the effect of Myotrophin was not just a symptomatic effect, as has been suggested today, but an effect on the objective disease parameters as a measure of progression and morbidity, including strength and function of bulbar, respiratory, and peripheral muscles.

In addition, secondary efficacy variables also revealed statistically significant effect of Myotrophin at the .1 milligram per kilogram dose.

This is a robust effect. As several of you on the panel have pointed out, when you look at the diagrams, you noticed that there was a 3 or 4-month effect on disease progression during the 9-month trial. This is equal to the effect of riluzole on survival. You've heard from several others this is a robust effect in ALS and something that all of us are looking for to help our patients.

It is also clear that the positive effect of Myotrophin on ALS was dose-dependent because patients taking .05 milligram per kilogram per day had a slope that was intermediate between the placebo and the .1 milligram per kilogram per day dosage.

We should also keep in mind that riluzole, again the only approved drug for ALS, did not show a dose-dependent response. In that study, 100 milligram dosage was most effective while the 50 milligram and 200 milligram doses showed less of an effect.

Study 1202, the European study, did not reach statistical significance in the effect of Myotrophin. Post hoc analyses, however, reveal that the randomization was unbalanced and that for important risk factors for survival, which were age and forced vital capacity, that there was a significant effect when patients were stratified for those parameters. And this was by a logrank analysis. Of course, as you know, the FDA has not necessarily agreed with that value of .045.

The other thing I might point out, a couple of things about 1202 I think to keep in mind, is I think it's

pretty clear to me that the increased excess deaths were because patients with more severe disease were randomized to the Myotrophin arm of the study.

Another aspect that has not been discussed today and I know the company has not wanted to discuss it is that the patients were stratified for more rapidly progressive disease, and this was data that I think was given to you. When patients were stratified for more rapidly progressive disease, you could see a benefit of Myotrophin in the 1202 European study. And that was not discussed.

I want to point out one other information in terms of data that was not discussed today, and this was also data that was a part of a post hoc analysis. And that is that patients in the North American trial who were on placebo and then were subsequently switched to .1 milligram per kilogram per day of Myotrophin in the open label, after 9 months on Myotrophin, they showed a significant slowing of clinical disease progression at a p value of .001. I don't want to argue if it's .001 or .005. It was a significant change in the rate of their disease

progression.

Dr. Munsat has spent most of his life showing us that ALS patients tend to have the same rate of disease progression throughout their course. Yet, when these patients on placebo were switched to Myotrophin, there was a highly significant change in the rate of disease progression.

DR. GILMAN: Dr. Jubelt?

DR. JUBELT: Yes.

DR. GILMAN: We have not seen those data that you're now referring to.

DR. JUBELT: This is post hoc analysis data and I don't honestly know if it was presented to the FDA or not.

DR. GILMAN: That was not presented in our books. It was not analyzed by the FDA staff. So, these are new data that you are discussing at the moment.

DR. JUBELT: But this is in the report of the open label trial.

DR. HOBERMAN: These are Appel scores, are you saying?

DR. JUBELT: This is the change in slope of the ALS Appel score. Right.

DR. TEMPLE: This is the placebo group crossing over onto therapy, right, in the 1200 trial?

DR. HOBERMAN: Were we aware that Appel scores were taken for people who had endpointed the trial? After they failed in the trial, were Appel scores taken on these people?

DR. JUBELT: Yes. They were continued in the open label and Appel scores were taken, and they all had at least one point. Some had more than those.

DR. LEBER: Well, either that data is available for analysis or it's not. I think the persons who ought to have it, I assume, are the firm. Is there such an analysis that took those people who were leaving the study, looked at their slopes before they left and then looked at their slopes after they had it?

DR. TEMPLE: This is the same group that's in the extended survival analysis. So, we know they exist.

DR. LEBER: Yes, but he's saying the change in slope, pre and post, leaving the study.

DR. SCHARSCHMIDT: Maybe I can summarize what happened as the patients went to open label. This was not discussed today.

If you remember from the trial design patients entered into open label either at the end of the study or by early exiting. The slopes were examined in two regards. One, the entire slope extended into open label, which captured about 60 percent of patients equally distributed between the groups. There were differences among the groups. There was not statistical separation between the groups.

When we looked at now the much smaller number of patients, we had slopes prior to open label and then post open label, three Appel measurements after open label. So, it was possible to compare two slopes. The high dose group did not change in slope, and the slope of the placebo group decreased by about 10 percent.

DR. LEBER: Did it achieve a statistical significance of .001?

DR. SCHARSCHMIDT: No, it did not.

DR. LEBER: How about .005?

The discrepancy here is that maybe somebody did look at a subset of patients who had been on placebo who were then converted and given open Myotrophin. But you're providing p values. We won't argue about them, but we'd just like to know what the evidence is if they exist.

DR. JUBELT: Well, this is data that I've seen. In the data from the open label trial that the company has accumulated, that information is in there.

DR. LEBER: In where?

DR. JUBELT: In their information --

DR. LEBER: It's something they showed you but not us. That's the way it stands at the moment. It may be that we have it somewhere. It's always possible. There's a lot of paper, but we've never seen it.

DR. GILMAN: Well, if the company wishes to present those data, if they are relevant to this day's discussion, then we should see those data.

DR. DOBBINS: The data that are being mentioned were not part of the randomized experiment. They were simply Appel scores taken during the open label portion. They were submitted as part of the NDA under the 1200A

study report. So, they represent approximately 155 of the 266 patients total who had, for example, at least one Appel taken in open label.

DR. GILMAN: Thank you.

DR. JUBELT: In conclusion, I think taken together, the results of the clinical trials, along with extended survival and the slower progression with Myotrophin and effect on the course and morbidity of this severe disease, which is the agency's substantial evidence of effectiveness requirement, in my opinion has been met and Myotrophin should be approved for the treatment of ALS.

DR. GILMAN: Thank you, Dr. Jubelt.

(Applause.)

DR. GILMAN: Marianne McGettigan?

MS. BABISKY: Marianne could not be here today, and if time is a problem, we have her typed testimony that we could go ahead and put in the record. Is that all right?

DR. GILMAN: Yes, please do so. Thank you.

Abbey Meyers, our last person. Abbey Meyers?

MS. MEYERS: Thank you. I'll be very brief.

1 I'm Abbey Meyers, President of the National
2 Organization for Rare Disorders, which is known as NORD.
3 We do have an interest in the approval of this drug.
4 We run the lottery, the random selection
5 process, for giving away Myotrophin to ALS patients, and we
6 have a contract with Cephalon to do that.
7 I don't want to do it. If you approve this
8 drug, we won't have to do it. And that's the main point
9 that I want to make. It's awful to do a lottery. You
10 know, in Europe they don't even allow them. It's like
11 throwing out one life belt at a time. The agonizing cries
12 that we hear from patients whose names aren't selected.
13 And we have to make sure everything is randomized on a
14 computer and done without a heart. So, we can't give it to
15 the sickest patients or the poorest patients or the richest
16 or the most influential. It has to be totally done by a
17 computer. I hate doing it. I don't want to do it and I
18 don't want Cephalon to give us money to do it. I want the
19 drug to be in a corner drugstore so that every patient who
20 wants it can get it.
21 That's the point about making this whole

process be dragged out so much more by saying let's try another trial, let's wait another year or two. The patients who testified today are going to be dead in a year or two when you finally get around to reviewing this again.

I want to bring out one more point and that is that about a year, a year and a half ago, I remember being down here when you were reviewing Rilutek. We were so grateful when you voted yes and Rilutek got on the market, and we remain grateful today for Rilutek.

But Rilutek was basically approved on the efficacy evidence of one controlled trial. There were two trials but one didn't show efficacy in the United States, and the other one did show efficacy in Europe.

You approved betaseron also I believe on the efficacy from one trial for multiple sclerosis.

The other day I was reading about a drug called Rescriptor that you just approved for AIDS that looked like it was approved with no evidence of efficacy. The two trials did not show efficacy, and the committee in that case voted against that drug. Yet, FDA approved that drug.

These people here today are much more desperate

1 than patients with AIDS. People with AIDS have options.
2 They have a wide variety of treatments available to them
3 and their lives are being saved with a cocktail.
4 What the woman said before I think is the most
5 moving thing, that when her mother died of cancer, she went
6 to her grave with hope because she knew research was being
7 pursued and new treatments were being developed.
8 If you disapprove this drug, if you vote
9 against this drug, you're sending a terrible, terrible
10 message not just to the patients, but also I want you to
11 understand it will be to the pharmaceutical industry
12 because it will say to them in certain circumstances you
13 make exceptions. You made exceptions for the AIDS drug,
14 for betaseron, for these other drugs. You didn't make an
15 exception for this.
16 The evidence in that one trial shows efficacy.
17 You have to approve this and vote for approval.
18 Thank you.
19 (Applause.)
20 DR. GILMAN: Thank you, Ms. Meyers.
21 Have we heard from all people who want to

speak?

(No response.)

DR. GILMAN: If so, then we will get to our deliberations. The Food and Drug Administration has asked this panel to answer three questions.

I think I'd like just to start by saying this is a particularly difficult task today to serve on this panel. I personally care for patients with amyotrophic lateral sclerosis. I realize what a dreadful disease it is and I understand the hope that is in the hearts of the people who have spoken here today and others who cannot be here today.

Nevertheless, our task as a committee is to determine, on the basis of our own expertise with the data that have been presented, the answers to the questions to the best of our ability that have been posed by the Food and Drug Administration.

To move this process along then, I'd like to make some statements about each of these points and see whether the committee goes along. That may be one way to expedite this discussion. So, let me proceed.

Question number 1, does NDA 20-654 provide evidence from more than one adequate and well-controlled clinical investigation supporting the conclusion that Myotrophin is an effective treatment for ALS?

I believe the answer to that is no. There is one trial that has shown efficacy. The robustness of that we can deal with under question 2, but I believe the answer to that is no.

Let me see if my colleagues agree and if you wish to vote if there's some disagreement.

(No response.)

DR. GILMAN: In the absence of dissent, can I assume that that is unanimous? Dr. Temple?

DR. TEMPLE: I want to be sure you're explicit on what you think of 1202. I hear your bottom line but various thoughts have been presented on why it should be considered somewhat supportive. You need to be explicit on why you do or don't, or it will help us most if you're explicit on why you do or don't.

DR. GILMAN: All right. Study 1202 was unconvincing in showing a statistically beneficial effect.

1 The post hoc analyses that we heard about in some detail
2 previously were unconvincing for any sort of efficacy, and
3 I personally was not convinced that this trial showed any
4 evidence of efficacy.
5 Let me defer to my colleagues again and see if
6 there is agreement or disagreement.
7 (No response.)
8 DR. GILMAN: Did that answer your question, Dr.
9 Temple?
10 DR. TEMPLE: Yes.
11 DR. GILMAN: Item 2, if not, do the findings of
12 any single adequate and well-controlled clinical
13 investigation lend support to a conclusion that Myotrophin
14 is an effective treatment for amyotrophic lateral
15 sclerosis?
16 I find that to be a particularly difficult
17 question. If I could put it into words, I think that what
18 we have heard today is that we heard of a beneficial
19 effect. We've heard it described as robust by some,
20 marginal by others, and at a .055 level from the firm, .05
21 from the FDA analysts --

DR. HOBERMAN: .01 from the firm, .05 --

DR. GILMAN: Thank you. .01 from the firm, corrected to .055 from the FDA, and with the FDA's independent analysis, .05.

I would say that the data do not look robust. They look modest. That would be my own personal interpretation of those data, including the various permutations and combination subset analysis and so on. So, I see a modest effect.

Again, let me defer to the panel and see if you all agree with that conclusion.

(No response.)

DR. GILMAN: I see no dissent around the table. Dr. Kawas?

DR. KAWAS: I would just like to make the comment, a 25 percent change in rate of decline I consider perhaps more than modest, but in order to call this effect robust, I'd like to see it again or replicated. I think there are two issues with regards to the size of the effect, as well as can it be repeated, and both of those speak to the issue.

1 DR. GILMAN: Thank you. That gets to the next
2 point.
3 Dr. Drachman, go ahead.
4 DR. DRACHMAN: Really to enlarge on that, it's
5 not so much the modesty of the size, but the modesty of the
6 reliability. It appeared to be marginal. If this had been
7 an exceedingly positive study with only one month or only a
8 very small benefit, that would be phrased rather
9 differently. That is, it is the degree of certainty of
10 that study that I think is modest. Is that the sense of
11 your comment as well?
12 DR. GILMAN: That's a very nice amplification
13 and just about where I was going to go next. I will not go
14 there.
15 Any other comments from the panel about
16 question number 2? Dr. Temple, you have a question?
17 DR. TEMPLE: I have a question. Some of the
18 people who spoke and representatives of Cephalon and Chiron
19 adduced various reasons for thinking that this was a
20 powerful study, perhaps showed more than it seemed to. I
21 guess I'd like to hear some discussion of that.

The ones I remember are that you see an effect on two rather differently constructed measures of effect, the Sickness Impact and the Appel, that survival is sort of leaning at least in, as Dr. Leber pointed out, a sort of unfavorable environment because you crossed the people on placebo over to active drug, and that you should take it more seriously because of all this.

I'm not offering an opinion. I just hope you'll address that because the company put that forth as reasons.

I guess related to that is the idea that what's being observed is not a, if you like, mere symptomatic improvement but a fundamental effect on the disease process. I don't think the explanation of why one should think that has been very good, but I guess the explanation would be that something that operates the way this drug is supposed to doesn't affect symptoms and therefore must be affecting the underlying disease or maybe the animal data. Or whatever the reason, that's sort of offered by a number of people as a reason to believe more, and I'd be interested in comments on that question.

DR. GILMAN: Well, I don't think that we can comment on that because we're here to evaluate clinical studies. We have heard hypotheses about how this agent may work. The basic data are very interesting. In fact, they're quite fascinating, but they do not prove or disprove an effect in the patient populations that we've observed that we've heard about. So, I'm not sure that we can say anything about mechanism or lack of mechanism from the information presented, only that we have heard potential mechanisms and interesting animal data.

DR. TEMPLE: Okay. That's important. The reason I pressed the point is that if one were to believe that you were seeing an effect on the underlying process or on real irreversible morbidity, we have been known to say we have a somewhat different attitude toward the data in that setting. How different it should be I leave to discussion.

But the distinction between the symptomatic improvement and what might be or is or is plausibly an effect on disease could be important. You may just feel there's nothing you can say about that, in which case I

take your word for it.

DR. GILMAN: You will recall that we asked the question -- members of the panel wanted to know whether there had been examination of people with amyotrophic lateral sclerosis who had been treated with drug to see whether the spinal cord had been examined, electromyographic examination of muscle, action potential. Is there any other marker? And none has been done as yet.

Accordingly, all we can do is cite the animal studies and say they are very interesting and possibly relevant. We cannot connect the animal studies with the clinical studies at this point in the absence of further data.

Dr. Leber?

DR. LEBER: I want to clarify and expand on something Dr. Temple is just raising because I believe this is the central point repetitively made. The AALS score itself is a measure directly -- although it measures muscle strength and other things, is in some way measuring progression in the illness. You see, that's what people are implying.

We want to know whether you believe it. Actually there are different standards of how one would attempt or different strategies to finding out whether a drug had a lasting effect on the course of an illness. In dementia we've talked about re-randomization designs and withdrawal designs. But here you have an allegation, an assertion, that the measure itself directly tells you that the disease is progressing and that you slow progression because you slow the score change. I think you need to discuss that.

To throw out a seed to the discussion, for example, in Parkinson's disease because you slow the progression of symptoms, have you slowed the course of the illness would be the parallel. What do you think of symptomatic muscle strength as a sign of the underlying disease process in this disease? Do you have any hunches about it? Do you think it's credible? Where do you come out?

DR. GILMAN: Well, let me try an answer to that and then I can defer to my colleagues.

The Appel score, as I understand it, measures

muscle strength by a clinician relative to bulbar function, upper limb, lower limb, and so on, various muscle groups that are known to be affected in ALS. They do nothing more or less than tell us the motor pool size that's available to carry out a muscle contraction. That motor pool size could be influenced by a number of phenomena and any change in it from a drug does not necessarily imply that the basic disease itself has been altered by the drug. There are many other possible explanations for that.

DR. LEBER: Well, if you really believe that the 1 to 1 correlation between the AALS score and the muscle -- underlying the muscle volume or the innervation or whatever --

DR. GILMAN: Oh, I didn't say that.

DR. LEBER: -- there is an anatomical correlate. The thing you have to argue is that when we say symptomatic, that although the AALS score is a nice surrogate for the natural disease and tracks very well with the state of the underlying neuropathology, that in the presence of a treatment, it may no longer do that. It may in fact improve performance at a given level of muscle mass

loss that displaces you from what you would have been without the drug. That would be a symptomatic effect. Take the drug away, it goes away.

We may not have done those tests, but I want to draw that distinction out. It depends on the tightness of the linkage between the two. Do you think it occurs in the natural illness? Do you think it occurs -- change the AALS, have you changed the course of illness?

DR. GILMAN: I would not make a linear relationship between the number of motor neurons responsive at any point in time in response to a test like the test for the Appel score because of changes in the subliminal fringe, for example. If a person is particularly excited, energetic, enthusiastic, whatever, grits his or her teeth while carrying out a task, the strength may be better at that point in time, as Sherrington showed a century ago. It's possible to enlarge or contract the size of the subliminal fringe and therefore have an active motor neuron pool that's bigger or smaller at any point in time. So, I don't think one can say it's linear.

DR. LEBER: So, the question we're really

1 getting at then is it is conceivable that the changes
2 observed on the AALS score in study 1200 could reflect
3 something like that in the presence of Myotrophin and not
4 have to be an underlying neuroanatomical change. That's
5 the critical question. I mean, doubt is good enough.
6 DR. GILMAN: Yes, again, what you're seeing is
7 the active motor neuron pool. If the person makes a
8 maximal contraction of the biceps muscle, you can see by
9 measuring force a rough estimate of the size of the motor
10 neuron pool at that point in time. That motor neuron pool
11 may be influenced by dead neurons or by other activities
12 going on within the nervous system, the level of
13 neurotransmitter, et cetera, et cetera, the amount of
14 inhibition that's coming in. So, there are many factors to
15 be taken into account there.
16 Dr. Temple, then Dr. Gennings.
17 DR. TEMPLE: I just want to press this point a
18 little bit. In cardiac muscle there are inotropic agents,
19 things that don't improve the state of the muscle but make
20 it contract better. One can imagine I suppose something
21 for skeletal muscle. Maybe an amphetamine would do that or

something like that.

This stuff, Myotrophin, is as far as we know, pharmacologically inert with respect to those kinds of things, although maybe there's something I don't know about.

So, one of the things one might consider is whether something with these pharmacologic activities plausibly have an effect on muscle of the kind you're talking about, recruitment or something like that, or whether one needs to consider that if you see a difference, it isn't plausibly due to some other pharmacologic effect.

I'm pressing it and I want to say I'm not offering an opinion. I'm trying to elicit yours.

DR. GILMAN: We're involved in some theoretical discussion here. I'm not sure that we have any direct data to bring to bear here. Could the drug have an effect directly upon muscle? It doesn't seem likely, but I suppose that's possible, yes.

DR. LEBER: We're also interested, Sid, I think in your conclusions, all of your conclusions. If you say you can't know, that's as good an answer than saying you

have. There are experimental methods to get at that.

DR. GILMAN: Yes.

DR. LEBER: And we've talked about withdrawal designs and re-randomization designs and random start designs that might address that question. We haven't done that here, so we're not doing it experimentally. To some extent, it has been launched by other people who said this is an effect on the course of illness. I guess we want your opinion about whether that's simply hope or whether it's a credible hypothesis or whether you can't tell from what we know. That might be a reasonable answer.

DR. GILMAN: Well, my own position is that you can't really know with certainty. You're measuring the sizes of motor neuron pools which will be influenced by a number of things besides the number of cells that have fallen out. Therefore, you're not necessarily seeing a direct surrogate of disease progression. You're seeing something related to it, but how direct is it is not clear.

Let me see if my colleagues agree or disagree. Dr. Coyle?

DR. COYLE: If I hear what you were asking, I

do not think there is enough data here to say that the drug acts on the natural history of the disease. There's simply not enough data. It may but the data is not there.

MS. PHILLIPS: But the point I was going to ask is this whole discussion is based on the attempt to try to gain more evidence from a study that could still be considered a well-controlled, adequate trial on its own, but you're trying to add information to that or add strength to that --

DR. LEBER: I think you may misunderstand another point that was made earlier about the role of concentration. What I'm asking is about the observed treatment effect. You can have an effect like, say, in analgesia where you don't treat the underlying disturbance but you do relieve the symptom. For example, muscle bulk, muscle mass, innervation could be lost but you could have a way of increasing the residual pool to function in a normal way.

Classic example, Parkinson's disease. You know you're losing neurological substrate all throughout it, but by providing a precursor, for a while at least, you can

1 make up for the functional deficit by providing something.
2 You don't have a structural effect. You have a symptomatic
3 effect.
4 Is it conceivable that something akin to that
5 is happening here because if it is, we look at the results
6 of this single trial differently than we will if we thought
7 it really measured directly. As in the betaseron trial,
8 remember the CT-scans -- not the CT-scans --the MRIs showed
9 something that made people think they were looking at
10 structure not just at a functional change in terms of some
11 symptom. So, there is an important regulatory reason for
12 getting at this, as Dr. Temple was getting at.
13 DR. GILMAN: Moreover, there is a very high,
14 robust change with an objective measure when one measured
15 areas of MR scan lesions.
16 DR. LEBER: That was the betaseron.
17 DR. GILMAN: In the betaseron trial.
18 Dr. Drachman?
19 DR. DRACHMAN: Well, I clearly have no way of
20 beginning to judge those questions based on the data we
21 saw.

What I really thought I would say is something that's a little off that question, if I may. That is, for me this has been -- I guess I would use the word "disappointing" presentation. The reason that I would say that is that we find ourselves faced with a terrible disease, one that we deal with that we regard as requiring a treatment, where we are as anxious as nearly everyone who is not afflicted in the audience to find the right treatment. We said this last June. My sense is that we have seen cosmetic changes in the data, nothing substantial, and that's what's so upsetting.

Months have gone by. No further studies have been done that are really fundamental. A little bit of intimation regarding the relation of the blood levels to the effectiveness, which fundamentally are mere echoes of what we've already seen in 1200.

1202, with post hoc analyses of every sort that would adjust for all of the reasons that anyone has been able to think of why it failed, still has not been able to be brought into a realm where it appears to be effective by virtually any of these studies that have been done or re-

1 analyses that have been done.

2 So, we find ourselves fundamentally in my view

3 where we were last June when we said we wanted more or

4 better data.

5 The disappointment is that rather than going

6 about obtaining such data, which we expected, we hear that

7 there have been re-analyses of the old data, that the

8 Japanese studies that we had hoped by now would give us

9 some important data are now regarded, without having been

10 analyzed, as not having the power to help us for reasons

11 that I hear, but small trials. These things are obvious to

12 single patients. Then I'm not clear why scientists or

13 physicians who have been reasonably instructed would not

14 come up with these data.

15 So, my concern is that I feel rather as if I am

16 just where I was months ago. Now, I know we're supposed to

17 look at it with a fresh eye, which I've tried my very best

18 to do. As we have done this, I have not yet heard anything

19 different.

20 What I heard then was that this is a promising

21 drug with a single trial that was positive, another trial

that was negative, and that's what I've heard again. So, I'm not sure how I'm supposed to change my judgment. I wonder if someone could advise me how I should begin to look at these data. When I asked before for what was new, I didn't hear very much. So, again failing more data, failing an energetic reexamination with new patients, failing the ability to re-analyze the 1202 in a positive way, I'm just sort of stuck. I feel unfortunately squeezed because I would love to be in a position where I would say you showed me something really exciting.

DR. GILMAN: Well, the firm did show extended survival experience. That was what was new, but I must say my own view of that was that it was marginally convincing at best, for all the reasons that we heard today.

They also studied the impact of established risk factors on mortality, but we didn't see much that was highly significant or important in that review.

And then we heard data about the PK/PD material, the models that showed correlations for 1200 but not for 1202 which was puzzling at best. It was not helpful in the case. It explained post hoc the findings

with 1200, which we already thought was significant, if marginally significant, but it didn't help us understand 1202. So, I found that to be not very helpful.

So, Dr. Drachman, I'm tending to agree with your position, but I have to give the firm the benefit of the statement at least that they have presented three new pieces of information for us.

DR. DRACHMAN: Three new analyses and a little more data.

DR. GILMAN: Yes.

DR. DRACHMAN: Extended, yes.

DR. GILMAN: Yes, the extended data.

Dr. Zivin?

DR. ZIVIN: Getting on to a slightly different point here, I am strongly in favor of approving drugs on the basis of one trial if the data are convincing. As a matter of fact, I think it's unethical to continue a trial or start a new one if the data are already available that proves that a drug is effective.

Having said that, I can't look at only the one trial without paying any attention to the rest of the data,

and the problem here is that the rest of the data suggests that the one trial that was positive was marginally effective. The other trial showed that it wasn't. The fact is that when you put together two trials like that, it's not a shock that on average it didn't work very well.

Maybe, based on the information that has become available, we can redesign a study that points to a better way of testing the drug. I think under those circumstances, it's likely that we'll find a better way to use the drug and then have no problem approving it.

DR. GILMAN: Ellen Phillips?

MS. PHILLIPS: I would just like to answer Dr. Drachman. I think if there was something exciting and marvelous, we probably wouldn't have been convened today.

I am the consumer representative. It's no shock to all of you that I work closely with ALS patients and am very strongly in favor of drugs that can help ALS patients.

I think that if something is marginal, if something is modest, it is still more than nothing, and that is the situation that we're faced with today. I think

that's what you have to look at, not is something exciting, but do you have something that will make a difference.

(Applause.)

DR. GILMAN: Dr. Khachaturian?

DR. KHACHATURIAN: I'd like to split the difference between the marginal and exciting results. The reason I'd like to split the difference is that, yes, speaking strictly statistically, the results are very modest from the study. But the problem that hasn't been addressed is the likelihood that we're dealing with a heterogeneous disease, that there are subpopulations on which the drug works quite well and that because of that, it's getting washed out. Some of the individual data we saw seems to indicate that kind of trend.

So, I'd like to see the study be done in a way where it could be done more carefully and expanded to look for those kinds of effects. Obviously it's doing something. We don't know what the effects are. It seems to be delaying the progression by as much as three months or so. That's an effect. We need to really work that out, find a way in which that can be useful for some segment of

1 the patient population.

2 DR. GILMAN: Well, you said, "Obviously it's

3 doing something." That's really why we're here, to see

4 whether it is obviously doing something.

5 Clearly 1200 showed significant results.

6 DR. KHACHATURIAN: That's what I'm talking

7 about.

8 DR. GILMAN: I agree. 1202 did not, and it's a

9 vexing situation we're in now. Had we looked at only 1200,

10 we might be in a very different position today. But the

11 fact that we had two well-controlled trials with placebo

12 creates a serious problem for us.

13 Well, at this point, shall we go on? We're up

14 to -- yes.

15 DR. BALDINO: Mr. Chairman, I'd like to clarify

16 some of the points perhaps Dr. Drachman was touching on

17 because I think it bears some answers, if that's okay with

18 you.

19 Specifically relating to additional clinical

20 studies and I guess the rhetorical question is what have we

21 been doing for the last nine months. Just for the record

-- and I think you really need to know this -- we are absolutely committed to doing additional studies in this disease provided we get approved.

The reason we put it that way and the reason why I want to mention this to you is that developing a clinical protocol for this disease takes time. We've been working diligently with the leadership in this field trying to come up with a design that makes sense. We have such a design. It has been down at the agency. We submitted it in the last 30 days or so or 35 days. I forget exactly the time. It was nine months of effort to get this clinical protocol designed and ready to go.

The other factor that bears on our decision here is that this is not Alzheimer's disease, depression, or schizophrenia, and it's not a small decision to put the kinds of dollars to work in this disease that we have put to work to date. We have put over $180 million to work in ALS. That's probably more than anybody in this country has put to work. And the results of it were one significant study and, from the ALS experts we've heard here who actually treat the disease, it is the only significant

study ever developed in this illness.

Now, we understand Dr. Leber's point about the rigors associated with clinical methodology, and we live by those rigors. We're scientists as well.

The problem is when you're dealing with the economic issues associated with a disease like ALS, it's extremely difficult to justify further investment, and it's almost impossible for us to idly throw $20 million or $30 million at another study to try something new. A combination study has a completely different hypothesis. It tests whether or not the drugs synergize. It will never address directly whether Myotrophin has an effect. So, if we were to come back with a study showing that it synergized, it would have no bearing on the confirmation of the protocol 1200. So, we thought it would be a little prudent to be very careful about what we do here before we go forward.

So, I didn't want the panel to think that we have been sitting idly by doing nothing. We've been diligent. We've been focused, and we've got a protocol that we think advances this field.

1 DR. GILMAN: Our job here today is to determine
2 whether the studies that have been done to date show us
3 convincingly that there is an effective treatment in this
4 agent for amyotrophic lateral sclerosis. This panel cannot
5 take into account whether you do or do not carry on a third
6 trial. That is up to you to decide. We are here to advise
7 the FDA about these trials that have been done, given our
8 own expertise, our having read the material multiple times,
9 and having heard it today.
10 Dr. Temple?
11 DR. TEMPLE: I just want to be sure of one
12 thing. We've said in the evidence document that we passed
13 to you and we've said many times in the past that we'd
14 consider evidence that Myotrophin added a muscle function
15 improvement to people who were already on riluzole as the
16 kind of evidence that would clearly support a trial of
17 monotherapy. So, let there be no doubt about that. I'm
18 sure we said it years ago.
19 I'm sure it's true that there are risks in
20 carrying out further studies, but that kind of trial, if
21 successful, would unequivocally support approval in our

view.

DR. LEBER: And I think we use it in epilepsy all the time. We do that on designs. So, we don't have to call it an additive trial. There is a risk and that is if you do such a study and you do the full -- not the full factorial with the three components, that you may show an effect with Rilutek but not show an effect with Myotrophin. So, it could be a double-edged sword and I could see why someone might not want to conduct a study under circumstances where it may be more difficult to show an effect in that sense. And there are considerations for not considering that.

DR. GILMAN: Again, our job tonight is to ensure that we have done our task here, that we have advised you about the studies that have been done, irrespective of whether you decide to go ahead with a Rilutek and Myotrophin trial. So, I'd like to get focused back on that issue.

Dr. Gennings?

DR. GENNINGS: I agree with what you're saying but I'm still concerned about the study that that you all

are talking about. I think a combination study needs to be done, but if it's approved today, whether or not a placebo group could be included in such a trial, patients may not want to be randomized potentially to placebo.

DR. TEMPLE: You don't need a placebo in a study like that, although it could be informative if you could do it. If the combination is better, just to put it in what would be a favorable outcome, than Rilutek alone, that unequivocally shows a contribution from Myotrophin. You don't heed a placebo.

DR. GENNINGS: Which could be a more difficult thing to show, and I guess that's what you're saying.

DR. TEMPLE: Well, it's more difficult but on these functions, Rilutek hasn't done anything. So, we don't know how much more difficult.

DR. LEBER: To say the evidence is missing doesn't mean it hasn't been -- I mean, it didn't, from what we know so far, do anything. It has had an effect on two trials, contrary to what was told you, on survival.

Now, one other thing. This business about whether placebo can be included, obviously is a matter of

1 judgment because the Japanese trial which is still
2 recruiting patients that last I heard is randomizing
3 patients to placebo. Evidently the Japanese physicians
4 involved must know the results of studies 1200 and 1202.
5 We've had this kind of problem in the past
6 where some people are adamant they won't do a placebo-
7 controlled trial in an antidepressant, and yet half a city
8 away or in the same city in a different IRB they will.
9 I'm not saying that if you are absolutely
10 convinced that you would have any ethical basis, convinced
11 this is an effective therapy, to do a trial with placebo.
12 But if you still had equipoise, doubt, you are totally free
13 to do it and that's one of the problems with these kind of
14 ethical arguments about placebo.
15 DR. TEMPLE: But in any case you wouldn't need
16 that for this trial to be interpretable.
17 DR. GILMAN: All right. Can we move along
18 then?
19 Let me get back to item 2. The question is, if
20 not -- that is, if we don't have two trials that show
21 effect -- do the findings of any single adequate and well-

controlled clinical investigation lend support to a conclusion that Myotrophin is an effective treatment for ALS?

Well, again, the data show that it is marginal at best and the question of effective becomes an important word. My inclination is to say, no, it does not.

Let me ask what my colleagues think.

DR. DRACHMAN: What about the expression "lend support"? What does that mean?

DR. LEBER: It was done two-stage. Look, maybe I can explain it because basically this group of us wrote the questions.

The first question, is the ordinary standard met? Are there two studies that would allow us to conclude there's substantial evidence? It's a token question that enters you into the question. Ordinarily you would expect two sources of evidence, and you could be in the state where one trial provided one leg for the table that requires two to stand.

So, the second level of the question is, if this were being considered in an ordinary context, would

1 you accept this as one source of support for approving a
2 drug? And I think that's one level of evidence.
3 And then there's the level of evidence -- and
4 Dr. Temple can confirm or reject this view -- that the
5 results of a single study are so impressive, so strong and
6 demonstrate an important effect in a deadly disease that
7 lacks an effective treatment that you are compelled to act
8 upon it or want to act upon it. "Compelled" is too strong
9 a word. And that's the third level.
10 So, we're asking you to place this positive
11 study along the dimension of negative, supportive in the
12 sense of an ordinary approval level of evidence, or so
13 overwhelming on face that it would meet the evidence
14 documents', proposed documents, conditions for considering
15 one trial. And we've said in the past we've used this kind
16 of thing with a dramatic effect. Dr. Temple can speak to
17 those specific examples better than I.
18 DR. TEMPLE: Well, the document that we
19 provided provides examples that are persuasive on their
20 own. They mostly involve mortality, although not all, and
21 they mostly involve studies in which the statistical values

are very extreme. But it's worth pointing out that in the case of betaseron, a single study was considered persuasive at least in part because it looked at two totally independent measures. I want to absolutely distinguish between two measures that you think are measuring the same thing like the Appel and the SIP, although measured in quite different ways. So, that's a different question. In this case it was MRI and recurrence rates or relapse rates which were thought to be -- you could argue this I suppose -- really completely independent things where you wouldn't worry particularly that randomization would have given you extreme views in other cases. Anyway, that's probably the main case of that I can think of that didn't involve mortality.

But conceptually we've said that a very persuasive study on a very important endpoint, generally referring to mortality or irreversible morbidity, is the sort of thing that we're obliged to treat somewhat differently.

DR. LEBER: Can I elaborate on one thing Bob said? And some of you were at the meeting on the approval

of betaseron. I recall many people looking at the evidence from the subset of Paty's study that had looked at the MRIs were convinced that they might as well have had the brains in their hands, examining the tissue and seeing an effect on the neuroanatomical, pathophysiologic events that account for the course in MS. That is, it made total sense, given that these enhancing lesions and other lesions, lesion volume, were accounting for the course. It isn't just an exacerbation rate that changes perhaps by chance, but the people who were making the decision were persuaded that they were looking at an effect on the irreversible morbidity, that this disease had to progress by the function of the time and space location of these enhancing lesions. They could have been wrong, but this is what I think drove that. And so, they were convinced they had an effect that couldn't be explained by anything other than an effect on the basic, fundamental pathogenesis of the illness. And I think that made it very persuasive.

I think the minute you talk about phenomena or symptoms, you're never really sure exactly how you're producing them. It is still possible, if you're not

1 looking at enhancing lesions -- and I'm not suggesting this
2 is going on here -- that a breaking of the blind unknown to
3 all of us, for reasons that we don't understand, could have
4 amassed activity. Now, I'm not saying it's a probable
5 explanation to account for. So, you're less certain about
6 the power of the result.
7 That's why I -- and I wasn't happy necessarily
8 personally about the betaseron decision in terms of an
9 epistemological standard, but I can understand it because I
10 think the outcome variable, at least what was looked at if
11 we interpreted the MRIs correctly, really seemed to capture
12 something that was real.
13 Now, one of things we were trying to ask you
14 is, do you think this is equivalent? Do you think that the
15 Appel score has any measure of that kind of strength of an
16 outcome measure? That's what we were getting at earlier.
17 DR. GILMAN: Are you trying to relate the Appel
18 score to looking at MR scans?
19 DR. TEMPLE: Do you feel similarly about it I
20 think is what we're asking.
21 DR. LEBER: The idea would be that you can draw

1 some inference about the underlying state of the
2 neuroanatomical process that's causing the degenerative
3 disease, maybe not causing it but is involved in its
4 degenerative process, as distinct from something which may
5 be more superficial in its action. Therefore, if it could
6 be more superficial, it need not be an effect in the way --
7 DR. TEMPLE: But we in fact asked you that
8 before and I think you gave your answer to that.
9 DR. GILMAN: Yes. The answer was no.
10 DR. LEBER: But it ties to this central
11 question of how important the study may be because it would
12 include certainly consideration of its outcome. What are
13 you affecting? If you had a big, robust effect on
14 mortality, those are the ones that Bob has discussed are
15 examples where we have acted on a single study.
16 DR. TEMPLE: The other thing is to some extent
17 how powerful it is as a matter of judgment. You've had
18 people who are well-known neurologists stand and say I
19 think we're looking at a fundamental change in the disease
20 here. So, there are elements of judgment in this and we
21 ask you for your judgment on whether there's something

about this study that is sufficiently persuasive that would want to make you recommend on the basis of a single trial that we should approve the drug. There is some judgment involved in that.

DR. GILMAN: Testimony is not a very good substitute for data showing directly an effect upon the motor neurons themselves.

Dr. Coyle?

DR. COYLE: The real problem for me is you have a second study that says, hey, it doesn't work, and there's no good explanation for a well-designed study as to why that failed except the possibility that maybe this drug doesn't work. That's the problem I have.

DR. LEBER: Well, in fairness, there is an explanation. If a drug has a relatively small effect compared to the variability extant, it is possible for you to have great difficulty replicating it, and we shouldn't kid anyone about that. That is always possible. But the problem is, if you find two studies that by design structure look pretty much the same, how do you pick between them?

1 So, nobody on the FDA side has ever said that
2 we have reached a definitive conclusion about this drug not
3 working. What we are asking you is the level of evidence
4 that would support a conclusion that it is working. It's a
5 very different kind of question.
6 The second level of question, to clarify once
7 again, was the question, in the ordinary set of things,
8 does it lend support. If this were part of several studies
9 and the others were showing toward support for approval,
10 would this study contribute? I think the answer is, yes,
11 you've all said it would. The question is does it reach
12 the higher standard.
13 DR. GILMAN: It contributes. Yes, there is a
14 significant effect. I will revise what I said before.
15 Yes, it does have marginal beneficial effects. It is
16 statistically significant. It depends on which set of data
17 you want to accept, but I think that it's reasonable to
18 say, yes, it does support -- lends support, yes.
19 Let me see if the panel agrees with that
20 assertion then.
21 DR. COYLE: Yes.

1 DR. LEBER: In short, if you had another one
2 just like it, you'd approve the drug.
3 DR. GILMAN: Yes, it's likely. Very likely.
4 In my own case, yes, definitely.
5 DR. LEBER: You would recommend approval.
6 DR. GILMAN: Yes, we would recommend.
7 Dr. Khachaturian?
8 DR. KHACHATURIAN: What are the choices we
9 have? What are the consequences of the decisions that we
10 make? If we say this is out, what other treatments are in
11 the pipeline? What other things are likely to come? What
12 would be the consequence of that decision versus this
13 decision of let's approve it, let it go? What's the
14 consequence of that? What are the benefits and the risks
15 to society?
16 (Applause.)
17 DR. TEMPLE: I have to say you're here because
18 you're technical experts on neurology and with other
19 technical expertise. It's not that those questions are
20 trivial, but we're really asking you about the data and the
21 evidence and what you think. I think we've tried to convey

that there's fairly substantial flexibility and judgment involved, but I don't think you can tell us other things. There's a law. There are rules, and while we interpret them flexibly, as I feel fairly sure we've tried to indicate, there still is a law and rules, and wishing isn't enough. So, it's not that those are not relevant considerations, but we haven't brought before you a list of other INDs. We could do that sometime in closed session, but that's really a different kind of question.

DR. GILMAN: We're here actually to advise. information that we have at hand.

Dr. Coyle?

DR. COYLE: If this drug doesn't work and we say that it does work and it doesn't work, then that's a disservice. My problem is I'm not convinced from this data really that it works. So, it would be wrong in my opinion and a disservice to give it a stamp of approval and say approve it as working. I don't think we can do that.

DR. GILMAN: All right. We're up to question 3, yes. If so -- and we have said yes to item 2 -- can the committee, on the strength of the evidence provided in this

1 single study and taking into account the failure of the
2 only other completed adequate and well-controlled clinical
3 investigation to confirm its findings, conclude that there
4 is substantial evidence that Myotrophin is effective in the
5 treatment of ALS?
6 Again, we come to the word "effective," and
7 again we come to the problem that 1200 showed a modest but
8 significant effect and 1202 showed no effect.
9 My inclination is to say, no, I don't think the
10 strength is adequate myself. I think I would have to ask
11 my panel colleagues what their thoughts are about this.
12 DR. TEMPLE: We would, if possible, everybody
13 on the record on this one in either a vote or its
14 functional equivalent.
15 DR. GILMAN: Well, perhaps we should go around
16 the table, as you wish. Dr. Drachman?
17 DR. DRACHMAN: No.
18 DR. ADAMS: I think the problem is the word
19 "substantial." There's evidence but is it substantial? I
20 don't think so.
21 MS. PHILLIPS: How important is that word

"substantial" to this discussion?

DR. ADAMS: Critical.

DR. GILMAN: It's critical. We have to say that this is a drug that we as a committee can say in good conscience is clearly going to be beneficial to people. I'd love to be able to do that. I think all of us would love to be able to do that if the data were here with us. The data are just not here to convince at least three of us so far.

Dr. Kawas?

DR. KAWAS: I essentially agree. I think that there's considerable evidence that Myotrophin is safe for ALS patients. I think that there is evidence in one study that it is effective in the treatment, but that does not qualify as substantial to my mind which requires another level of convincing.

DR. GILMAN: Dr. Coyle?

DR. COYLE: In my opinion, there is not substantial evidence here.

DR. GILMAN: Dr. Zivin had to leave, but he left me his vote and he felt there's insufficient evidence.

In other words, no to question 3.

Dr. Gennings?

DR. GENNINGS: This is a very tough thing for me to do. I'm not a neurologist. I'm a biostatistician. So, I am at the disadvantage of not understanding a lot of the biological discussions.

But I also agree with the physician that stood up and said that sometimes we have to understand the art of medicine a little better. I do think that the ALS community -- maybe they don't want as strong of a standard as maybe we would otherwise hold. I know that goes against what the FDA wants to hear, but it's hard for me to be dispassionate about this.

I don't think it's strong evidence. I think there is one study that has a reasonable show of efficacy. The other did not, but maybe that's good enough. That's where I'm standing.

DR. GILMAN: So, your answer is yes to item 3.

DR. GENNINGS: Yes.

DR. TEMPLE: And I have to say you don't know what we want to hear. You certainly don't know what I want

to hear. You know Dr. Feeney's opinion because he presented it candidly, but you don't know what the agency wants to hear. You really don't.

DR. GILMAN: We're not here to second guess what the agency wants or does not want actually. We are here as a dispassionate panel. Based upon the data that have been presented and our own experience, whether it is in biostatistics or neurology or both, we're here to evaluate the data.

DR. GENNINGS: I guess my point is that sometimes I think there's a need for flexibility and statistics can be cold and hard sometimes. What makes .05 such a big deal? It's just history. Maybe in the ALS community we should be using .1. I don't want to rewrite all the regulations that the FDA uses. That's what I mean to say maybe the FDA doesn't want to hear that, but I think this very possibly could be a --

DR. LEBER: FDA wants to hear what you believe in your heart and what you conclude with your mind. I don't think we are here to tell you what to think. You're here because we value your opinion. Tell us what it is.

Don't apologize. I mean, really. My moralization of you in this case is if you believe in your heart -- forget what everyone else says -- you tell us what you believe on this data.

DR. GENNINGS: Well, I'm saying I think this should be a special case.

DR. LEBER: And you want to approve the drug.

DR. GENNINGS: Yes.

DR. LEBER: Okay.

(Applause.)

DR. GILMAN: Ms. Phillips?

MS. PHILLIPS: I think the ALS community deserves this drug, and I vote for approval.

(Applause.)

DR. KHACHATURIAN: I think that for the total subject population, the effects are very weak, but for some of the patients, it seems to work. I think we treat individuals not populations. So, I think it should be approved.

(Applause.)

DR. GILMAN: Does the FDA want any further

1 discussion from the committee?

2 DR. LEBER: I don't know. Bob, do you?

3 DR. GILMAN: Dr. Temple?

4 DR. TEMPLE: No. I do have some curiosity?

5 How can one know when you have results in a large trial

6 that, for example, overall show nothing in study 1202 --

7 how are you able to deduce the effects in an individual?

8 If one could know that, clinical development would be very

9 easy. How did you reach that?

10 DR. KHACHATURIAN: Well, I know from other

11 diseases that diseases are heterogeneous, that it works in

12 some subpopulations because of genetic variability, other

13 factors. I think in such clinical trials, there are always

14 pockets of individuals that the drugs work. I think the

15 burden is to tease those out to find out which

16 subpopulation it works and approve it on that basis.

17 DR. TEMPLE: But granting that, are you saying

18 that you feel that such a group has been identified?

19 DR. KHACHATURIAN: There seemed to be evidence.

20 I saw some trends that there might be some subgroups that

21 might be benefiting. When you looked at individual groups,

there seemed to be tremendous differences in the responses to placebo and to the drug.

DR. LEBER: I think from our perspective on this side of the table, we thank you. We know this is an extremely difficult and vexing issue, and I just want to repeat once again that if there were a way, we would want to see a treatment approved if we thought it was safe and effective for use. So, that's not the issue of our wants, but it's our mandate under the law to behave in a given way.

Bob, do you have anything that you want to add?

DR. TEMPLE: No. For various reasons clearly illustrated by the people who came forward and spoke, which we greatly appreciate, this is very hard and the committee has labored long. I don't envy your position in having to give us advice any more than I envy our position in having to make use of it. Thank you.

DR. GILMAN: Then we are adjourned. Thank you, all.

(Whereupon, at 6:42 p.m., the committee was adjourned.)

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