FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

8:05 a.m.

Wednesday, September 24, 2003

Holiday Inn
Versailles Ballroom
8120 Wisconsin Avenue
Bethesda, Maryland

ATTENDEES

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ATTENDEES (Continued)

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STEVEN T. DeKOSKY, M.D.
STEVEN FERRIS, PH.D.
LLOYD FISHER, PH.D.
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JEFFREY JONAS, M.D.
LAWRENCE OLANOFF, M.D., PH.D.
FRED SCHMITT, PH.D.
LON S. SCHNEIDER, M.D.
PIERRE TARIOT, M.D.

ALSO PRESENT:

BARRY A. COOPER, MHA

C O N T E N T S

NDA 21-487, memantine hydrochloride,
Forest Laboratories, Inc.,
Indicated for Treatment of Moderate to Severe Dementia
of the Alzheimer's type

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P R O C E E D I N G S

(8:05 a.m.)

DR. KAWAS: Good morning and welcome to the September 24th, 2003, meeting of the Advisory Committee for Central and Peripheral Nervous System Drugs. My name is Claudia Kawas. I'm a neurologist from the University of California, Irvine.

We're going to have a very interesting day, I think, and I know that many of the panel members today are new, so I want to remind you of some of the logistics. All of these proceedings go on transcription and so we need everybody who wants to speak to speak to a microphone. That includes the panel that's sitting around the table. You have your mikes in front of you and if you'll raise your hand when you want to be recognized and turn on your mike. In addition, the sponsor and any other public speakers need to come to a microphone whenever they want to speak.

So I'd like to begin by introducing the members of the panel, as well as the FDA, and maybe we could start over with Dr. Russell Katz.

DR. KATZ: Yes, hi. Russ Katz from the Division of Neuropharmacological Drug Products, FDA.

DR. OLIVA: I'm Armando Oliva, Team Leader for the NDA, Division of Neuropharmacological Drug Products.

DR. MANI: Hi. I'm Ranjit Mani. I'm a medical reviewer at the FDA.

DR. PACKER: Roger Packer, child neurologist from Children's Hospital here in Washington, D.C., and a virgin to the process, so we'll see how it goes.

DR. KAWAS: It gets over quick, you'll see.

DR. KATTAH: Jorge Kattah, University of Illinois, neurology. I'm also a virgin here, so I plan to learn a lot.

MS. PATEL: Anuja Patel, executive secretary for the FDA Advisors and Consultants Staff.

DR. WOLINSKY: Jerry Wolinsky, neurologist from the University of Texas who's been around the block.

(Laughter.)

DR. KIEBURTZ: Karl Kieburtz, neurologist, University of Rochester. I'm not telling.

DR. van BELLE: Gerald van Belle from the University of Washington, Statistics.

DR. GANGULI: Mary Ganguli, University of Pittsburgh, psychiatry.

DR. EBERT: Steve Ebert. I'm a pharmacist at Meriter Hospital and Professor at University of Wisconsin, Madison.

DR. AZARNOFF: I'm Dan Azarnoff, a clinical pharmacologist and President of D.L. Azarnoff Associates.

DR. TEMPLE: I'm Bob Temple. I'm the Office Director here.

DR. KAWAS: To begin with, we will have a conflict of interest statement. Anuja Patel.

MS. PATEL: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

Dr. Karl Kieburtz has been granted a waiver under 18 U.S.C. 208(b)(3) for consulting on behalf of the sponsor of a competing product, memantine, and on behalf of a distributor of competing products whose subsidiary is also the manufacturer of a competing product. Each interest is valued at less than $10,001 annually.

Dr. Kieburtz has also been granted a waiver under 21 U.S.C. 355(n)(4), an amendment of section 505 of the Food and Drug Administration Modernization Act, for ownership of stock in a distributor of a competing product

to memantine whose subsidiary is also the manufacturer of a competing product. The stock is valued at less than $5,001.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

In addition, we would like to disclose that Dr. Daniel Azarnoff is participating in this meeting as an acting industry representative acting on behalf of regulated industry.

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

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

Thank you.

DR. KAWAS: Thanks. Today, we will be discussing a new drug application, NDA 21-487, memantine hydrochloride, Forest Laboratories, indicated for the

treatment of moderate to severe dementia of the Alzheimer's type.

Dr. Russell Katz will give us opening remarks.

DR. KATZ: Thank you, Dr. Kawas. I'll be brief. The company is going to present the specific data. So I just want to make a few general remarks about the sorts of issues we'd like the committee to discuss.

First, let me welcome the new members, we do have a number of new members, and thank you for agreeing to protect and to serve, I suppose we can say. I would particularly like to welcome back the veterans. We have a number of members of the committee who seem to have been on the committee as long as I've been here. That's probably not exactly true, but thank you very much. Maybe the new members should have spoken to the veterans before they agreed to serve, but thanks very much. And we have one invited guest, Dr. Ganguli, who we've asked specifically here for today's discussion to help us out. So thank you again very much for that.

Anyway, as Dr. Kawas says and as you know, we are here to discuss NDA 21-487 which was submitted in December of last year by Forest Laboratories, and this is for the use of memantine hydrochloride, a putative NMDA receptor antagonist, for the treatment of moderate to severe dementia of the Alzheimer's type.

As you know, we have currently four treatments approved for Alzheimer's disease but for patients with mild to moderate disease specifically, and this is the first application we've had for a treatment for patients with moderate to severe disease, so-called. So we thought that it raised a number of interesting and important issues that we wanted to discuss with the committee and that's why we've brought this issue before you today.

As you know, the application contains the results of three studies that the company believes are adequate and well-controlled to support this claim and, of course, safety experience in the population. As I say, I'm not going to talk about the data really very much. The sponsor will do that. As a general matter, we pretty much agree with the results of their analyses, but there are a few issues that we wanted to discuss with you today.

I think the issues can fairly be broken down into two broad categories: one I would call generic issues related to the study of any drug for moderate to severe disease, and then more memantine-specific or data-specific questions. I hope you've had a chance to read the information that we sent you and that the company has sent you. It's voluminous, I recognize that, lots of reviews, lots of data, so I appreciate your efforts, but if you haven't gotten through all of it, these are some of the

questions I'd like you to keep in mind as you do hear the specific data presented by the company.

First, I want to start with the so-called generic issues. As you probably know, to date, all the treatments that have been approved for Alzheimer's disease have been approved on the basis of findings on what we call two co-primary outcome measures. We've required that these drugs show an effect on a cognitive measure and a global or functional measure.

The reasons for this are that, first of all, we think it's inappropriate to grant a specific Alzheimer's claim if the drug doesn't have an effect on the so-called core symptoms of the disease, which would be the cognitive dysfunction. So that's why we require an effect on a specific cognitive measure. And as far as the global or functional measure, one can imagine that a treatment could have a statistically significant effect on a very sensitive cognitive measure but that that might not really translate into anything particularly meaningful for the patient's functioning. So that's why we require an effect as well on a global or a functional measure, so as to, to the extent possible, ensure that the effect that's seen on the cognitive function actually translates into something clinically meaningful.

The sponsor has and, of course, in discussions

with us, adopted a similar approach for the patients with moderate to severe disease, and so we want to first ask the committee whether or not you think that that's an appropriate way to proceed in this population, again a new population with which we have little experience from a regulatory point of view. Some have maintained that it's not important or it's inappropriate to measure cognitive function in these patients who are very severely impaired, and some have said global function is difficult to measure and doesn't need to be measured as well. So we want to know what the committee thinks about this approach which again is very analogous to the approach we've taken with the other treatments.

Then with regard to specific scales used or measurement instruments used to assess effects on cognitive or global functioning, the sponsor has chosen for the most part to rely for its cognitive assessment on a 51-item test battery called the Severe Impairment Battery, or the SIB, and as a measure of global or functional assessment, they've chosen to look primarily at the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale. That's the ADCS-ADL. This scale is also designed to look at functional measures, functional capacity in moderate to severe patients.

So these scales, though, have never served as

the basis for drug approval in the past. Typically, in all cases for the four drugs approved for mild to moderate disease, we've looked at the ADAS-cog as a cognitive measure, although that is not specifically required, and a global functional change, the CIBIC or CIBIC-plus. So we've never used them and never relied upon these particular measures of cognitive functioning or global functioning and we'd like to know whether or not the committee thinks that those are appropriate measures to use in this population.

I'll briefly now turn to the drug-specific questions that we have with regard to the data that the sponsor has actually submitted. As I said and as you know, the sponsor submitted three studies that they believe support the approval, and we have specific questions about two of those studies.

The first study I want to talk about is study 9605. In this study, there was no cognitive measure prospectively designated as primary, which again is atypical for Alzheimer's studies, and we have provisionally focused on the results on the SIB. There was at least one other measure of cognitive function that turned out not to be statistically significant when we looked at the analysis and that's the MMSE, the Mini-Mental Status Exam, which is a standard exam that's used to rate patient severity. At

least in previous Alzheimer's studies, it hasn't been used as a primary outcome, but it has been used to assess cognitive function to designate patients as either mild to moderate in the past, and here, it was used, in fact, to help decide if patients were severely impaired.

So as I say, there was no statistical significance on that particular measure, even though there was on the SIB. So we're interested to know whether or not the committee thinks that that finding calls into question the findings on the SIB.

There were two primary outcomes in that study prospectively designated, but they were both global measures: one truly global, the CIBIC-plus, and which I say is what's been used to measure global function in the previous treatments; and the ADCS-ADL scale. Again, for purposes of this study, by protocol, the co-primary outcome did not reach statistical significance, although the ADCS-ADL scale did. So we're interested to know whether or not the committee thinks that that lack of significance on the CIBIC raises questions about the drug's effect on global functioning in these patients.

But there's one other finding that we are particularly concerned about and we would like to hear the committee's thoughts and that relates to the findings on the subset of patients who are actually designated or

classified as severe. You'll recall that this is a treatment that's designed to treat severe patients, that's unique, and so we looked at the subset of patients who had MMSE scores less than 10 which would define the more severe patients. Patients with MMSE scores between 10 and 14, which were the remainder -- I think that was the upper limit -- are patients who are similar to patients, presumably, who have been included in the previous approved treatments, mild to moderate.

So we were particularly interested in looking at the severe patients, and we know that this was a post hoc retrospective look. It wasn't planned for in the protocol, but we thought it was particularly meaningful to look at this subset because again the drug is presumably effective in severe patients where the other drugs haven't been shown to be.

So when you look at that subset, there were not statistically significant differences on the two primary outcomes, the global primary outcomes that were designated in the protocol, and we don't think that that is related to a power question. Perhaps it was in the right direction but just too few patients because in fact, the group that had higher MMSE scores did show positive findings on that and that was actually a smaller subset. So we're very interested to know whether or not the committee thinks that

that finding calls into question the effect of the treatment specifically in the severe subset.

So I just want to move now to finish up, to raise a few questions about another study. That's study 9403. That was the study that was performed in Latvia.

Again, as we note in our documents, the primary outcome used in that study is an outcome measure that we have no experience with, that we've never seen before. There was no specific cognitive measure. The primary outcome was sort of a global measure, but there was no specific cognitive measure. The company retrospectively created a cognitive measure out of the elements in the primary global measure that seemed to assess cognitive function, but that scale, as far as I know, this created cognitive scale has not been validated with previous data sets, as far as I know. So we're interested to know whether or not the committee thinks that, from a clinical point of view, that study really provides or can serve as a source of evidence that the drug is effective.

There was another finding in that study which we also thought was interesting. The patients were retrospectively, again, categorized by the sponsor as having either had Alzheimer's disease or vascular dementia, and we're particularly, of course, today interested in the subset of patients who were diagnosed with Alzheimer's

disease. This diagnosis, after the fact, was based on a rating on the Hachinski scale, which is a scale which is designed to distinguish clinically between Alzheimer's disease and vascular dementia. So the sponsor applied the Hachinski scale with a cutoff score and decided these patients have Alzheimer's, these patients had vascular dementia.

Nowadays, the diagnosis of vascular dementia relies at least in part on the finding of vascular lesions on an imaging measure, and about half of the patients in this particular study had CT scans at baseline, but again that data was not used to categorize the patients as vascular versus Alzheimer's, but we looked at the reports, the translated reports of those CT scans. We did not look at the CT scans, but we looked at the translated reports and even though many of them were incomplete and difficult to make sense of, when we looked at them independently, about half of that half -- so that's about a quarter of the patients -- we thought that the diagnosis, based again on imaging, was different from the diagnosis that the sponsor applied, based on the Hachinski scale.

So we're not exactly sure which patients really had Alzheimer's disease in that study and who didn't. So I'm sure the company will speak about that, but we're interested to know whether or not the committee thinks that

that is an important factor in looking at this particular study.

So we're interested to know whether or not the committee thinks that this study, taken as a whole, can contribute to a finding of substantial evidence of effectiveness, and if not, we're interested to know what, if anything, the committee thinks that study can be used for.

So those are the specific and the general questions that we'd like the committee to think about. Of course, if there are other issues that come up, we're obviously very eager to know what the committee thinks about those. So let me just read into the record, although you have this in front of you on your agenda, but let me read into the record the specific questions we actually would like you to formally vote on at the end.

So the first question is: has the population for which use of memantine is proposed been adequately identified in studies included in this application?

The second question is: are the designs of the key studies in this application adequate for evaluating the efficacy of memantine for the proposed indication? In particular, are the instruments used to evaluate efficacy in these studies appropriate for patients with moderate to severe Alzheimer's disease?

The third question is: has substantial evidence of effectiveness of memantine for the proposed indication been demonstrated by the studies included in the application?

The last question is: has the sponsor submitted adequate evidence of the safety of memantine in this population?

So I think with that, I'll end. Again, thank you very much for your work to this point and for your work today, and I will turn the microphone back to Dr. Kawas.

DR. KAWAS: Thank you, Dr. Katz.

Our first presentation is coming from the sponsor, Dr. Lawrence Olanoff, Executive Vice President of Forest Laboratories, Incorporated, who will give us the introduction and overview.

DR. OLANOFF: Good morning, Dr. Kawas, members of the committee, invited guests, FDA staff, Dr. Katz, members of the audience. My name is Lawrence Olanoff. I'm the Executive Vice President of Forest Laboratories.

My colleagues from Forest and Merz and our academic consultants welcome the opportunity today to present the relevant efficacy and safety data on memantine for consideration for approval for the treatment of moderate to severe Alzheimer's disease.

The presentation today will consist of five

parts. I will provide an introduction which will include comments on the clinical development history and some of the key points that the committee will be discussing further.

Dr. Timothy Greenamyre, Professor of Neurology and Pharmacology from Emory University, will follow me with a discussion of the pharmacology of memantine.

Dr. Lon Schneider, Professor of Psychiatry, Neurology, and Gerontology, University of Southern California, will then speak on the efficacy of memantine.

Dr. Jonas will follow him. He is Vice President of CNS Drug Development of Forest Research Institute and he will speak on the safety of memantine.

And finally, Dr. Steven DeKosky, Professor and Chair of the Department of Neurology, University of Pittsburgh, will close with comments on the staging of moderate to severe Alzheimer's disease, the clinical need for a product in this category, the relevance of the clinical efficacy data that we will discuss, and a closing comment on risk-benefit.

We believe that memantine has demonstrated efficacy and safety in a number of clinical studies in patients with moderate to severe Alzheimer's disease. It is a low to moderate affinity, uncompetitive NMDA receptor antagonist. It's excreted primarily in the urine,

essentially as parent drug, and it's fully bioavailable after oral dosing.

The indication we're proposing for its use will be for the treatment of moderate to severe Alzheimer's disease. We appreciate that this claim constitutes a new category of patients who have unique treatment needs and require unique clinical trial designs and outcome measures.

Memantine was first introduced in the German market in 1982, where it was used for the treatment of organic brain syndrome, Parkinson's disease, and spasticity disorders. Merz then conducted a series of clinical trials, which are shown on the top of this slide, which were then applied to a centralized European registration package and ultimately led to the approval of the product for moderately severe to severe Alzheimer's disease in the EU in 2002.

Forest licensed the product in the year 2000 and then went ahead and started a new development program, submitting an NDA for the treatment of moderate to severe Alzheimer's disease in 2002.

Since the time of its introduction, memantine has been exposed to approximately 600,000 patient-years, estimated.

The clinical development program with memantine is long and complex. Many of the trials were actually

conducted after its initial introduction in Germany.

The first large-scale trial, placebo-controlled trial in dementia was performed in nursing homes in Latvia, and these were patients with severe dementia, either Alzheimer's or vascular dementia, all with Mini-Mental Status scores of less than 10. Importantly, this was an indication in a patient population for which there were no drugs approved or really under serious study at the time. So it was a real opportunity for Merz to explore a novel indication.

At the time this study was initiated, the European regulatory guidances called for emphasis on global and functional outcomes. There was some question at that time as to whether cognition really was measurable in these patients with severe disease. So the primary outcomes chosen for this study were in accord with those guidances and both outcomes, prospectively defined, showed a statistically significant advantage for memantine over placebo in the total population of patients under study.

The dose in this study was chosen as 10 milligrams once daily and this was based on the concept that these patients would be thought to be frail and perhaps with greater medical illnesses than in the general Alzheimer's population.

About the same time Merz performed two studies

in Europe, large-scale studies in vascular dementia, and again at this time, in the early to mid-1990s, it was an opportunity to explore an indication which the other sponsors of other anti-dementia drugs were not actively pursuing. Here, the dose was 10 milligrams b.i.d., and this was chosen on early tolerability and safety experience in normal subjects and in some early patient trials. In these trials in mild to moderate dementia patients, memantine showed a significant effect on cognition as measured by the ADAS-cog but not on the global endpoints that were specified as co-primary measures in these studies.

Building on the results of study 9403 in severe dementia patients, Merz went on to create a new study, trial 9605, which was initiated in the U.S. This is the study that was published by Dr. Reisberg, et al., in the New England Journal of Medicine. As an aside, I should state that since that study was published, we've been receiving over 1,000 calls per month in our Professional Affairs Office in St. Louis inquiring as to the availability of the drug.

Given the past experience in the European regulatory needs, again a functional and global outcome were chosen as primary efficacy measures. The ADCS-ADL19 was the functional endpoint and the CIBIC-plus was the

global endpoint. However, in this trial, at the time it was initiated, the Severe Impairment Battery had just become available for use in a clinical trial, and it was prospectively added to the trial as a secondary endpoint initially and then elevated to a key endpoint for consideration under a responder analysis that was required by the European regulatory authorities. This was added as such an endpoint prior to the unblinding of the study. The dosage again was 10 milligrams b.i.d. based on the past vascular dementia experience.

After licensing the product in the U.S., Forest began a new clinical development program in moderate to severe disease, and here, we chose cognitive and functional endpoints as primary outcome measures. A CIBIC-plus was also included as a key outcome measure. 10 milligrams b.i.d. again was the dosing regimen based on an attempt to duplicate the trial 9605 experience, and trial MD-02, which we'll describe in more detail later, which was specifically designed to assess the effect of memantine in patients on chronic stable doses of donepezil, was the first study to complete, and in fact it demonstrated efficacy on all the key outcome measures.

At this time, we have ongoing development programs in mild to moderate Alzheimer's disease, as well as in neuropathic pain, and Allergan is sponsoring a long-

term program in glaucoma.

I want to comment on the mild to moderate program briefly. The first study to complete in this program was MD-12 and this was a study in mild to moderate Alzheimer's patients, MMSE 10 to 26, which was similar to the MD-02 trial in that all patients were randomized, had been on stable chronic doses of a cholinesterase inhibitor. It could be donepezil, rivastigmine, or galantamine. The difference in this trial, aside from the patient inclusion criteria, was that the primary endpoints were the ADAS-cog appropriate for this patient population and the CIBIC-plus.

In this study which we obtained the results this summer, about 6 or 7 months after we submitted the data for moderate to severe Alzheimer's disease, memantine failed to separate from placebo. Perhaps what was more evident in this study, looking at the ADAS-cog information, was that the placebo group -- again, these are patients on chronic cholinesterase inhibitor therapy -- did not demonstrate any substantial deterioration from baseline.

As you may be aware in traditional mild to moderate Alzheimer's studies, one of the key attributes of these studies is that they're designed and powered to separate drug from placebo with a general acknowledgement that placebo will decline over time. So this study failed to provide us with any evidence for support in mild to

moderate disease. However, we realized it was also a very aggressive design in that trying to get effects in patients already on a stable therapy for the disease is always difficult to show because of the noise created by that background therapy. But we do have other monotherapy studies in progress and we await the results of those studies.

I would now like to talk about the key points that will be discussed by the committee today. We believe that moderate to severe Alzheimer's disease is a clinically identifiable stage of Alzheimer's disease and can be identified as such both in clinical practice and by suitable inclusion criteria within clinical trials. Although there has been a study reported in this population which showed a benefit for donepezil in patients with moderate to severe disease, interestingly enough, also using the Severe Impairment Battery as a cognitive measure, there are no current drugs approved for the treatment of patients with severe disease.

If you look at this cartoon, you can see that over time, there's a steady decline in the ability of patients with Alzheimer's disease, and I think what I'd like to make evident is that as patients go through the various stages of disease, one can assess their abilities not only in terms of their cognitive decline but also in

their functional decline. Importantly, when patients reach the most severe stage of their disease, not only are they losing essential activities of daily living but they may also suffer from serious behavioral disabilities. This creates a major burden on the part of the caregiver.

Another point that we discussed by the committee is a choice of endpoints for these trials. For the U.S. trials, 9605 and MD-02, the key endpoints consisted of function, cognition, and a global endpoint. The cognitive endpoint was the Severe Impairment Battery and the functional endpoint was the ADCS-ADL19. Both these endpoints, we consider to be reliable and validated, and more importantly, both these endpoints have been structured and designed specifically to pick up differences in patients with moderate to severe disease.

I'd now like to turn to a brief comment on the overall database. When looking for the clinical safety information, we tried to include all available data within our review and this consisted of clinical trials, clinical pharmacology studies, and other clinical experience, both the postmarketing experience with memantine in Europe, specifically in Germany, as well as ongoing studies. There are quite a few of them going on in the United States today and many of them in dementia.

We looked in detail at the core safety studies.

These were studies which Dr. Jonas will present in more detail which looked at safety data in a systematic fashion and contain information on a wide variety of safety parameters. Dr. Jonas will summarize that information in a moment.

However, we did look at the overall database in some detail relative to the appearance of any rare or serious adverse events, and our assessment was that there did not appear to be any drug-attributed serious adverse events in this overall experience.

I'd now like to comment briefly on the efficacy database. I've described these trials in brief before and Dr. Schneider will review them in some detail.

The nursing home study 9403 was a monotherapy study. All patients had severe Alzheimer's disease. 10 milligrams q.d. was the dose, and it was 12 weeks in duration.

The two U.S. trials were performed one as a monotherapy trial in outpatients with moderate to severe disease. 10 milligrams b.i.d. was the stable dose, and it was of 6 months' duration.

And the final trial was MD-02. As I described, this study was designed to evaluate the effect of memantine as an add-on therapy to patients already on chronic donepezil treatment. Again, outpatients of a moderate to

severe Alzheimer's disease degree, 10 milligrams b.i.d., and again approximately 6 months in duration.

Finally, I'd like to comment that we believe that moderate to severe disease is an identifiable stage of a diagnosable disease, that is, Alzheimer's disease, and was adequately defined in the clinical trials that we will review for you today.

We also believe that in these clinical trials, that memantine demonstrated evidence of efficacy across a range of endpoints, both as monotherapy and as add-on therapy to chronic cholinesterase inhibitors, specifically donepezil.

And finally, in these trials, we found that memantine was safe and well tolerated.

Thank you for your attention. I'd now like to introduce Dr. Timothy Greenamyre who will speak to the pharmacology of memantine.

DR. GREENAMYRE: Thank you, Larry. Good morning. Dr. Olanoff mentioned that memantine is safe and efficacious. I'm pleased to have the opportunity to tell you about the preclinical pharmacology and the clinical pharmacokinetics of this drug.

We know a great deal about the pharmacology of memantine, receptors with which it interacts, receptors with which it does. Do we know the exact mechanism of

memantine in Alzheimer's disease? We can't say with certainty. Do we have a good hypothesis? We think we do.

Memantine is an aminoadamantane derivative, the structure of which is shown here. It has three known sites with which it interacts in the brain. All of these are ionotropic receptors. The best characterized of these and what we think is the most clinically relevant is the NMDA receptor where it's an uncompetitive or open channel blocker with low to moderate affinity.

At lower affinity, it interacts with the serotonin 5-HT3 receptor where it's an allosteric antagonist. It enhances desensitization. At substantially lower affinity, it interacts with the nicotinic acetylcholine receptor, but given this low affinity, we don't think this is likely to be clinically relevant. Also of clinical relevance, memantine does not interact with or inhibit acetylcholinesterase activity either alone or in combination with clinically used cholinesterase inhibitors.

Having told you what memantine interacts with and how it acts, it's probably equally important to point out the sites with which it does not interact. At concentrations of 10 micromolar or less, it does not interact with any of the receptors shown here: the intracellular enzyme systems, neurotransmitter uptake

systems, or ion channels.

As I said, the best characterized action of memantine is as an NMDA receptor antagonist. This is a cartoon of the NMDA receptor. The NMDA receptor is a ligand-gated ion channel, meaning that when the ligand glutamate binds together with its co-agonist glycine, it can activate this receptor. However, the receptor is normally blocked in the ion channel by magnesium ions. As the cell is depolarized, the degree of blockade by magnesium is relieved. Magnesium can come out of the channel, and under these conditions of ligand binding, together with relief of the magnesium blockade, memantine can bind to this channel. So it's an open channel blocker and it has low to moderate affinity. In the human receptor, it has an affinity of 0.5 micromolar and this is particularly relevant since clinical dosing at 10 milligrams b.i.d. results in plasma concentrations of about .3 to .5 micromolar.

Having told you that memantine acts at the NMDA receptor, can we say with certainty that this is its mechanism in Alzheimer's disease? Probably not. However, we do have what we think is a reasonable hypothesis, and according to this hypothesis, increased glutamatergic activity with persistent activation of NMDA receptors contributes to the impaired cognition and memory seen in

Alzheimer's disease.

Some of the supportive evidence for this hypothesis is shown here. Firstly, it's been demonstrated that the glutamate transporter and the specific subtype, the EAAT2, is decreased in the brains of people who have died with Alzheimer's disease. If this is modeled in mice by knocking out the EAAT2 gene, these animals show an increased NMDA receptor activity with impaired long-term potentiation. Now, long-term potentiation is a cellular or physiological correlate of learning and memory in animals, and as I say, with the increased glutamatergic activity, it's impaired. Importantly, it can be restored with an NMDA receptor antagonist.

Additionally, beta amyloid peptides, strongly implicated in the pathogenesis of Alzheimer's disease, inhibit glutamate uptake and increase NMDA receptor activity.

Finally, excessive NMDA receptor activation impairs long-term potentiation in learning in animals.

In this context then, memantine is hypothesized to ameliorate the excessive NMDA receptor activity that may occur in Alzheimer's disease without affecting normal ongoing synaptic neurotransmission.

As would be expected of any NMDA receptor antagonist, it's neuroprotective in a variety of in vivo

and in vitro models. So, for example, it protects basal forebrain cholinergic neurons from excitotoxic insults. It protects the hippocampus against beta amyloid toxicity, and in cell culture, it protects against a wide variety of excitotoxic insults.

Let me turn to the effects of memantine on learning and memory. In contrast to what might be expected of an NMDA receptor antagonist, at therapeutically relevant concentrations, memantine not only does not inhibit long-term potentiation in vivo or in vitro and does not inhibit spatial learning in the Morris water maze, it actually can prolong and enhance LTP, improve learning and memory in the aged Fisher rat. It also restores LTP and memory under conditions of excessive glutamatergic activity, and it's these latter two mechanisms that we think may be particularly relevant to its actions in Alzheimer's disease.

All NMDA receptor antagonists, as I mentioned, can block excitotoxicity, but you're probably aware that certain NMDA receptor antagonists have undesirable properties. They can impair learning and memory. They can have psychotomimetic effects. The drugs that do this are called dissociative anesthetics. These include drugs like MK-801, ketamine, or PCP. So these drugs, when administered at concentrations that partially inhibit the

NMDA receptor channel, will impair learning and memory and will cause psychotomimetic effects.

In contrast, memantine at a concentration that partially blocks the NMDA receptor does not impair learning and memory and does not cause psychomimetic effects. Of course, this is a dose- or concentration-dependent phenomenon. So if one pushes the dose of memantine, say, 10-fold higher than that which is required to partially block the receptor, one can impair learning and memory. Even pushing it much higher than that, there is very little indication of any kind of psychomimetic effect.

Turning now to the clinical pharmacokinetics of memantine, it has linear dose proportional kinetics over a wide dose range. It's completely bioavailable when given orally. It reaches maximum plasma levels in 4 to 6 hours, and it has an elimination half-life of 60 to 80 hours.

Given that pharmacokinetic profile, why is it dosed twice a day, or b.i.d.? This is largely historical. It was found in early trials that b.i.d. dosing tended to be better tolerated than once-daily dosing, and this may relate to the fact that b.i.d., or twice-daily, dosing reduces the maximum plasma levels by 10 to 15 percent. I should also mention that titrating up the dose rather than starting immediately at the targeted dose improves tolerability.

Moving on with clinical pharmacokinetics, all of this information is in your briefing book. I want to point out a couple of points. Memantine has very limited metabolism. It's excreted almost entirely in the urine as the parent compound. Its metabolites, what few there are, are pharmacologically inactive. There's little, if any, effect on the cytochrome P450 system, suggesting that there will be few drug-drug interactions in this regard, and finally, I want to point out that there are no pharmacokinetic or pharmacodynamic interactions with donepezil.

In summary then, memantine demonstrates predictable clinical pharmacokinetic characteristics. The preclinical data support memantine's safety profile and provide potential mechanisms for efficacy in Alzheimer's disease.

And with that, I'd like to introduce Dr. Lon Schneider who will talk about the efficacy in Alzheimer's disease.

DR. SCHNEIDER: Thanks, Tim. Dr. Kawas, Dr. Katz, Dr. Temple, advisory committee members, I'm Lon Schneider. I'm a professor at the Keck School of Medicine and the Alzheimer's Disease Research Center at USC.

Dr. Olanoff reviewed the development program for memantine and overviewed the clinical studies that I'm

going to talk about in detail. Dr. Greenamyre reviewed clinical pharmacology and preclinical pharmacology. I'll review the three key trials that are in the various briefing documents that you have, trial 9403, trial 9605, and MD-02.

9403 was the trial that Dr. Katz described as severe dementia in Latvian nursing homes. I want to tell you a bit more about it before proceeding to the other two key U.S. trials. This was done, again, in institutions in Latvia. The inclusion criteria were DSM-III-R criteria for dementia syndrome, supplemented by requiring the patients have Mini-Mental States below 10 to confirm a severe dementia status. They also needed Global Deterioration Scale stages between 5 and 7.

Exclusion criteria are important in this study. They could not have evidence of other psychiatric or neurological disorders that may cause or exacerbate cognitive impairment nor could they have concomitant medical disorders that might exacerbate cognitive impairment.

This was a 12-week trial. Patients were randomized to 10 milligrams of memantine or placebo after a 5 milligram per day one-week titration period, and the primary outcome measures were the BGP-care dependency and the traditional CGI-C. There were other outcome measures

as well.

166 patients were randomized in equal allocation ratios and 95 percent of each group completed the clinical trial. Mean age was 72. They were mostly women. Mean Mini-Mental State score was 6.3 at baseline, and importantly here, as Dr. Katz was describing, about half of the patients had modified Hachinski Ischemic Scale scores of 4 or less.

Here are the essential results for the two co-primaries and then for the retrospectively derived BGP-cognitive subscale. They were statistically significantly positive in favor of memantine in both observed case and ITT LOCF analyses.

Here's a closer look at the primary BGP-Care Dependency Scale. Over the course of the 12-week trial, patients randomized to memantine showed greater improvement in function than patients randomized to placebo, who also in this institutionalized setting showed an in-study effect and improvement with being in the trial.

On the traditional CGI-C done using the guidelines from the NIMH manual, patients on memantine also were rated to be substantially more improved globally than patients randomized to placebo and again significant on both analyses.

The BGP-Cognitive Subscale was derived after

this trial was over and it was based on five items in the BGP that were considered to be assessments of cognitive function. On that scale as well, patients on memantine improved to a greater extent than patients on placebo.

Those are the essential results of the trial overall, but as Dr. Katz mentioned and as contained in your briefing book, subpopulation analyses were done. In the analyses done by the sponsor, the Alzheimer's disease subpopulation was essentially defined as modified Hachinski scores of 4 or below. 75 patients were identified and in the analyses, both the two co-primaries were statistically significant in favor of memantine.

The FDA reviewed the reports of the neuroimaging of essentially all CT scans in a proportion of the patients and classified an Alzheimer's population with the sample size somewhat different, an overlapping population with a sample size somewhat different. In that analysis as well, both co-primaries were statistically significant.

It was this trial in severe dementia 9403 that informed the two U.S. trials in moderate to severe dementia of the Alzheimer's type. As Dr. Olanoff described, outcome measures different from the usual ADAS-cog were used to assess cognitive change. I'm going to first describe the measures used in the U.S. trials and then move on to

describe the design and the results from these trials.

The trials in question are 9605, Reisberg recently published in the New England Journal last spring, and MD-02, randomized trial of memantine in patients already taking donepezil. The outcomes were similar in both trials: the ADCS-ADL, the Severe Impairment Battery, and a Clinician's Interview-Based Impression of Change with Caregiver's Input.

Two different versions of CIBIC-plus were used, the NYU version in 9605, and the Alzheimer's Disease Cooperative Study version that tends to be used more commonly in clinical trials was used in MD-02.

In addition, as Dr. Katz pointed out in 9605, the ADLs and the CIBIC-plus were designated as the co-primaries. In MD-02, the ADL and the Severe Impairment Battery were so designated.

Furthermore, in 9605, a prospectively identified responder analysis was determined requiring stabilization or improvement on the three key outcomes.

A word on the Severe Impairment Battery, in part, because many of you may not be familiar with it. It's a structured cognitive examination. It involves 40 items. The scaling is from 0 to 100 with 100 being the highest score. It can be looked upon as a less-difficult extension of the neuropsychological assessment items and

particularly of the domains in the Alzheimer's Disease Assessment Scale. In this way as an extension, it minimizes floor effects of the ADAS-cog. There are subscales addressing domains with attention, orientation, language, memory, visuoperception, construction, and practice.

The Alzheimer's Disease Cooperative Study instrument studies demonstrated the SIB to be reliable and valid, as have other studies and as have the developers of the instrument. It's also sensitive to clinical progression at 6 and 12 months, and that's been demonstrated in the ADCS instrument protocol in the placebo groups of the two memantine trials I'll discuss and in the placebo groups of the donepezil randomized trial in moderate to severe dementia patients.

The Alzheimer's Disease Cooperative Study Activities of Daily Living is another key primary used in these two U.S. memantine trials. It was developed by the NIA's NINCDS Instrument Committee specifically for use in clinical trials. It's administered to a caregiver who is asked to assess performance during the past month. Each ADL is rated from non-performance to independent performance. There are 19 items in the subset used for the memantine trials. The scaling is from 0 to 54 with 54 being higher function.

It, too, has been demonstrated reliable and valid and sensitive to clinical progression in the Alzheimer's Disease Cooperative Study Instrument Protocol and in the placebo groups of the 2 memantine trials.

With that as a brief discussion of two instruments, I want to review with you the trial designs for the U.S. trials. In part, I'll do this together because they are fairly similar. Again, the trials to be discussed are 9605 and MD-02. Both require that patients fulfill NINCDS-ADRDA criteria for probable AD, that the patients be outpatients. Both trials were approximately 6 months in duration, 28 weeks on the one hand, 24 weeks on another, and used the same dosage, 10 milligrams b.i.d., after a 1-month up-titration from 5 milligrams per day. There were additional and overlapping outcomes, as well as the key outcomes I mentioned before.

The trials differ in their Mini-Mental State inclusion criteria. 9605 bracketed the Mini-Mental State between 3 and 14 inclusively; MD-02 used the Mini-Mental State range between 5 and 14 inclusively.

The trials also differed in another important way, and that is that 9605 was monotherapy, memantine or placebo. MD-02 required that patients had been on donepezil for at least 6 months and to have been on stable doses of donepezil for 3 months before being randomized.

In fact, the mean usage of donepezil in MD-02 was nearly 2.5 years, and 87 percent of the patients had been maintained on a stable dose of donepezil for greater than a year. This was essentially a 10 milligram dose. 86 percent of patients were maintained on 10 milligrams with the rest on a clinically effective 5 milligrams as well.

So those are the overall similarities and differences in the design.

This slide is demonstrating patient baseline characteristics in both trials. Patients in both trials were about 76 years of age, mostly women, mostly of European descent. As one might have predicted, a baseline Mini-Mental State score is a bit lower in 9605 than in MD-02 where the mean MMSE was 10, and similarly, the Severe Impairment Battery and Activities of Daily Living baseline scores were a bit lower as well.

Here's an overview of trial 9605 results. 252 patients were randomized in equal allocation, and importantly, there was a trend for more memantine patients to complete the trial than patients randomized to placebo. Overall, there were positive effects in favor of memantine on cognition, ADLs, and the CIBIC-plus.

I'd like to go into detail on each of the outcomes, to take a closer look. Here's the Severe Impairment Battery. As you can see, patients randomized to

memantine maintained cognitive function throughout the course of the trial to a greater extent than patients on placebo who continued to deteriorate. This was significant in both the specified OC analysis and the ITT last observation carried forward analysis.

Similarly with the ADCS-ADLs, patients randomized to memantine maintained function to a greater extent than patients on placebo who continued to deteriorate, again statistically significant in favor of memantine in both of the protocol-specified analyses.

This is a closer look at the CIBIC-plus, again the Clinician's Interview-Based Impression of Change with caregiver input performed by an experienced study clinician. As you can see, again in the observed case analysis, patients randomized to memantine, by the end of the trial, were rated as performing better or having worsened less than patients randomized to placebo. This was statistically significant in the observed case analysis. It was not significant in the ITT analysis. The p value was .064.

In an attempt to better understand this difference and on the advice of Lloyd Fisher from the University of Washington, a statistical consultant to Forest, we did a post hoc mixed-effect model repeated measures analysis to help to account for dropouts, and

these would be dropouts missing at random. So we again post hoc modeled the data and found a p value of .02. Now again, this was exploratory and not meant to substitute for the protocol-defined two statistical standards.

Trial MD-02, again the memantine add-on to donepezil. 404 patients were randomized in equal allocation, and again more patients on memantine completed the 6-month trial than patients randomized to placebo. Here's the overview of this trial. The Severe Impairment Battery, ADLs and the CIBIC-plus were all statistically significantly positive and in favor of memantine compared to placebo on both the observed case analysis and the last observation carried forward analysis.

Here is a closer look at the Severe Impairment Battery. Patients randomized to memantine improved cognitive function and maintained that improvement throughout the course of the 6-month trial while patients randomized to placebo continued to deteriorate as one might expect.

With respect to the ADCS-ADLs, Activities of Daily Living, similarly again patients randomized to memantine maintained functional activities to a greater extent than patients randomized to placebo.

And lastly, on the Clinician's Interview-Based Impression of Change with caregiver input, clinicians rated

patients randomized to memantine as having changed to a lesser degree than patients randomized to placebo, again significant in both specified analyses.

Dr. Katz discussed the FDA's post hoc analysis of trial 9605, the monotherapy trial, by MMSE severity. This is contained in the FDA sections of the briefing document, and he pointed out the following. Let me draw your attention to the Severe Impairment Battery first.

When splitting the Mini-Mental State scores into two strata, less than 10 or 10 and above, and this is essentially to categorize severe dementia on the one hand and moderate dementia on the other. When doing this split and then doing the stratified analysis, both patients in the moderate range and patients in the severe range showed significant drug-placebo differences in cognition in favor of memantine and the effect sizes are about the same in each group.

However, on ADLs when the same split was done, there was statistically significance in favor of memantine in the group with Mini-Mental States of 10 and above but not so in the group of 9 and below. The effect size also diminishes substantially. Similarly with the CIBIC-plus, in the moderate group, Mini-Mental State scores 10 and above, there was a robust effect. In the more severe group, the effect size diminishes substantially. It's

barely nominally in favor of memantine and certainly not significant.

In an effort to try to understand this, we also did some post hoc descriptive analyses as well and I'd like to take you through this. Again, it's trial 9605 and what this is displaying -- and I apologize to people in the back of the room -- is drug-placebo differences, memantine-placebo differences on various outcomes with the 95-percent confidence interval as according to baseline Mini-Mental State scores. 9605, so the Mini-Mental State scores range from 3 to 14.

For instance, what you can see with the Severe Impairment Battery is that overall at each Mini-Mental State strata taken, there is a positive drug-placebo difference in favor of memantine, in favor of better cognition with memantine than placebo, and you can also see that occasionally, one will show either no drug-placebo difference or a drug-placebo difference nominally in favor of placebo, for instance, here a Mini-Mental State score of 9.

We similarly did this exercise for the ADLs and the CIBIC, and I think you can again see with the ADLs that for the most part, in most of these strata, there are positive differences in favor of memantine and occasionally differences nominally in favor of placebo. And similarly

with the CIBIC-plus, generally differences in favor of memantine but also differences in favor of placebo.

In FDA's post hoc analysis, dividing the sample between 9 and 10, this group, as I showed you before, very definitely has a small effect size compared to the larger group in favor of memantine, but I think you can also appreciate the variation here in this descriptive analysis and also some of this effect depends on where you choose to make a cut. If you cut between 10 and 11, the effect size would change rather substantially. If you took a cut between 5 and 6 and another between 9 and 10 or 10 and 11 to essentially create tertiles, there would be yet a different relationship.

I think, also, you can see visually that one can draw a line, a regression line in essence, through the confidence intervals and find that it's fairly flat.

We were offering this as just a further examination of the variation within the cognitive severity strata in trial 9605. Certainly I agree with the post hoc analysis put forward by FDA previously.

This is another way of looking at the variation, and again this is the same data display as before but added to it is now the trial MD-02 data and that's in green here. I think the advisory committee members who are sitting closer can see that they're

essentially consistent with trial 9605. The point estimates are very close and certainly there are overlapping confidence intervals, and in MD-02, also, there's not an apparent difference between outcomes based on Mini-Mental State at baseline. So I wanted to put this up for consideration and further discussion later in the afternoon.

So what I did here is I tried to review as briefly as possible the three key trials. I wanted to show that overall in patients with moderate to severe Alzheimer's disease, there were clinically meaningful and, of course, statistically significant outcomes on cognition, function and global impression. Efficacy was clearly demonstrated. Cognitive efficacy and global efficacy was clearly demonstrated in the two U.S. trials, and global efficacy with regard to function was clearly demonstrated in the initial severe dementia trial.

So with that, I'd like to thank you for your attention. I apologize for going over a bit in time and introduce Dr. Jeff Jonas, Vice President of CNS for Forest Research Institute.

DR. JONAS: Good morning, everyone. I'm Jeffrey Jonas. I'm the Vice President for Central Nervous System Therapeutic Area at Forest Laboratories, and I'll be providing an overview today of the safety and tolerability

of memantine.

This slide again shows you the development history of memantine. In the 1990s, as the pathology of Alzheimer's dementia and the mechanism of memantine were better delineated, the development of the drug was pointed more systematically towards Alzheimer's dementia. We see here, therefore, laid out chronologically those studies that comprise our NDA and which we'll focus on today in reviewing the safety and tolerability of memantine.

Earlier, you heard Dr. Olanoff comment that there were an estimated 600,000 patient-years of exposure with respect to memantine. We've examined these data as well as the clinical trial data and as Dr. Olanoff mentioned earlier, we found no evidence for rare serious signals in the postmarketing clinical practice or overall clinical trial experience with respect to memantine.

This is a schematic of our core safety trials. There were 10 double-blind, placebo-controlled trials, 8 in dementia and 2 in neuropathy, comprising 390 patients exposed to memantine. In the eight placebo-controlled dementia trials, there were 940 patients exposed to memantine, 396 with Alzheimer's dementia.

There were, in addition, four open-label extension trials. These were all comprised of patients treated in the dementia program. There were 417 patients

in these open-label trials who received their first exposure to memantine; that is, these are patients who were treated with placebo in the double-blind portion of the trial and then switched to memantine during the open label segment of the studies.

In total, therefore, we have 1,748 patients treated with memantine. 1,357 of these were patients with dementia and 1,331 were patients derived from the double-blind trials.

Throughout this database, all adverse events, discontinuations due to adverse events, laboratory values, vital signs, and ECGs from patients, were systematically reviewed for safety signals.

Looking at treatment duration, this is a summary of exposure data from the core safety trials. As a brief note, these columns are not cumulative and this is the total. The two take-away points here, number one, nearly half the patients had been exposed to memantine for a duration of 24 weeks or greater, and the large majority of patients received the 20 milligram dose of the drug.

Looking at summary demographics for the double-blind, placebo-controlled dementia trials, you can see here that there's good similarity between the placebo groups and the memantine groups on most measures. The average age was about 76 years. The bulk of the patients were 65 to 84

years of age. They were predominantly female and of European descent.

This slide presents a summary of the deaths that occurred during treatment and within 30 days of treatment cessation. A brief word about format. The rates here are presented as deaths per 100 patient-years. The top row shows the death rates in the double-blind, placebo-controlled trials and as you can see, there's good similarity between the placebo and the memantine groups. In the open-label extensions, there was no parallel placebo arm, and here the death rate was 7.9, similar to that seen in the double-blind, placebo-controlled trials.

In the conduct of the trials, no death was assessed as due to drug. The causes of death were quite similar in all three of these groups.

In addition, subanalyses showed no clinically relevant effects of sex, age, dementia diagnosis, or severity relative to placebo.

In looking at serious adverse events during treatment and within 30 days of treatment cessation, we again followed a similar format for data presentation, looking at rates per 100 patient-years. We utilized a standard definition for SAE, serious adverse event, which you can read here on the slide.

Overall, in the double-blind, placebo-

controlled trials, there was good similarity between placebo and memantine in the overall rate of SAEs. Likewise, in the open-label extension trials, the rates of SAEs were similar to that seen in the double-blind, placebo-controlled trials.

Subanalyses revealed no clinically relevant effect of sex, age, dementia diagnosis, or severity relative to placebo.

Discontinuations due to adverse events, or ADOs, were the most common cause of discontinuation in the core dementia trials. Again, a brief word about format. We're now discussing percentages, and in the top row, you see, in the double-blind, placebo-controlled trials, the rates for ADOs are similar between placebo and memantine. Likewise, in the open-label extension, the rates for discontinuation are also similar.

The bottom half of the slide presents a summary of discontinuations due to adverse events seen in greater than 1 percent of patients in either treatment group. There's good similarity in these causes of discontinuation between placebo and memantine as you can see here.

Subanalyses revealed no clinically relevant effect of sex, age, or dementia diagnosis or severity of illness relative to placebo.

Looking now at adverse events that were

reported by greater than or equal to 5 percent of patients in either treatment group, we see here the memantine cases listed on the right in descending order. Overall, there was good similarity between these groups. In some instances, events occurred more frequently with memantine and others more frequently with placebo. However, no adverse event was reported at an incidence of greater than or equal to 5 percent in the memantine group and at a rate greater than or equal to 2 times that of placebo.

We chose to look at adverse events, also, by looking at point estimates of relative risk, here seen as a dot, and the 95 percent confidence interval, seen as the horizontal bar. In this chart, increased relative risk is on the right-hand side. That is an increased relative risk with respect to memantine. Here, a decreased relative risk on the left-hand side of the chart with respect to memantine or an increased risk associated with placebo.

Overall, there's clustering around the no-effect line for most of these events, with some events, headache and constipation, occurring somewhat more frequently in patients on memantine; others, agitation and inflicted injury, occuring more frequently in patients on placebo.

I discussed earlier that in looking at the core safety trials, we would be combining all of our patients

treated with memantine with dementia. In order to validate the approach of clustering Alzheimer's dementia with vascular dementia, we compared the adverse event profile seen in patients, greater than 5 percent of patients, in patients with vascular dementia and patients with Alzheimer's dementia. Here, Alzheimer's dementia is seen on the top line, the open circle is vascular dementia.

Overall, in this slide and the next, you'll see there's good comparability between both disease groups. The exception here is headache which occurs somewhat more frequently in patients with Alzheimer's disease, although there's overlap here between Alzheimer's and vascular dementia, and on this next set of slides, again good overlap between patients with Alzheimer's dementia and vascular dementia, again with constipation here with vascular dementia, not crossing the no-effect line but again overlap here. Overall, we felt this validated our clustering of these two disorders in assessing safety.

Earlier, we heard Dr. Greenamyre comment that memantine belonged to a class of agents, some of which have been associated with psychotomimetic properties. In this slide, we examine a series of selected CNS events of interest and analyze them for the Alzheimer's population and the total dementia population.

The top four events are events that might be

termed "thought disorders," hallucination, delusions, paranoid reaction, and psychosis. Taken as a whole, we see little evidence of any psychotomimetic effect associated with memantine use.

Two other CNS events of interest of note. Confusion occurred somewhat more frequently in patients with Alzheimer's disease and in the total dementia population. However, when confusion was reported, it was typically transient, mild to moderate in severity, and usually occurred during the titration phase of treatment. Agitation was seen less frequently in patients on memantine, both in the Alzheimer's population and in the total dementia population.

In summary, with respect to adverse events, we saw no evidence of differences based on subanalyses by dementia diagnosis or severity and no evidence of differences compared to placebo based on subanalyses by sex or age. In addition, as seen in the briefing booklet, we saw no marked effect of donepezil on the adverse event profile.

During the double-blind, placebo-controlled dementia trials, we assessed vital signs and weights. These included diastolic blood pressure, systolic blood pressure and pulse. There were no clinically relevant differences between treatment groups in the mean change

from baseline in blood pressure, pulse, or weight, and the overall incidence of potentially clinically significant, or PCS, vital signs were low.

As an aside, in these trials prospectively, we designated parameters that would be termed potentially clinically significant, or PCS, and I'll present some of those summaries for you as we go along.

Here we see the PCS vital sign and weight measures that were reported by more than .5 percent of patients in either treatment group. As an overview, you can see there's good comparability between the placebo and memantine patients.

Laboratory results were also obtained during the conduct of the clinical trials. These included clinical chemistries, hematology, and urinalyses. There were no clinically relevant differences between treatment groups in the mean change from baseline in laboratory values and no clinically relevant differences between treatment groups in the incidence of PCS laboratory values.

This slide presents a summary of the PCS laboratory parameters that were reported by greater than or equal to .5 percent of patients in either treatment group. Taken as a whole, there's similarity between those patients on placebo and those on memantine in the course of the clinical trials.

Finally, with respect to ECG, we examined ECGs in four clinical trials in the core safety database in approximately 800 patients on memantine and 600 patients on placebo. There were no clinically relevant differences in change in mean ECG interval values versus placebo and no clinically relevant difference in the incidence of PCS ECG interval versus placebo.

In summary, we therefore conclude that memantine at a dosage of 20 milligrams per day exhibits a safety profile similar to that of placebo and is well tolerated and safe for the treatment of Alzheimer's disease.

I'd now like to turn this over to Dr. Steven DeKosky, the Chairman of the Department of Neurology, to summarize our discussion today.

DR. DeKOSKY: Good morning, Dr. Kawas, Dr. Katz, Dr. Temple, members of the advisory board, and guests. My name is Steve DeKosky, and I'm the Chair of the Department of Neurology at the University of Pittsburgh and the Director of the Alzheimer's Disease Research Center at Pittsburgh, and I want to give you a bit of context, summarize some comments about the context in which this medication is proposed for use in Alzheimer's disease, and give you some commentary about the risk-benefit of the medication.

One of the issues that has been discussed in detail by a variety of us is the staging of moderate to severe Alzheimer's disease. I want to comment about the demographics and the need for treatment, as well as the definition, diagnosis, and the clinical transitions that mark the movement of someone from mild to moderate to severe disease and how one does that clinically and selects patients for trials, and then I'll briefly review the efficacy data and the safety data.

This is a graphic of the prevalence of Alzheimer's disease over the next 50 years by half-decade and what it shows is a striking increase in the number of cases that will develop in the United States over the next 50 years. It also indicates the levels of severity because these are detectable as a staging of the disease and at the bottom half of this startling increase is the projected increase in cases with moderate to severe Alzheimer's disease over the next 50 years.

This is a composite bar graph that shows prevalence in treatment rates for Alzheimer's disease. It also indicates the splits of people from a very recent paper by Hebert from the Chicago population study indicating levels of mild, moderate, and severe disease, the approximate percentage of cases in each group that are prevalence diagnosed cases and then also an estimate of

those cases which are treated with the currently approved medications, the cholinesterase inhibitors. You'll notice that approximately 60 percent of the prevalent cases are estimated to be diagnosed and that there are varying percentage of those cases who are treated for Alzheimer's disease with the cholinesterase inhibitors.

Now, one of the issues about moderate to severe disease, especially in moderate disease, is that it's very frequently the stage at which people are diagnosed with the disorder. There are a variety of reasons for that. One is that part of the illness itself is a lack of insight into one's cognitive deficits, so that people who have the disease don't realize they have it and it is not until they have difficulties with activities of daily living or maintaining their own lives that someone else notices that there is something wrong and brings them to a doctor.

There also is an accepted prejudice in our society still that it's okay to lose your memory when you get older but it also delays other members of families recognizing that people will develop dementia and not bring them to the attention of a physician or a health care provider until they have reached a moderate stage of disease. And there is surely some level of denial on the parts of families that someone is losing cognition as they move into later life.

There are no approved treatments right now for the more severe stages of Alzheimer's disease in the U.S., and there are some limitations to the currently available therapies which, as Dr. Katz described, are all cholinesterase inhibitors.

Now, there are a number of benefits to treating this group. One comment to make is that over the past 5 to 7 years, we have made significant progress in examining both in imaging studies and other kinds of non-invasive looks at living patients as well as in autopsy examination of patients with mild to moderate disease and learned that the levels of degeneration in the brains are substantially less than we thought they were from the groundbreaking studies of the 1970s and 1980s, and that there is much more in the way of cellular content and circuity that remains until quite late in the disease that represents an opportunity for intervention with a variety of therapies.

The opportunity to impact both the functional as well as the cognitive status of patients in these more severe levels of disease is increased, I think, by this knowledge that the brains are not as far degenerated as we thought they were from earlier studies, and also, since this is a time of increasing caregiver burden, any sort of intervention that symptomatically improves or slows the decline of patients would be an appropriate and useful

thing to have.

The identification of patients who have moderate to severe disease is basically done the same way we do it with patients who have mild disease. In many cases, clinicians who are experienced with these patients will say that it's easier to tell someone has Alzheimer's disease if you see them first in a moderate stage for two reasons. One, because there's a longer history of the progressive changes in the history of decline that patients have, and second is that the pattern which is the diagnostic inclusion pattern of cognitive function change in patients is usually much more apparent than it is in the very early stages when it sometimes is difficult to differentiate from normal aging or from other early manifestations of other neurodegenerations.

The criteria are the same, the NINCDS criteria for probable Alzheimer's disease and the DSM-III and DSM-IV criteria for dementia syndrome and for Alzheimer's disease, respectively. So there is no difference with respect to the kinds of standards to which people are held for diagnosis.

The severity of Alzheimer's disease, though, in these more severe categories of symptoms is done a bit differently. First, usually the coin of the realm is still the Mini-Mental Status Examination and the range of the

score of a patient who's seen determines how the subsequent questions and interviews with patients and families will be directed, such that the level of function that one would ask about either family members or the patient would be very different if someone presented with a Mini-Mental of 24 versus a Mini-Mental Status score of 11 or 12, and the global impression that one has is a multidimensional assessment of people's cognition, ability to maintain their daily lives and how much they are being supported by a family member or a caregiver.

A number of things that mark the transition from mild to moderate disease, I have listed for you here. Probably the premier one that people would agree on is a loss of what we call instrumental activities of daily living. This would include such things as being able to use the telephone well, to be able to maintain a checkbook or one's own fiscal status of one's household, and something as straightforward as being able to travel perhaps from one city to another without either needing help or having the family worry unduly about someone's safety or ability to stay oriented.

Also at this point, there's a constant need for memory aids to be able to maintain one's self in the home or to be able to take medications or do other things that are required and recurring. At this time, the varying

behavioral changes and psychological changes of aging occur which include most commonly, I believe, earliest on a social withdrawal and subsequently paranoia, suspiciousness, uncertainty about others or about the interactions with the world.

The transition from moderate to severe Alzheimer's disease is a bit more serious and sobering. Now, patients cannot handle their own affairs without continuous help from other people in the community or in their family, and now, as opposed to instrumental ADLs, they lose basic activities of daily living, the ability to feed themselves, to maintain personal hygiene, and to do other similar tasks.

Substituted judgment for these people is needed in all cases because they cannot make everyday decisions in a rational way themselves and the behavioral and psychological disturbances that occur in AD increasingly interfere with their ability to maintain normal lives. This includes delusions and hallucinations and a variety of the other behavioral symptoms listed.

Mobility and speech may be maintained well until very, very profound levels of Alzheimer's disease, but in people with moderate to severe disease, their recognition and interaction with family and friends may be limited to gestures or to facial expressions, but family

members and people who take care of patients with moderate to severe disease in nursing homes will tell you readily that they have interactions, that they have communications, and that they are still both valued and maintained.

I've tried to give you here a sense of the dynamic of how people lose function over time with the recognition that these are unidimensional aspects of what is very clearly a multidimensional change in people, but these are the sorts of things from which the scales that we discussed today are derived in terms of trying to get a handle on the nature of how people change once they cannot have a high-level verbal discourse.

So attending to a conversation and being able to both interact and respond in a conversation is progressively lost through mild stages, and by the middle of a moderate stage, it's very difficult to engage someone in the same level of conversation as they would have before illness.

The progression of loss of basic activities of daily living, marked here by being able to run water for washing to maintain one's own hygiene, progresses steadily in terms of loss into the severe stages.

And the most fundamental activity of daily living, being able to feed one's self, begins to decline slightly in mild disease, at least as far as choices are

concerned, begins to become more problematic in moderate disease. Some time in the moderate to early severe stages, people lose the ability because of loss of praxis to remember how to use forks or knives or other utensils but still can eat and feed themselves until late in the disease when it must be substituted. So the decrease is progressive and it's along a number of dimensions that these scales have tried to capture for this population.

The efficacy of the studies has been shown in three different domains, I think, and you've seen a great deal of data from Dr. Schneider and a summary from Dr. Olanoff about these data. There was a monotherapy study versus placebo that showed benefit in cognition in global domains and in activities of daily living. There was an add-on study to the current prevalent drugs, the cholinesterase inhibitors, that also showed a positive outcome, and there was a trial done in a nursing home which is a place where a large number of patients with more moderate and more severe disease live that also showed positive outcomes. So three different types of studies, all of which showed positive outcomes in a number of domains.

The clinical relevance of and picture of the treatment effects that you've seen today are also shown in this responder analysis. In this particular case, the

primary responder analysis was defined by improvement or stabilization in the cognitive domain, which was the Severe Impairment Battery or the SIB, and then either stability or improvement in one of the other two domain markers, either the CIBIC-plus or the ADCS-ADL scale, so cognition plus either the global or the functional scale. As you can see in both 9605 and in MD-02, there was a statistically significant increase in the number of responders in memantine versus the placebo case.

The safety data which was presented by Dr. Jonas of almost 1,750 patients basically showed no signal for significant problems with complications with either dementia or the neuropathy cases in terms of adverse events, cardiac problems, or drug interactions, of major importance in a frail elderly group who take lots of different medications. There was not a signal that there was a problem with these medications and interactions, and so the safety profile of the medication appears quite solid.

There's no question, as I showed you earlier, that this is a burgeoning population who need treatment. We also in our progress in research in this disease have identified increasingly improved methods of early detection of disease, the initiation of studies for prevention of Alzheimer's disease. At the same time that we make this

progress in moving back to try and stop the disease before it gets started, we have a very large number of cases who we would like not to leave behind with respect to both developing and implementing interventions, both symptomatic and preventive.

So, in summary, I believe that memantine has a very favorable risk-benefit ratio. It has been shown to be efficacious in the domains that we have expected them to be and hoped them to be positive for, both as a monotherapy and as an add-on, in a number of different environments as well, and it's quite clear that the drug is very safe and well tolerated for use.

Thank you very much.

DR. KAWAS: Thank you to the sponsor and to Steve, and the floor is now open for questions from the committee to the sponsor.

Dr. Temple.

DR. TEMPLE: I just want to make sure nobody on the committee wants to ask something first. They always get to go first.

DR. van BELLE: I have one or two questions with respect to the statistical analysis, Dr. Kawas. Could I ask them?

DR. KAWAS: Please.

DR. van BELLE: I think the most challenging

issue to me is the subgroup analysis done by the FDA of the severe versus the moderate groups and the efficacy issues related around that issue. I'd like to ask the sponsor. They did that one thing that I was going to ask them to do, which is to plot the efficacy data versus the Mini-Mental scores which is exactly right. But I didn't see any statistical analysis of that.

For example, you could do an analysis of covariance of the efficacy with the Mini-Mental score as a covariate, so that you basically adjust for the severity level and if there was no pattern there, then the slope should be 0. If it's not 0, if it was in the direction suggested by the FDA, then that would suggest that there was less efficacy at a lower level of the MMSE. I think that's important clinically because a physician would have to say to a family member that if, say, the Mini-Mental score was 8, the expected efficacy is going to be much less than if the clinical score was on the order of 14 or 15.

So I'm wondering whether the sponsor did any analysis of covariance or some kind of systematic analysis of the efficacy using the Mini-Mental as a covariate.

DR. OLANOFF: I will ask Dr. Fisher to address that. Before I do, though, I want to emphasize a couple of things. One is that a similar analysis was done of MD-02 to look at the treatment effect size in the severe and

moderate groups. If anything, in MD-02, the treatment effect size was actually a bit larger in the severe than in the moderate group.

Interestingly enough, the only difference between the two protocols was that MD-02 did not allow for inclusion of 3's and 4's at baseline Mini-Mental Status Exam. So I would point that out.

Also would comment that in trial 9403, which was the initial trial -- and we focused only on functional and global outcomes -- that in fact that study was all severe patients, and in fact, both those outcomes were positive independent of which substrata you look at with the Alzheimer's disease population.

Both those analyses, by the way, were performed by the sponsor. The designation of patients into the Alzheimer's disease category was on a clinical diagnosis for the sponsor, but for the FDA was based on a CT scan diagnosis and there were disparities between the two, but in the end, the global outcomes were still statistically significant in that group.

I'd like to ask Dr. Fisher then to comment specifically on the covariance analysis.

DR. FISHER: Yes. Actually, I was going to start out first with the comments that Dr. Olanoff just made. With three studies and so on and any number of

possible cuts, there's a big multiple comparison problem here, and subsetting has been an issue that has bedeviled drug development and virtually every advisory committee meeting actually from time immemorial.

Two sorts of analyses were done on 9605. The first one, because the agency had taken a dichotomous cut, was to look for the interaction using their dichotomy, and there is no statistically significant interaction for any of the three. The worst one they focused on, the p was .22 for interaction. If you took that worst stratum and did a covariance analysis using a continuous case, it was significant at the .05 level.

However, again this is one scale out of three studies, one possible cut, and I could have reduced it below .05, of course, because the reason you think of it is you happen to see the ordering of the way the things fall out. If I had used a spline and broken it right with the last three, I'm sure I could come out with an even lower level of significance in response to the data.

But as was noted -- and it's actually one thing I pointed out to them -- in every case, the estimated effect is the right direction. So even if there is an interaction and there can be, it's my opinion that if it's there, it's a quantitative and not a qualitative interaction. For those of you who aren't used to the

statistical discussions, that might mean there's lesser benefit, but you haven't switched to a situation where you actually have no benefit or, worse yet, even doing harm which is very important in consideration of compounds.

I guess I don't get to ask questions, but I'd be interested to hear Bob Temple's view because he's been through so many subgroup discussions that I've been party to. These are always difficult decisions, but I think by longstanding tradition, it's very wise we don't overreact to such things.

DR. TEMPLE: No. Dr. Van Belle's question is the same one I was going to ask, and it seems important that the MD-02 didn't really show the same distinction as Dr. Katz's memo pointed out.

Dr. Schneider had sort of hinted that if you make the cut in different places, the results come out different, but nobody showed those data. But I don't disagree with what Lloyd says. You can find a lot of things if you keep slicing the data. There's no question about that.

DR. KATZ: Just one clarification. It's of course true that where you make the cut may have an important effect on the result. We made the cut at 10 because that's been the lower limit of MMSE for the mild to moderate studies. So for whatever reason, right or wrong,

it has been, I'll call it, tradition to say that an MMSE of 10 and above, you're labeled at least moderate, but below 10 is presumably where the severe patients are.

DR. FISHER: No, and being privy to a lot of the sponsor's discussions as they rehearsed, they realize that. Otherwise, the statistician would have had an adjustment for what's called a scanning statistic where you move the cut point along to get the smallest possible p value.

DR. KATZ: I recognize that the sponsor knows why we did that. Just for public purposes and for purposes of the committee's understanding, we didn't choose that arbitrarily. We chose it because of where the cut has been made in diagnosing patients in terms of severity.

DR. OLANOFF: One other comment to add. We agree that that's a commonly determined definition for marking severity, but another factor which we haven't discussed and we can, if necessary, is that although the scales themselves are validated across the entire population that we looked at, per se, they may, as all scales, have varying sensitivity to pick up differences at varying ends of the scales. So that may also influence it in terms of the treatment difference. But I would also reiterate what Dr. Fisher has stated, is that the directions typically are going in the right direction, so

to speak, at least qualitatively.

DR. KAWAS: Would the sponsor like to show us the data with the cut above 10, between 10 and 11, as Dr. Schneider referred to? They're thinking about it.

Dr. Kieburtz, and then Dr. van Belle.

DR. KIEBURTZ: I'd just like to pursue this discussion. It seems that 10 and above is a cut point using the MMSE which at least has a previous regulatory history, but it strikes me that at least 10 was a lower boundary around what was defined as moderate, but it doesn't strike me that there's been evidence to suggest that that is the boundary at which you start defining severe. In fact, there's this other scale, the Clinical Dementia Rating Scale, which does fall into mild, moderate, and severe, which we haven't heard much about.

In fact, the SIB and the ADCS instrument protocol was assessed primarily in CDR2s, moderates. Very few severes are included and the scores observed in the SIB here are very analogous to more moderate stages of Alzheimer's disease.

I just wonder if CDRs were done, if you have the distribution of those who entered 9605 and MD-02, or if you have some discussion about another mechanism of rating severity that does not rely on some cut point within a scale which is primarily driven at cognitive function.

DR. OLANOFF: Dr. Schneider.

DR. SCHNEIDER: Karl, we presented this data stratified this way in response to the questions asked. In 9605, patients were also characterized by a Global Deterioration Scale into a 5, 6, and 7 category. So that's a partial answer to how we defined severe and moderate.

But insofar as doing the clinical trials, we felt that using the MMSE brackets was substantial enough to get the group and to maintain consistency from site to site on that.

DR. KIEBURTZ: Were CDRs done?

DR. SCHNEIDER: CDRs, Clinical Dementia Rating Scales, were not done. Global Deterioration Scales were done in 9605, and then we felt that in MD-02 and others, we could describe the severity using the descriptive scales.

Did you have another question?

DR. KIEBURTZ: No. That was it. Thanks.

DR. SCHNEIDER: One other aspect of the cutting is just to put on the table that the Mini-Mental State Exam test used was serial 7's and not "world" spelled backwards. So there's another .8 of a point adjustment that one might make against speaking to do you cut at 9-10 or do you cut at 10-11, to some degree. As Dr. Katz brought up, there's a convention.

DR. KAWAS: Dr. van Belle.

DR. van BELLE: Well, first of all, I have very little love for the Mini-Mental at that low level, but nevertheless that's what's being used clinically.

Just one other point. This is probably a value judgment on my part. At that kind of level of disease, you're more interested in functional status rather than cognitive status, I would guess. If you can keep down the agitation and so on, that's more important than the cognitive aspects. Yet that's precisely the endpoint that wasn't doing so well when you cut the data at 10 or less.

So one question would come up again in terms of advice to a caregiver. What could the sponsor say to a caregiver with a loved one with a score of 6 in terms of what this drug is going to do in terms of their functional status, given this particular drug?

DR. KAWAS: Dr. Katz.

DR. KATZ: Yes. I would just ask sort of again the question we've asked but a more sort of fundamental question to follow up on Dr. van Belle's question, which is not so much what would you tell a caregiver if your husband or wife has an 8, but first and foremost, do we think it works in the patients with severe, again, severe defined at least in part by an MMSE less than 10.

I think that's a discussion I think that needs to be had obviously, not necessarily at this point, but

when we discuss whether or not you think there's evidence of effectiveness. But I think from a regulatory point of view, that's the real question. Do we think there's evidence of effectiveness there? Cutting it down to an 8 or a 6 is --

DR. FISHER: I would like to make a comment for Gerald and I'm sure Gerald is aware of this, because when you start focusing on one scale and one subgroup and the inference on the comment is if that's all the data. To my mind, the most striking data in the really severe is the study in Latvia, and the only knock on that is it doesn't have cognitive which wasn't the part that you were emphasizing anyway, Gerald. But the data there are really quite striking and then you have 02. So I'm not saying you should ignore 05.

But I just plead with the committee whenever you make a decision, of course, you have to somehow integrate in your mind, formally or informally, the totality of the data. So I think as you discuss these things, you want to bring up that.

DR. KAWAS: Rusty.

DR. KATZ: Yes. I want to actually ask a question or raise a point about this so-called totality of the data. Typically, in the typical case -- well, in all cases, we have to have substantial evidence of

effectiveness, and in the vast majority of cases that's defined as at least two trials that independently show what you wanted to show. So, yes, there is the question of totality of the data.

But I think another question that I would like the committee to discuss explicitly when we get to the point of is there evidence of effectiveness is whether or not there are two studies that independently provide evidence. So there might be a global in one study and there's a cognitive measure in another study, and when you put it all together, you have a couple of cognitive measures all told and you have a couple of global measures all told across three studies and you might find that compelling. But I need to know whether or not the committee thinks there are two independent sources which on their own terms are positive studies.

Again, I don't think we necessarily have to discuss that right now. I think we're still in the questioning period, but that is an explicit question I would like the committee to address when we get to it.

DR. KAWAS: Dr. Wolinsky.

DR. WOLINSKY: So I know the issue in front of us is memantine, but I have, I guess, a question as a non-expert in the field of Alzheimer's disease to understand the data that's been put in front of us and also to ask

additional questions of data.

So if perhaps the Alzheimer's experts could give me some insight into whether or not donepezil has an effect that extends beyond 1 year of continuous treatment. This seems to be important for me to understand, first, the MD-02 study and whether we're looking at a question of whether there's adverse drug interaction or whether we're looking at combined effects or whether we're looking at an effect of the drug of interest.

DR. KAWAS: For lack of anybody better to answer that question, I would say that the sponsor would say that donepezil has an effect after 1 year.

DR. SCHNEIDER: Well, I'm not the sponsor, but I'm a consultant.

(Laughter.)

DR. SCHNEIDER: First, the one trial that has direct evidence is a 1-year placebo-controlled donepezil trial done in Scandinavia and in the Netherlands, and there, the cognitive outcomes were a portion of a scale called the Gottfries, Brane and Steen Scale where a portion of that includes mental status questions and the Mini-Mental State Examination.

On the direct parallel group outcomes at the end of the year, in both the observed case and the last observation carried forward -- and there were about a third

of patients who did not complete the year -- there was a significant effect for the Mini-Mental State after a year and, as I remember, not on that subsection of the Gottfries, Brane and Steen Scale for cognition. Others might have a better memory of that. That's the direct evidence for a continuing effect of Aricept for 1 year.

Now, there are also the 6-month studies in which patients had been followed in an open-label way, and in those studies, patients randomized to donepezil as a group, ignoring dropouts, seemed to maintain function over 1 year.

We have a dilemma in this trial in that on average, patients were maintained on donepezil for 2.5 years, and we just gave you the 86-percent statistic for 1 year. At that point, at entry into the study, mean Mini-Mental State scores were 10. So it was already half of the population was below the mild to moderate range, the 10 to 26 range, in which the drug was tested.

So one way of looking at MD-02 is patients were being maintained on donepezil. They were randomized to placebo or memantine. There were drug-placebo differences in favor of memantine, and in the placebo group, patients continued to deteriorate. It's just, I think, not known whether that rate of deterioration was being influenced by the donepezil on an average of 2.5 years later.

DR. KAWAS: Dr. Kieburtz.

DR. KIEBURTZ: I'd just like to take another slight run at this. I think the entry criteria are clear to me that at least moderately affected patients were included, and we're talking about previously using MMSE to help identify a group that might be accepted as severe. I'm still struggling with trying to see data regarding who in MD-02 and 9605 might have met a definition of severe beyond the Mini-Mental Status one.

So there's no sort of histogram of the GDS at entry or the proportion of people at entry, for example, who could not, using yours and Dr. DeKosky's definition of severe, feed themselves, could not dress themselves, could not groom themselves. I think that would help me to understand at entry the proportion of the randomized population that meet a definition of severe beyond solely those using the MMSE.

DR. OLANOFF: I think what we can do is discuss some of the other criteria that was measured at baseline, not necessarily sometimes as inclusion criteria but with some commonality across the two studies.

Dr. Schneider, do you want to comment?

DR. SCHNEIDER: Well, Karl, I believe we have the data on the breakdown between GDS scores of 5 and 6, 6 is severe, 5 is roughly comparable to moderate. I don't

think we have data on patients changing status, going from 5 -- that's not what you were looking for.

DR. KIEBURTZ: Just baseline.

DR. SCHNEIDER: Okay, just baseline. So we're looking for that to see the proportion of patients who were in 4 compared to 5. I'm pretty sure we haven't done a combined categorization where we might categorize by Mini-Mental State and GDS as well. We'll either have it for you or we won't.

Larry is reminding that another functional scale, the FAST Scale, was used. We had a limit in 9605 of a stage 6c or so. We can also categorize by essentially stage 6 and beyond to give you a better indication. I just don't know whether this data is accessible at the moment.

DR. KAWAS: I have a question. Given the mechanisms that you showed us in how this drug potentially may work, do you think that the severity is relevant for whether or not a patient would respond?

DR. OLANOFF: I'll ask Dr. Greenamyre to address that.

DR. GREENAMYRE: I would say that given our uncertainty as to mechanism and the lack of suitable preclinical models to guide us, we have no preconceived ideas about whether it should work better in one stage of severity versus another.

DR. KAWAS: But the indication that you're asking for is very dependent on severity. What's the rationale behind this then?

DR. OLANOFF: I think that the rationale was not so much based on the pharmacology of the drug, which wasn't all that widely known up until the last decade or so, but more on the opportunity that presented itself from a historical basis in terms of the patient population of interest. So the initial trials that were done in severe dementia were done largely because that was an area that other people weren't addressing and Merz decided to pursue that largely for European registration, to pursue actually a novel indication that was important to them for registration purposes, and based on that experience, that carried on into the construct of the 9605 study which was pursued in the U.S.

It gave them an opportunity to pursue patients that essentially weren't under competition by the other acetylcholinesterase inhibitors. So it was more historical precedent than it was based on the pharmacology of the drug. I don't know if anyone from Merz wants to comment further on that, but I think that's more or less the basis of how the indication was built.

We have no presumption or indication at this time that the drug wouldn't work in mild patients. We just

don't have any data to demonstrate that, and we are pursuing a mild to moderate program, and I would remind you, we did talk briefly about data in mild to moderate vascular dementia patients. Of course, the studies didn't reach the desired endpoint on the global side but did show some effects on the ADAS-cog in these mild to moderate patients.

DR. KAWAS: Dr. Packer.

DR. PACKER: Also not being an Alzheimer's expert, still could I get a little clarification on this issue of two study versus the global results?

The only study that showed a statistical difference in the severe group was the 9403 study for global outcome. Yet, the statement was made that when we take the totality of this, that there is an improvement in global outcome in these patients.

Can you clarify for me why one study would show benefit where another would not, not so much in global abilities, and whether it was a function of entry criteria? 9403 didn't have perspective entry criteria. It was all patients in a nursing home. Can you try to clarify that for me?

DR. SCHNEIDER: I may need you to repeat the last part of your question, but I'll start with the beginning.

First, as you saw, overall, the globals, either the CIBIC-plus or the ADL, which might be also considered as an index of clinical meaningfulness, in both the studies 9605 and MD-02, the two U.S. studies, overall in the trial, they were statistically --

DR. PACKER: I'm sorry. I was meaning the severe group, under 10.

DR. SCHNEIDER: In 9605, as demonstrated by the FDA post hoc dichotomized analysis, most certainly the Mini-Mental State-defined severe group did not show statistical significance. In MD-02, it did. In MD-02, the dichotomization at 9 and 10 showed statistical significance in both groups.

DR. KATZ: Actually it didn't for the ADL. I think the p value was .168 or something.

DR. SCHNEIDER: I'm sorry.

DR. KATZ: Now, again, in that study and the reason we didn't really make much of it was that if you actually look at the treatment difference within each strata, MMSE less than 10 or 10 or greater, the treatment effect looked about the same in both of those strata and there are fewer patients in the severe strata. So you wouldn't necessarily expect an actual statistically significant difference because the numbers are small.

I don't recall what the CIBIC showed, but in

any event, the ADL, we thought, was sort of a numbers question there. We were more concerned in the other study. The CIBIC was actually significant in both strata or at least in the low strata. In the low strata, I believe.

So we were more concerned in the other study -- I guess it's 9605 -- because the numbers in the severe group, as defined by the MMSE, were actually larger, there were more patients, and the more moderate patients actually showed a statistically significant difference in that study. So that's why we were concerned about that finding. In 02, the treatment effect looked about the same and the numbers were small.

DR. SCHNEIDER: This is the 02 results. The CIBIC stratified are demonstrated here, and as you can see, the effect was as it was.

You had another?

DR. PACKER: Not so much the MD-02 but the 2 other trials, why there would be a difference in that severe group, why you weren't able to show the same difference between those two groups in the severe group in overall global abilities in that group. Is it entry criteria? Are they truly the same group? Because in the 9403, it was all patients in a nursing home, wasn't it? You didn't prospectively identify them by score, did you?

DR. SCHNEIDER: They were identified as

patients in residential care facilities who had DSM-III-R criteria for dementia syndrome and, yes, had to have Mini-Mental State scores of 9 or below to be enrolled.

DR. PACKER: So if they are the same group, why were the two studies different in their results in that subgroup, from your perspective?

DR. SCHNEIDER: I think it's a matter of speculation. They were two different studies, slightly different instruments. A traditional CGI-C was performed in 9403, a clinician's interview-based impression of change and this was now with caregiver input, the NYU version in the other trial. Caregivers were informants in the outpatient study. In the institutional study, the clinicians were observing patients directly. Again, two different trials.

DR. KAWAS: Dr. van Belle, did you have a question?

DR. van BELLE: No.

DR. KAWAS: Dr. Wolinsky?

DR. WOLINSKY: I want to go back to this. I think I heard that the expectation for this class of patients is that they should, without specific treatment, show progressive decline and deterioration and that certainly seems to be true in terms of how the placebo group is behaving in 9605 and MD-02 and also in terms of

the difference we see in the rates of decline on therapy.

But in 9403 and I gather that while there are differences in these instruments that were used, that there were also similarities in the instruments. The placebo looked to be extremely effective, probably less expensive.

How do you account for this difference in behavior?

DR. OLANOFF: I'll ask Dr. Schneider to comment. As he comes up, I think the one comment he made during his presentation is that these patients received an unusual amount of care than relative to their past experience and there was a great deal more attention spent with these patients perhaps because of their entry in the study. There's always that issue of a placebo effect.

I think, also -- and Dr. Schneider can comment further -- you have to look in part at the duration of the trial, too. This was a 12-week trial versus a 6-month trial, and while we believe the differences would be preserved, as they are in the 6-month trial, oftentimes in 12-week trials, you start to see some positive motion in some of these endpoints early in the trial.

DR. SCHNEIDER: I think that's the answer that most of us favor, that in a nursing home trial, there is a greater and more acute increase in care when patients are entered into trials. The milieu is improved. The staff

are more involved. The patients are getting more time and on a daily basis over a short period of time, of course, while in the outpatient studies, these are patients living at home usually with their spouses. They're evaluated at screening, at baseline, then they'll come back in 4 weeks, and aside from the medication, the increase in attention and level of care is not quite of the same intensity. And then again, the trials are going for 6 months rather than 10 weeks or so.

DR. TEMPLE: I guess I wanted to respond to something Lloyd Fisher asked earlier. In the cardiovascular area especially, where you have large outcome studies, people always do subset analyses because they're intriguing, and the number of times something weird comes out of those is very depressing and it's always impossible to deal with.

My most favorite recent example is in a trial of a metoprolol-controlled release product in people who have heart failure where there was a 50 percent reduction in the rest of the world in mortality and 0 effect in the United States which had a quarter of the patients in the trial. We eventually danced around it in labeling but took a lot of heat from most of the world which said you can't rely on things like that. They're unstable. They show up all the time. And they do show up all the time, and you

never really know whether it's a true bill, telling you something you didn't quite understand yet but real, or is just a spuriosity.

So it's a very important discussion, but I'm always amused by the challenge. Well, please explain this. Of course, you never can. You can speculate and it's never satisfactory and it's really hard to know what the answer is. The only real remedy is to have more data, repeated studies and see if it shows up all the time.

One might say that there's some element of that here because one of the studies of very similar design didn't seem to show that difference. That's sometimes considered more useful than just speculating on why the thing happened, but it's an extremely common finding. I'll give you many more examples, if you want to be bored with them, but they always show up and we never quite know what to do with them.

DR. FISHER: Just to make one comment on that that I think is important people understand. I've been in a lot of those discussions over the years, and I say, well, in my opinion, it's probably a chance finding, given everything. They say yes, but why? Why did it happen? I say, well, if it's truly chance, just truly the flip of other coins, we'll never know why. If we can find a why, if there's a good explanation, then that would make it more

believable.

The second thing I'd like to mention about the two-study paradigm, which actually I'm not a great fan of for all kinds of reasons -- and I'm in print about that. But in this package, there are two studies that are clearly positive studies by their predefined endpoints. You may not like the endpoints. 03 is very positive. It didn't have a cognitive endpoint. They went out and got an ad hoc one, mainly because of the mild to moderate criteria in the U.S. That post hoc ad hoc endpoint might be a little better than it seems because they did it blindly. They didn't look at the data to construct one that had an outcome. They went through the material and said, well, this has some sort of face validity.

But there are true positive trials, even if you don't count 05 as positive, because of the 064 and I'd be happy to discuss that in some detail, but the reason I didn't -- here's part of my answer -- is you already have the two positive trials. I don't think that's a big issue in the totality of things, whether it's 064 or 022, using a mixed model, which is post hoc, after seeing the data, and it also makes certain assumptions about what happens to the missingness of the data. One of the problems of missing data is you can never verify the assumptions.

DR. OLANOFF: Russ.

DR. KATZ: I have a different question. If you want to continue with that discussion.

DR. OLANOFF: Yes. Actually, could you put that slide on for a second? We were just going to show it. There was a question earlier about where do you take the cut, and I just want to comment again that, as reiterated by Dr. Fisher, there are two trials that don't seem to reproduce the finding in 9605, for what it's worth.

In addition, I think what's not been said is that none of these trials were designed to assess efficacy in each strata independently. They weren't prespecified tests and because of that, they weren't powered in a prospective manner. What I mean by that is yes, you can get statistical findings in underpowered studies, but in looking at individual strata, you need to look at the sensitivity of the tests employed. They're valid tests, but they may change and we can show you some data if you're interested on the CIBIC-plus by example. They may change at different rates and your ability to pick up those changes may be influenced about which strata you specifically look at.

I'd like to show this slide here and this was in answer to the question about where you cut. If you look at the analysis in 9605, you can see clearly that the effect on the CIBIC-plus is substantially less in the less

than 10 group than in the greater or equal to 10 group. But if you drop to 3's and 4's from 9605, those effect sizes, independent of the statistics because now the numbers are coming down, are equivalent, and further, when you look at MD-02, you see the effect sizes. Of course, this should be near equal because essentially the patients less than 10 are essentially all 5 through 9. There really weren't 3's and 4's in this study. But also very similar to the greater than 10.

So I think that's a pretty good graphical description of what we saw, and I think the point we were making is that, depending on where you cut it, in this case we're cutting out the 3's and 4's -- now, I have to tell you in 9605, the 3's and 4's were a substantial number of that population. That's probably what contributed to that statistic. They were about 25 percent of the population and one has to start to question 3's and 4's. Sometimes the sensitivity is the scale is going to be a little more difficult and you would have to size a trial much larger to pick up that kind of a difference and show a statistically significant difference. You could argue even that their treatment effect is too small no matter what size you used.

But the reality is it's not necessarily pointing to the fact that the 3's and 4's aren't getting a benefit, but that the trial has to be designed to test that

specifically as opposed to doing subset analyses and trying to make inferences, especially when you can't reproduce them across the trials.

Dr. Tariot wanted to comment on the question that was raised about inclusion criteria.

DR. TARIOT: My name is Pierre Tariot. I'm an internist and psychiatrist at the University of Rochester. I was involved in the MD-02 trial, and I've been mulling over Dr. Kieburtz's question from a little while ago.

We're going to put up the FAST Scale. You asked about supplemental ways of looking at who was included in the MD-02 study and you don't understand how many people were significantly impaired. If you look at, for instance, level 4, decreased ability to perform complex tasks, this would include things like using a microwave or a telephone or remote control. Approximately 98 percent had at least that level of impairment in MD-02.

If you look at 5, which in a way addresses Dr. van Belle's question from awhile ago, in plain English what sorts of difficulties are you seeing here, by the time somebody has trouble getting dressed independently and needs their clothes laid out for them, they are on the cusp of complete dependence on others. Approximately 80 percent of patients in MD-02 were in that category.

I can go through the other cutoffs if you want,

but perhaps that addresses your question. We didn't have a slide made based on these cutoff scores, but I have the trial report here.

DR. van BELLE: Do you know what proportion were 7's?

DR. TARIOT: Yes. 7 or below -- let me do the math -- I may be off a bit, but approximately 7 or 8 percent.

DR. van BELLE: And that's MD-02?

DR. TARIOT: That's for MD-02. Those would be profoundly impaired patients.

DR. van BELLE: Thanks.

DR. TARIOT: You also asked a question that I can follow up on, if you want, about the ADCS instrument study. We didn't use the CDR in the MD-02 because it's not readily accessible to clinicians and we wanted to do a study that general practitioners might be able to understand.

In the ADCS instrument study, I can tell you about changes in SIB scores by MMSE strata, if you want.

DR. van BELLE: No. I've got the publication.

DR. TARIOT: Okay.

DR. van BELLE: Thanks.

DR. KAWAS: Dr. Katz, and then Dr. Azarnoff.

DR. KATZ: Yes. I have a question about the

functional scale, the ADL scale that was used in most of these studies.

When we first started to think about what trials in Alzheimer's drugs should look like, we came to the conclusion that there should be a global measure because we wanted to ensure, as I said earlier, that whatever you saw in the cognitive measure actually meant something clinically. Originally, the global was chosen or the type of global we endorsed at that time anyway was designed specifically to be fairly coarse and we called it holistic at the time. But the point was, we wanted to make sure that whatever was happening with the drug actually made a big difference, quote unquote, in the patient's life. So we thought that if, on sort of a vague mildly improved/very markedly improved, which are the sort of criterion of CIBIC-plus, if you saw movement on that, you sort of assumed that it actually meant something clinically, right or wrong.

When you talk about an ADL, as we've heard, there are explicit categories, can dial a phone, balance a checkbook, find your way home, whatever the criteria are. So when you see movement, a statistically significant difference on an ADL, the implication, I think, is that patients who couldn't balance their checkbook can now balance their checkbook. Patients who couldn't find their

way home, now they can find their way home. In other words, that they actually can do things that they weren't able to do before, not just press three numbers of their phone number but actually dial the whole phone number.

Given the treatment effect size that we've seen here, what can we say about that? Do we think or do we have evidence that patients actually couldn't do something before and now they can actually complete that task? I mean, do they actually improve on specific activities that they couldn't do before or is there just a little bit of movement but they still get lost?

I'm trying to get a sense, because that is now in this context what we're using to ensure that the cognitive benefit meant something clinically. Perhaps we fooled ourselves with an unstructured global that we actually were seeing something clinically important. But here, the implication is that these patients can do something they couldn't do before, and I'd just like to hear whether or not we think that is evidence that that's true.

DR. SCHNEIDER: Could you put this slide up, please?

Just to recap, also, part of the premise behind the global was that if an experienced clinician can judge a change in the patient, that change must be clinically

significant and that was a standard by which clinical meaningfulness is judged, and then as you said, then any statistically significant change on a global should then indicate that there is a clinically significant effect in the numbers of patients.

Here's the ADCS-ADL and the items used in this test. Separately from some other scales, this is a set of ordinal ratings and as you said, Dr. Katz, you're rating patients on ordinal levels, on discreet levels of improvement in these activities, in some basic activities of daily living and then in some more closer to instrumental activities.

So in these trials, we're showing effects of several points overall. The question is, do those several points translate into clinical meaningfulness, and the short answer is I think so. If the average difference is, let's say, 3 or 4 points or more, well, then, well over half of the patients are showing greater than that as an improvement. But in order to score several points more, patients need to, on average and on sum, be able to do these individual activities to a greater extent and to an extent that the caregiver is able to observe and appreciate.

Another way of looking at this in terms of clinical meaningfulness is if we can go to the ADCS-ADL

outcomes, the trend drug-placebo differences in, say, MD-02 or 9605. Well, the S curve would be good, also, but also the outcomes that I showed in the core presentation. To go to the ADCS, just scroll through to the ADLs. We'll use this one as an example. Please put that up and then we can use the other.

So here are the sum of the ordinal scores on the ADL for drug or placebo. Here's a difference of about 4 points. This can also be looked at as part of the slope analysis where you can look at the difference in time between when a placebo patient loses 2, 3 or so points on the ADL and hence is losing these individual activities to the time when a memantine-treated patient is, and that's another way of looking at the clinical significance of ADLs.

And then lastly, with the cumulative probability, the cumulative response curves. I think we can again use 9605 to example this, but we could also show the others.

I think many of the committee members are familiar with these kinds of curves from package inserts from prescribing information for the cholinesterase inhibitors. This is showing the cumulative percentage of people achieving certain change scores, certain improvements on the ADCS-ADL, the placebo group, the

memantine group, and here's the continuum of drug-placebo difference.

What you're able to see is if we want to use a cutting score, a particular cutting score to indicate clinical improvement and clinically significant improvement, no matter where we take that cutting score throughout the range, there will be overall and on average substantially greater improvement in the memantine group. So these are just three ways of trying to address the concept of clinical meaningfulness.

DR. KATZ: Right. I agree they sort of address it, but I mean I guess what I'm trying to ask is, let's say you improve 5 points. Maybe you can go back to the slide that actually has the elements of the scale, if you could just put that up.

It seems to me that you can improve 5 points on the scale and not really be able to do much of anything that you couldn't do before. I don't want to make too much of this, but there are 4 points there on the watching television slide. Now, I don't know how you can tell someone watches television better than they used to.

(Laughter.)

DR. SCHNEIDER: It's an art form. In California, we practice it.

DR. KATZ: No doubt, no doubt. We're all

watching California on television now.

But seriously, you can move 1 point on attend to conversation, 1 point on dressing, 1 point, and all of a sudden you've got a 5-point improvement. But I'm wondering whether that still can be independently considered a meaningful difference. You move 1 point on a number of those items, you still may not be able to dress yourself, you still may not be able to feed yourself, that sort of thing.

DR. SCHNEIDER: I think an answer to that question requires a greater understanding of the scale for people to make their own decisions. So for example, here are the items and here are the anchorings for the items. For example, for the first few regarding grooming in the past 4 weeks, which best describes optimal performance? The hierarchical levels are 0 for needed help, 1 kept face and hands clean, 2 something in between, brushed/combed hair, 3 cleaned and cut fingernails. These anchors, I think, serve to demonstrate that there are potentially clear and important levels of improvement, quantum differences in improvement.

Similarly, using examples of items for items number 7 to 15 and using one item in particular, did he help in disposing of garbage or litter? Yes or no? This is a big event. This is an important event. This is

something that a caregiver can assess and can value and I think committee members can also do that. And then the degree to which the person can participate in that activity, with supervision with physical help, with supervision and without.

So I think you can assess the degree of clinical significance yourselves as you consider all 19 of the items.

DR. KAWAS: Dr. van Belle, is your question about this in particular?

DR. van BELLE: Yes.

DR. KAWAS: Yes? Then please, and then Dr. Azarnoff and nobody comes between the two of them.

DR. AZARNOFF: I have a question which might have a simple yes or no answer for a change. I assume that caregivers are no different than the rest of us in compliance with administration of medication. Since this drug is primarily controlled by renal function, I wonder if the sponsors obtained blood levels in any of the subjects and, if so, whether there was any relationship to efficacy.

DR. OLANOFF: I can address that. In one of the studies, the 9605 study, blood levels were drawn at the terminus of the study and we did try to look for a relationship against the Severe Impairment Battery by example and we were not able to show any distinct

relationship between blood level in these patients and the Severe Impairment Battery. Of course, that's all at one dose, too. So there is some fluctuation of blood level around that dose, but it wasn't that wide a range.

DR. KAWAS: Dr. van Belle.

DR. van BELLE: Getting back to Dr. Katz's comment, there is a statistical technique called item response theory which is the one that I would have used in this case by going through each of these 19 ADL items and finding which ones changed and is there some systematic pattern there or is it just a global pattern. But I would predict from other areas that there are going to be some items that are non-responsive. The patient can do them or cannot do them and that function doesn't change over time.

So there are issues of which are the items that are sensitive to the treatment and that would be important clinically, of course, as well. I don't know -- I know that Dr. Schmitt is here with the sponsor -- whether they did some kind of an item response theory analysis or not, but that's what I would have recommended.

DR. OLANOFF: We'll ask Dr. Schmitt and Dr. Schneider to comment on that.

DR. SCHNEIDER: We both need to comment, Gerald. I'll be brief. Fred will fill some of this in.

First, we went through a method of item

identification and identified items from the ADCS instrument protocol that were most sensitive to change, and then insofar as the analysis of individual items -- would you put the slide up, please -- we did look on an item-by-item basis at which of the individual items at least gave statistically significant change at a p .1 or less level to identify that a few of them -- again, there are very few points, but at least disposing of garbage, turning on and off the light were ones that tended to be different.

I think, Fred, you'd like to comment.

DR. SCHMITT: There's another slide I'd like to bring up from 02, the same item analysis, if you would.

While people are looking at this, I think this is again a relevant question, and we have to bear in mind that we don't have any compounds that actually restore functions that I'm aware of in Alzheimer's disease, much less other neurodegenerative conditions. So to ask a compound to actually restore any given function that a patient has lost, at least at the present level of science, may be unrealistic.

But what we do see is we see a restoration or, let's say, an increasing competency, and I think Dr. van Belle's point about the item analysis is very critical because that's really how this ADL measure was identified. We went back to the Alzheimer's Disease Cooperative Data --

Dr. Galasko actually did the lion's share of the work -- and used item analysis to identify which items were showing change at more advanced levels of disease, which items were actually attempted by patients with Alzheimer's disease at different severity levels. It doesn't make a lot of sense to see if a patient with a Mini-Mental of 5 can balance their checkbook. They may be lucky to even know what the checkbook is or hold the pencil.

So if you actually look at where the change is occurring, in those important elements that those who follow Alzheimer's patients clinically can appreciate in advanced patients are the issues of grooming. This is very stressful for caregivers, as many of us in the audience and in the room know, when caregivers are struggling with actual grooming behavior, dressing behavior in the advanced patient. To see some of that ability return or show stability, that is important.

These are also critical. Watching TV, that may be the patient is interacting with the television more, but for instance, the attending to conversation has clinical relevance, I believe, in terms of just communicating with a patient. Can the patient attend to statements and requests by the caregiver?

If we can just put up the next slide just to mention the point again of how the ADCS-ADL19 was derived

-- and this manuscript is in review at the present time -- you can see that we really focused on the group of individuals represented by the Mini-Mental range in the trials that have been presented today by Dr. Schneider and colleagues, and we also made sure that patients could actually attempt the ADL. I think that's a critical issue based on Dr. Katz's points.

I think the final slide that I'll show here is that after we note that these items were sensitive to change in the ADCS studies -- if we could put up the next slide -- we can also show you some of the reliability based on that sample that was analyzed. You can see the interclass correlations and the kappa statistics are very good and then the analyses within the trials that have been presented today. Obviously, we don't have this for the Latvian study, but we have it for the two U.S. studies. You can get a sense that we're actually measuring something real and measuring it in a reliable fashion.

So the treatment difference we're seeing in the overall aggregate slides that Dr. Schneider showed you is actually telling us that activities of daily living are not progressing and that in some cases there may actually be some return, I wouldn't say there's a complete return, of function but at least some measure of competency coming back in certain functions, which is really what you were

addressing, I think, Dr. Katz.

DR. KAWAS: Dr. Kattah, then Dr. Kieburtz, and then maybe a break.

DR. KATTAH: I have a question. If a person was on memantine and again let's say their ability to dress or perform functions, was that correlated with the Mini-Mental Status score as a point gain? That is, you predicted that someone doesn't get lost any more or can dress again, maybe they can draw the pentagons better or they have better orientation questions. Was there any overlap of the different measures?

DR. SCHNEIDER: You're asking, if I can restate the question, about correlations between the cognitive and functional outcomes, and yes, we do have them and we have them here. We can show them to you on this slide. This is a demonstration of the Severe Impairment Battery and some indices of concurrent validity. I draw your attention here to the baseline correlations between the Severe Impairment Battery, the cognitive outcome, and the Mini-Mental State and here we were using the ADCS protocol, so we did have a Clinical Dementia Rating Scale score and some of the boxes score. So you can see the correlations at baseline, .65, .75. Similarly, with the Global Deterioration Scale, an overall staging instrument, and the FAST, an overall functional activities staging instrument.

With respect to change over time, you're seeing reasonable but low-level correlations with the staging instruments, .25, .19, .38, as I'd suggest you would expect because these are in fact different instruments. On the one hand, you're measuring cognition and on the other hand change in stage. So those are the correlations in the validation studies.

Did you have a follow-up or did I address that?

DR. KATTAH: It would provide a better measure of confidence if one sees the ADL improving and then you have the Mini-Mental Status that we're more familiar with improving as well. So I was just trying to get to that.

DR. SCHNEIDER: We don't have that.

DR. KAWAS: Actually, specifically in the 9605, the Mini-Mental change was not statistically significant.

Dr. Kieburtz.

DR. KIEBURTZ: Just for a point of clarification, we're talking about function improving. The vast majority of subjects in both arms had no functional improvement. Relatively, they did better, but only a third of the memantine-treated patients had any ADL functional improvement. If I saw the distribution curve quickly correctly, most were deteriorating, just deteriorating more slowly.

DR. KAWAS: Thank you. I think that this is a

good time to have about a 10-minute break. We're running behind but we'll reconvene at 11 o'clock for the FDA presentation.

(Recess.)

DR. KAWAS: Thank you, and we're reconvening the session of the Central and Peripheral Nervous System Advisory Committee which is considering memantine for the treatment of moderate to severe Alzheimer's disease.

In today's meeting, the FDA has not arranged a formal presentation. So we are going to continue to try and get any additional questions or issues answered for the committee or from the sponsor, hoping to break for lunch around noon and continue the meeting in the afternoon as necessary.

So I want to begin by refocusing the discussion on something that is of interest to me in particular. It came as a little bit of a surprise to me that the sponsor considers the Latvian study to be one of their most successful studies.

Putting aside for a second the issues about outcome measures being retrospectively designed, the entire study actually had to be retrospectively refitted to come up with a diagnosis for Alzheimer's patients since the study initially was done with dementia patients, whether they had Alzheimer's, vascular, or potentially maybe even

other dementias.

The FDA in their document did bring out the point that they felt that the diagnostic classification done by the sponsor with the Hachinski was quite different in determining who were the eligible patients compared to the analysis that they did using the CT scans and NINDS-AIREN criteria. So a lot of my questions right now for both the agency and the sponsor are going to have to do with better understanding the Latvian trial and this reclassification.

I think it's very important that the sponsor showed us when reanalyzing the data according to the FDA criteria that in fact their two primary outcome measures which were not cognitive but were the original measures of the study continued to be significant.

So for me personally to get a better handle on this, I'd like to ask the FDA a little more specifically how they arrived at this diagnostic classification, and then I'd like the sponsor to show us any other information with regards to the Latvian study and that reclassification that the committee may find useful for ensuring the likelihood that the patients whose data we're studying actually represent patients with Alzheimer's disease.

So, Dr. Katz.

DR. KATZ: Yes. Dr. Mani did it, so we'll let

him say it, tell what he did.

DR. MANI: Let me briefly explain what I did. We had requested the sponsor to supply us with the CT reports for the roughly 50 percent of patients in this study who had CT scans done at baseline, which the sponsor very kindly did. What I next did was to look at the CT reports for each patient without attempting to look at any individual clinical details. I looked at the CT reports essentially blinded. I also did not look at the treatment assignments.

The next step was to apply the so-called NINDS radiological criteria for vascular dementia. These criteria are incorporated solely for the purpose of determining whether any imaging abnormalities seen were relevant to the dementia, and this slide shows what these criteria were. They include multiple large vessel infarcts, a single strategically placed infarct, multiple basal ganglia and white matter lacunes, extensive periventricular white matter lesions or combinations thereof.

In each instance, I attempted to make a specific assignment as to whether the patient had vascular dementia or Alzheimer's based on the CT report. I should emphasize that the CT reports in the majority of instances were quite brief and it was possible to apply the NINDS-

AIREN criteria only to a limited extent. But I thought I'd show you two examples which endeavor to explain what I did.

The first was an instance of a patient who was assigned, based on the Hachinski Ischemic Scale, to having Alzheimer's disease. This patient had a CT report which stated that the fourth and third ventricles were localized in the midline. The lateral ventricles were symmetrically localized. One ventricle was wider than the other. And there were hypodensities in the frontal lobe and the left temporal lobe and the left parietal-occipital border region and that the cerebral sulci were enlarged. In applying the NINDS-AIREN criteria, this patient did seem to fit the criteria for vascular dementia.

In the second example, this was a patient who was diagnosed to have vascular dementia, based on the Hachinski Scale. Based on the CT report, there wasn't any evidence that was consistent with the NINDS criteria, and therefore we classified this patient as having Alzheimer's disease.

So this is just an example. These are just two examples of what we attempted to do. That's really all.

DR. KAWAS: Dr. Mani, if you can go back to the previous slide?

DR. MANI: Yes.

DR. KAWAS: Do you have any idea at all how

many people were reclassified based on, in particular, a single strategically placed infarct?

DR. MANI: I believe there was only 1 patient who fitted the bill. The patient had a single fairly large infarct, based on the description I had, in the posterior cerebral territory.

DR. KAWAS: I guess what I'm trying to get a handle on is, I mean these patients in the 03 study, which is what we're talking about right now, were in a nursing home with Mini-Mentals of below 10. So they were severely demented. I'm trying to get a handle on when you reclassified individuals, did anybody go, for example, based on CT scan with the thalamic lacune, from AD to vascular or is that a minority or maybe even none of the patients?

DR. MANI: As I said, I believe there was 1 patient -- and I need to go back and confirm this -- who had a single infarct in posterior cerebral territory who was classified as having AD based on the Hachinski Scale and whom I assigned to the vascular group based on the CT report.

DR. KAWAS: Thank you.

Any other questions for Dr. Mani from the committee?

(No response.)

DR. KAWAS: Now, the sponsor very helpfully showed us data, which at least I wasn't aware of before, with reclassifying individuals based on the FDA's system and showed us some positive results, and if they'd like to show us anything further, we'd be interested in seeing that.

DR. OLANOFF: Thank you, Dr. Kawas. I just want to make some introductory comments about 9403 to put it in perspective that we didn't have the opportunity to do during the time of the presentation, and then I'll ask Dr. Schneider to come up and talk more specifically on the inclusion/exclusion criteria because I think that's key to understanding the patient population.

We did the analysis of 9403 based on the clinical Hachinski Scale, largely because that actually was prospectively defined in the protocol as an exploratory analysis. It was not the intent of the protocol to prospectively stratify patients into VaD or AD patients. It ended up by coincidence, at least on the HIS scale, that in fact half the patients fell into either category.

As has been commented, about half the patients had CT scans, so that diagnosis was made based on reports that were centrally read. Copies of those reports were provided to the FDA.

In the context of the 9403 study, I can just

show that core slide, the final slide in the core presentation by Dr. Schneider, just to reiterate the p values here and to assign blame in terms of the analysis.

I just want to comment that in fact we became aware of the FDA's concerns about the study in terms of the diagnostic elements subsequent to our completion of the briefing book and provision of that briefing book to the agency. So we tried to address this once we became aware and the FDA was kind enough to provide us with a list of the patients. That's why that information was provided kind of late in the game, but we were able to do that analysis.

Can I have the core slide, please?

I just want to again reiterate that in the protocol exploratory prospective analysis based on HIS, again both of the co-primary endpoints were significant and this was in approximately half the patients in the study. In a somewhat smaller population, not entirely concordant with the 75 listed there, as the FDA has pointed out, again these same endpoints were significant.

I also want to comment on a couple other factors. The BGP-cog, which was a retrospective endpoint, is not a validated endpoint. We've not made any effort to validate it per se. It was done precisely because we knew that there was an interest in whether this study had any

cognition information that could be derived, could be talked about, and it was purely done retrospectively, both defined and retrospectively analyzed, for purposes of trying to pull up any information that could be construed as cognitive. The items were picked by a group of three scientists at Forest who were blinded as to the outcomes for those items and the analysis was done for that particular purpose. But no one is, I think, today trying to argue that the BGP-cog has the same weight or value, say, as the Severe Impairment Battery.

Russ?

DR. KATZ: Yes. Having said that, what is the result for the BGP-cog in the FDA-defined population?

DR. OLANOFF: It was significant, I believe, in both.

So I think that is a background issue.

I will also comment that this study was a very interesting study in time. Again, it was done because there was no one else approaching these patients at the time the study was done with acetylcholinesterase inhibitors or other drugs that we're aware of, and it was a unique opportunity.

Because it was done in Latvia, with Merz intervening actually with their local regulatory authorities, the local regulatory authorities actually did

audits of the ongoing trial for GCP purposes. In addition, the FDA has also done audits of two of the sites in the trial post its completion.

With that, I'd like to ask Dr. Schneider to come up and talk. I will say this is just the results of the BGP-cog in the FDA-defined population and the other parameters as well.

I would ask Dr. Schneider to come up specifically and talk to the inclusion/exclusion criteria because I think it's important to understand what these patients were and what they weren't.

DR. KAWAS: Before Dr. Schneider, can we look more closely at a couple of those slides?

DR. OLANOFF: Sure. Do you want to bring that slide back up, please?

DR. KAWAS: The one before first.

DR. OLANOFF: The one before?

DR. KAWAS: Since I haven't gotten my questions for that one together yet.

DR. OLANOFF: The core slide.

DR. KAWAS: I'm going to come back to this, so don't let it go too far.

DR. OLANOFF: Yes.

DR. KAWAS: On those graphs, what data am I looking at in those graphs? It finally occurred to me that

the p values on the AD doesn't match anything on the graphs. So what is the graph data, for starters?

DR. OLANOFF: Yes, that's a good point. I'm glad you mentioned that because it may have not come out adequately in the presentation.

The graphs depict the overall population in the study. That's how the study was defined prospectively. What was the effect of memantine in the overall population? That would include both the VaD and the AD patients. The specific analysis on the bottom is the treatment effects seen in the AD populations which were very similar in magnitude and, in fact, in significance to what was seen in the overall population.

DR. KAWAS: Which was my next question. I see that the significance levels are what they are, but the magnitude is similar?

DR. OLANOFF: Yes.

DR. KAWAS: The same? Bigger, smaller?

DR. OLANOFF: Actually, the AD population was a little larger than the overall population, but in general magnitude similar.

DR. KAWAS: And that's true for the FDA-defined analysis, also?

DR. OLANOFF: Let's bring that one up. So you can see the magnitude here. There's a little greater than

a 4-point difference on the BGP-care dependency, a 1.5-point difference on the BGP-cog, and a .6 and fraction difference on the CGI-C. So those are reasonably aligned with the magnitude you saw on the graph, if anything a little larger than, I believe, in the overall population.

Bring that other slide back up. Bring the core slide back up. You can see on the BGP-care dependency, you have a difference here of a little better than 2 points on the overall population, and we said 4 points in the AD group. In the CGI-C, the difference is about .4, which is a little larger in the AD population that the FDA defined, and in the BGP-cog, we said a difference of about 1.5 and here the difference is a little over 1, I believe.

DR. KAWAS: Dr. Wolinsky.

DR. WOLINSKY: Yes. I know that this isn't the patient population under consideration, but in those patients who, by virtue of the Hachinski score, were considered to have vascular dementia, how did they fare in this analysis?

DR. OLANOFF: In the vascular dementia patients, the three parameters -- bring that slide up, please -- in the top line is that they did not reach significance on all three parameters. The treatment effect sizes were in the right direction but were not significant, and we'll try to bring up a slide to show that.

Please, yes. Here, this is the BGP-care dependency. You can see the difference here is about 1.1, and we say in the overall population it was about 2 points. So it's about half the effect and it was not significant. Again, the study was prospectively defined for all patients. These were retrospective analyses done on an exploratory basis.

DR. OLIVA: I think it would be helpful to actually show the BGP-cog scale. Do you have a slide of that?

DR. OLANOFF: Yes. Dr. Schneider. We'll show the BGP-care dependency scale and the elements of the BGP-cog from that.

DR. SCHNEIDER: Let's start with this slide and then go to the items and then show you the cog items in a moment. If you'd put that up.

First, an overall introduction to the BGP. It's a comprehensive measure. There are 35 items. They're rated on a 0 to 2 point scale, and here are some of the areas: aggressiveness, disability, disorientation, depression, inactivity, impaired communication, et cetera.

Would you put up a slide of the items?

These are most of the items on the 35-item scale. I realize you can't read them. They are the items that were used in the Care Dependency Subscale that

comprised most of the BGP total. Within these items, we highlighted in yellow and italics the 5 items that independent Forest clinicians, without knowing the data, without knowing outcomes, identified from their point of view of what constituted cognitive outcomes.

So they identified patient makes himself understood, patient finds his way in the nursing home, patient understands in what home or clinic he is in, patient knows the names of staff, patient understands what you communicate to him. So these 5 items were considered the cognitive subscale. Obviously, a number of these assess languages as well. That constituted the 0 to 10 cognitive scale.

DR. KAWAS: Definitely leave that up for a minute and let us get a chance. For many of us, this is the first time we've seen it.

For example, my first question is how come patient keeps self occupied in useful activities, working, reading, playing games, hobbies, is not cognitive, but knowing where you are in the nursing home or something is?

DR. SCHNEIDER: Because the outcome criteria -- and the trial was designed as it was designed, that the CIG and the BGP-care dependency were the primary outcomes. It was later, before data were examined by Forest, that it was thought that a cognitive subscale, some index of cognition,

could be brought out from this that might help to inform the design of other studies.

This is what that set of clinicians identified by examining the items. I think if some others were doing it at a different time, 1 or 2 other items would have been brought in.

DR. GANGULI: A quick question about the scale, Claudia. Are all the items scored the same way?

DR. SCHNEIDER: Yes.

DR. GANGULI: Well, I saw something earlier that said never, often, sometimes.

DR. SCHNEIDER: Right.

DR. GANGULI: But there are some items that seem to be good and some that seem to be bad.

DR. SCHNEIDER: And some items are reversed to address the response time.

DR. GANGULI: And they're all weighted the same.

DR. SCHNEIDER: They're all weighted the same? Yes.

DR. KAWAS: Yes.

DR. EBERT: Just a follow-up. Do you have the baseline values of the scores at the beginning of the trial for the BGP scores?

DR. SCHNEIDER: Yes, we do. While we're

looking for the baseline values on that or perhaps somebody could just simply tell us what the mean baseline is. Here we go. Mini-Mental State, modified Hachinski, care dependency baseline values were 21, 22 points, plus or minus 7.7 standard deviation.

DR. KAWAS: Do you, by any chance, have the same numbers for the AD subset, which is what I'm trying to get a better handle on now? I mean, this is for the entire study obviously, given the Hachinski.

DR. SCHNEIDER: We don't immediately have that. We obviously have it because we did the analyses, but it looks as though we don't immediately have it to be able to describe differences in care dependency. We do have it. Okay. So it should be coming up. Here it is.

So there's about the same 19, 20, 21, 23 point baseline for care dependency when the groups are divided on the basis of Hachinski scores into greater than or lesser than 4 or above, and similarly, roughly speaking, cognition is about the same. The Hachinskis are, of course, different by definition, and the derived cognitive measures about the same at baseline and midway through the 0 to 10 scale.

DR. KAWAS: Now, on the BGP scores, the higher scores are better or worse?

DR. SCHNEIDER: Higher scores are better.

DR. KAWAS: Higher scores are better.

DR. SCHNEIDER: Claudia, Dr. Kawas.

DR. KAWAS: I can't hear. I'm not sure who's calling my name.

DR. SCHNEIDER: I am, I am.

DR. KAWAS: Dr. Schneider, you have the floor.

DR. SCHNEIDER: I just wanted to ask. You had asked about how patients were included in the trial, and by extension, how diagnoses were made in the Latvian study. I can go into that in brief detail, if you'd like, and describe that patients were, in fact, qualified by fulfilling DSM-III-R criteria for dementia syndrome, and after that, they needed to be of a GDS rating of 5 to 7 to be in the severe borderline moderate area. Then they needed to have dementia for over 12 months. So we were at least ensuring that patients had chronic dementia.

After that, exclusion criteria were actually fairly severe but very similar to the way we teach many physicians to diagnose Alzheimer's disease, to diagnose the dementia syndrome first and then to make sure that they have normal laboratory tests -- and a range of normal tests were required, including vitamins and normal hemoglobins, et cetera -- that they should have been on no active CNS drugs for 14 days before the trial, that there was no history of alcoholism or other drug dependency, no other

investigational drugs, et cetera.

DR. KAWAS: No, that's fine. I don't have any questions about that. I think the issue here that has been questioned by the FDA and also now is being revamped for this committee to look at data is how the diagnosis of vascular versus Alzheimer's was made, and I'm the first to say that is not an easy thing. I'm the first to say that CT scans probably don't do a whole lot different job than Hachinski does, but we need to understand how it was made in each case only.

DR. SCHNEIDER: And then, at the end, the Hachinski score was taken in part because that was in DSM-III-R as part of the diagnosis of multi-infarct dementia, remembering this is DSM-III-R now and not DSM-IV.

DR. KAWAS: Thanks.

DR. OLANOFF: I just wanted to correct what I think may have been a misstatement. I think lower scores are better on the BGP, but the curves were appropriately designed to show that.

DR. KAWAS: Thank you.

Dr. Katz.

DR. KATZ: Yes. I actually have a couple questions. Let me ask the potentially complicated one first.

A number of folks from the company earlier,

when we were talking about which items on the ADL had moved and what they meant, had mentioned and pointed to several of the items that looked like they were improving and said, well, this is important to the caregiver. Actually, watching television was one of the most significant. So I want to ask the question about those statements.

Typically, we approve drugs because they make the patients better, and in other settings, we've explicitly gone on record as saying that's what you've got to do, that's what you've got to show to get a drug approved. I'm wondering whether or not the findings on the ADL are actually reflecting ease of care of the patient or the patients actually themselves are functionally better, not necessarily that they have the insight to know that, but I want to just at least broach the question of who are we treating. The caregiver or the patient?

DR. OLANOFF: Fred, do you want to comment on that?

DR. SCHMITT: I think that's an important question, and I think those practicing clinicians would argue you almost end up treating both because the patient's quality of life is intimately tied to the quality of life of the caregiver and there's a lot of research associated with that.

But I think what you're seeing is you have to

bear in mind that the ADL function is reported by the caregiver. So it's the caregiver who's your informant saying my family member with Alzheimer's disease, my husband, my wife, whatever, is now better able to do the following. He's now able to eat independently. When he started the trial, he just used a spoon. He's now trying to use the fork or is using the fork better or something along that line, or before, I had to wash his or her face, now I can take them into the bathroom and they're attempting this somewhat successfully, successfully. You can't tell. That's a fine-grained split on this. But they're now doing that activity, and that's the report that you're getting back from the caregiver.

So, yes, the patient is being treated. It's the patient response that is then being translated by the caregiver, but at the same time, you're making the caregiver's life easier. So it's a dual effect in essence.

DR. KATZ: Well, no, I recognize that it's the caregiver who's giving the report, and I think your answer probably answers the question, but it's also possible that the drug could have the effect of making patients sleepy and more tractable and so they're in bed all day and that's easier for the caregiver, too. So I really want to make sure that we're talking about something that matters to the patient.

DR. SCHMITT: Yes. They're not saying that. You're absolutely right, Dr. Katz, and they're not saying that, and that's based in many ways on the other data that are collected in the trial. It's not that I'm getting the day off because the patient sleeps through the day. They're actually improving in their function. They're better able to communicate, et cetera, which is a more interactive style. It's a very good point.

DR. OLANOFF: I'd like to ask Dr. Tariot to comment because this goes back to the issue of clinical relevance, and I think he had some comments he wanted to make in that context.

DR. TARIOT: While we're pulling up the 9605 set, slide 36 on the ADLs, the comment is made in the heat of the moment about improvement. What you see as will be depicted on this famous S curve is the fact that, depending on where you cut, if you're reading this -- Dr. Kieburtz had said he only saw this in passing and so I wanted to show it again. This is change in the ADCS activities of daily living, 19 items score, from the 9605 trial, except the signs are reversed on the x axis to keep the picture in conformity with what we're used to seeing with the ADAS-cog S curves.

The major point is whatever level of improvement, which is over here, or deterioration, which is

over here, the drug-treated group ends up doing better. If you say what percentage of patients didn't change or improve, you take the cut here at 0 and you see that something like -- I don't have the exact number -- but about 37 percent remained the same or improved on drug versus approximately 22 percent on the placebo arm. So some patients improve, some stabilize, some deteriorate in both conditions, but the likelihood of a more favorable outcome is greater on drug.

If we go to slide 38 of the same set, really the same point is made with the Severe Impairment Battery, which is depicted here. A question came up before about correlations among these various outcomes which I can't address. Those were not articulated as a priori questions.

DR. KIEBURTZ: Just a conceptual question. Earlier this morning, when we were talking about the 9605 dividing on an MMSE of 10 or not, Dr. Temple and I believe Dr. Fisher had a discussion about the relative merits of that, and that was based on a prospectively defined measure that was done in the study.

Is dividing here based on vascular dementia and Alzheimer's dementia conceptually any stronger or weaker? I mean, it's the same kind of post-randomization, post hoc differentiation, and yet before, we were kind of saying, well, the MMSE analysis, we've got to take that with a

certain grain of salt is how I kind of heard things, and yet here we're making conceptually the same kind of split but it strikes me no one is saying, well, how do we take this with a grain of salt.

Dr. Temple, I don't know if you were going to say this.

DR. TEMPLE: Well, it's a good question in one sense. I mean, at first, it seems completely sensible. This is a drug for Alzheimer's disease, so you would want to get the people who have that or who are reasonably likely to have that. So it seems particularly sensible. But also dividing at 10 seems particularly sensible because that's what characterized the severe disease. So those are very sensible questions to ask.

The question is what happens when you ask them and you see a difference that is somewhat inexplicable. Why should 9 be different from 11? That doesn't make any sense. So they're sensible questions to ask. That's why they ask them. What to do with the results and how to interpret those differences is the hard part because they can show up when you look at multiple subgroups within a study and you never really know whether you should believe it as the truth or say, oh, well, that happens.

DR. KATZ: I have a completely different question, though. It's actually a safety question.

DR. OLANOFF: Yes. Let me just make a comment on that. I think the other point that was made today is when you do an exploratory analysis and you make a finding which you're presumably going to test in the next trial -- that's a hypothesis generation and exercise initially -- and then you go ahead and test it, you want to see if you can reproduce it in a prospective manner.

I think in terms of cutting the data in terms of individual strata for purposes of severity, that was purely retrospective and we've done it retrospective across two of the studies where we could do that and we can't reproduce it, but there wasn't a prospective hypothesis tested per se. We haven't done a study yet in severe patients to see if that effect was truly reproducible in 9605.

We can say we retrospectively did that study, if you consider 9403 important.

I think for purposes of the Alzheimer' disease designation, your point is entirely valid. Can you use 9403 on its face as the only study to support a population of Alzheimer's disease? The strength of 9403, if you can value the endpoints, is that it worked in the overall population. That's the way the study was designed.

Taking that as a signal in the AD patient was, in fact, how the study was then designed for 9605. So

there in fact we believe it was reproduced in 9605 and in fact was also reproduced in MD-02. So I think it's just a somewhat different perspective, but your comment is entirely valid.

DR. KAWAS: Dr. Katz.

DR. KATZ: Yes. I had a safety question. Dr. Jonas presented the blood pressure data for potentially clinically significant, and if I remember the criterion that you used for diastolic blood pressure, it was greater than or equal to 105 millimeters of mercury and I think an increase of 15 for baseline or something like that. That seems fairly high as a criterion for an elevated diastolic blood pressure. Did you look at any different cuts of the data, let's say above 90 or some other increment of change, from baseline?

DR. OLANOFF: Why don't we pull up the slide just to verify? I don't think we looked at other cuts. I think that's a standard approach that we've used in the past, but we clearly can go back and do those other cuts.

I think for what its value, the mean change essentially was nothing between the two groups.

DR. KATZ: No, right. It wasn't anything on mean, but that just seemed a little high.

DR. OLANOFF: Let's bring up the slide just to confirm.

Yes, that was correct. It was an increase of 15. Well, the increase of 15 had to occur leading to a value of a 105. So patients presumably would have had to have at least a 90 millimeter blood pressure value to start with and then they get an increase of 15.

DR. KATZ: But if they were at 80, let's say, and they went up to 100 diastolic blood pressure, would they be captured here?

DR. OLANOFF: No, they would not.

DR. KATZ: They wouldn't, right.

DR. OLANOFF: That's correct. That's a cut that we can do.

Dr. Schneider. We'll try to pull up some data on the average change. We know the average change itself, but we'll pull the range up as well. Put the slide up, please.

These are the baseline values on diastolic blood pressure across the groups that were measured. You can see the change from baseline was actually a little lower in the memantine group but not statistically significant. The standard deviation on that was about 10, roughly equal in both groups.

DR. KAWAS: I have another question. After lunch, this committee is going to be deliberating and voting on several questions, the essence of which are, are

there two pivotal or compelling independent studies?

Since we have data from three studies in front of us here, in the opinion of the sponsor, which of the two pivotal ones would you say we're supposed to be focusing on?

(Laughter.)

DR. OLANOFF: If I had three children, it'd be like asking which of the two go to college.

(Laughter.)

DR. KAWAS: It occurs to me you might have four or five children, too.

(Laughter.)

DR. OLANOFF: If I did, I wouldn't be here. I'd be long gone retired.

I think from the standpoint of studies that qualify in terms of having cognitive endpoints prospectively defined, one has to point to the U.S. trials in the moderate-severe population, and I think one should point to it in a context of also looking on its face in terms of analyzing the results or the outcomes of those results.

If you look at the two U.S. trials, both clearly showed a significant effect on the Severe Impairment Battery. Both of those studies within the Severe Impairment Battery showed no difference versus

severity.

Further, when you look at the two trials -- and we've configured the ADCS-ADL as a functional endpoint. We've talked about it differently than a traditional global. The agency has allowed us to use it as a co-primary endpoint in this population because they see it in fact as an alternative global.

If you look at the two studies independent of how you consider the CIBIC-plus p value in 9605, each of those studies in fact has a positive global. In fact, in MD-02, it has two positive globals, and in the 9605, arguably if you correct for multiple comparisons on the ADCS-ADL being the second global, it still makes borderline significance or makes the level of nominal significance. So I think on its face, we would argue that both trials, the U.S. trials, should be considered for purposes of the general support of the product.

I would also make the point, as Dr. Schneider had made earlier, on the CIBIC-plus, the fact that that value didn't hit the nominal .05 on the LOCF analysis we would argue is biased because of the greater number of placebo patients dropping out earlier.

I think one could also argue that the OC, as the statistical review that the FDA has, that the OC value may be biased for memantine because of the differential

dropouts. We would argue that the LOCF may be biased against memantine.

So the whole exploratory analysis -- and it shouldn't be weighted as the same way as the OC LOCF analysis which was exploratory on this mixed-model repeated measures -- was to try to get a sense how those dropouts should be weighted, and it looked closer, for what it's worth, to the OC. So we'll leave it at that. But I think those two trials should be most seriously considered.

The 9403 trial, one could also argue that if I did three studies in depression and one was an older study and perhaps not as rigorous as the later two, and that that study was negative, I couldn't arbitrarily not report that trial. The study has relevance. I have to report it. This study was very interesting. It's very novel in terms of the population it served. It was concordant in its time. I think it was a good quality study. It met its prospective endpoints, and I guess we're throwing that up to the committee in part, as the agency has, as to how to consider that.

Arguably, if you find that the first two studies are convincing, then how do you consider 9403 on its face for purposes of potential labeling and the use of the product? If you find that there's a potential deficit, an issue that you can't address in one of the two studies,

if it's the subpopulation, 9403 provides supportive evidence by way of at least patients with severe dementia and again only subject to all the problems with retrospective analyses of patients with Alzheimer's dementia of that severity. So with that long-winded explanation, I think that's how we regard the three studies.

DR. KAWAS: The second question I have is, in looking at the broader picture as you encourage us, I'm still trying to parse the severity issue, and it is a little concerning that when you divide the groups in some cases actually the effect seems to happen with less severe patients.

Since the sponsor doesn't think that severity is relevant for whether or not the drug would work, I'm also under the impression that there may be some studies ongoing with regards to mild and moderate patients, and I wondered if you could share some of that information with us.

DR. OLANOFF: Certainly. Again, I want to repeat that the reason that we're talking about moderate to severe patients today is not because we went in with a hypothesis it should only work in moderate to severe patients. There was some data, as I indicated, in vascular dementia that suggested it would work in mild to moderate

patients.

But the company, Merz, initially decided to put its focus on a population which was not being served by the other available agents or not being aggressively explored by the other available agents and it worked, I think, for their purposes logistically to move those studies ahead.

The 9605 study recruited very rapidly. The MD-02 study recruited very rapidly because allowing patients in who are on acetylcholinesterase inhibitor is a very nicely captured population for recruitment purposes.

We do have two mild to moderate studies ongoing, in addition to the third study which I described today. We have two monotherapy studies going. Forest is the sponsor of one of those studies and it's a traditional mild to moderate disease monotherapy study against placebo, a 6-month study, 10 milligram b.i.d. dose, range of 10 to 23 on the Mini-Mental Status Exam, and roughly 200 patients per group, a little less than that, I believe. And then Lundbeck, who's the other licensee of memantine in Europe -- they co-market with Merz -- is doing a separate study in mild to moderate patients in Europe and should be concluding about the same time as the study here in the U.S.

I should say that our intent is if the studies support a new indication, that we would like to apply for

an indication to include mild patients as well.

DR. TEMPLE: Neither of those are add-on studies?

DR. OLANOFF: No. Both those studies are monotherapy studies. It's also interesting from the historical standpoint. The add-on study in the mild to moderate disease was designed to see if we could get a study to -- that study recruited, for those who are aware of the problems in recruitment, that study recruited in about 3 months which is extraordinarily fast. Again, it's a population that no one else is studying for obvious reasons. So that was the reason that study ended up so quickly and was available to us. The other studies took a lot longer to recruit.

DR. TARIOT: Dr. Olanoff, I wasn't sure if it was two-part question, that you had reservations about the number of patients with advanced dementia who were included in the trials.

DR. KAWAS: No.

DR. TARIOT: No. I misunderstood.

DR. KAWAS: Dr. Ganguli.

DR. GANGULI: I believe I'm here representing the man in the street or the clinician in the street. So from that perspective, I have two questions.

One is, when I see my patients, am I going to

be telling them, if this drug is approved, that the goal as we tell them for cholinesterase inhibitors, the objective is to look for improvement or for less decline or stabilization? Because I've heard a lot said about improvement today and it's not clear to me that that's really what the data show. There's a little bit of improvement which is probably a practice effect in the first point or something like that.

The second question. Maybe this can't be done quickly, but again as a man in the street, what should we make of the information that was sent to us by Dr. Olney about some of the preclinical studies suggesting that the product is not quite as benign as it might appear and that it might, in the presence of cholinesterase inhibitors, actually do some damage?

DR. OLANOFF: Okay. Let me address the second question first because I'm not privy to the information that was sent to you by Dr. Olney. He did not share it with the sponsor. So I don't know what his comments were. Perhaps we can get through that issue first and then I'll ask Dr. DeKosky to comment.

I'll ask Dr. Greenamyre, who's quite familiar with this data, and actually we have some other experts with us that can go into great length on this, if people are interested.

DR. GREENAMYRE: What I'd like to do is tell you about the Olney lesions, as they're called, and explain to you what they are and their clinical significance. Can you put up the first slide, please?

So what has been found historically initially with a drug called MK-801 was that acute dosing of an NMDA receptor antagonist as a class could produce membrane-bound cytoplasmic vacuoles. These turn out to be dilated endoplasmic reticulum and the golgi in neurons, and it's a very discrete, very small population of neurons in two regions, the cingulate cortex and the retrosplenial cortex.

To see them, it requires specifically looking at aldehyde-fixed tissue. You don't see them if you use frozen tissue or immersion-fixed tissue, and in a population of these neurons, not all of them, the vacuolization may progress to actual necrosis or cell death.

In extensive studies that have been done by multiple laboratories around the world, this is rodent-specific. It's only seen in rats and mice. As I said, it's a class effect of all NMDA receptor antagonists, including some that are in clinical use. It's not observed in primates at dosing that would induce very significant motoric or behavioral intolerance. So in other words, even pushing the dose up to cause motor impairment or behavioral

impairment, you're not going to see these in primates, and the clinical relevance of these is completely unknown.

Can I have the next slide?

I also want to point out that in rats -- and we're talking about memantine specifically now -- and I'll tell you that we do see these Olney lesions with memantine -- the neuropathology is only seen in doses that are 12 times or higher than the maximum recommended human dose. The neuropathology is observed at doses that are substantially higher, 2 to 4 times higher than those which would cause ataxia. So the animals become motorically impaired before you're ever going to see this, and it's not observed in non-rodent species. So in dogs, at doses that actually cause the animals to die, it's never seen, and in baboons, it's never seen.

I should mention that these lesions have also been looked for in, as I said, a clinically used NMDA receptor antagonist, amantadine, in patients who died and the lesions were not seen. So we think that they do not occur in non-rodents and that their clinical significance is unknown, but probably not relevant.

DR. KAWAS: Just for public information, the letter that's being discussed right now is from Dr. John Olney, who is at Washington University School of Medicine, and a copy of this letter is available in the open public

hearing documents that are on the table outside, should anyone like to see it.

DR. OLANOFF: Dr. Ganguli, does that address your question on the Olney lesions, at least how we've looked at it?

DR. GANGULI: Yes.

DR. OLANOFF: I think I was talking with Dr. DeKosky, but it may have been mentioned that in the patients treated with amantadine, there was an autopsy sample that was done, and in fact, there was no evidence in humans on autopsy of any lesions in the brain.

These lesions, though, are highly dependent on the staining techniques used, and I guess the point we would make is that they don't appear to be at a dose which is clinically relevant, in fact wouldn't even be tolerated in any patients on a chronic basis.

DR. GANGULI: Just to summarize my amateur understanding of what's in Dr. Olney's letter is, one point is that what he considers the effective milligrams per kilogram dose is higher than the 20 milligrams a day that the sponsor is recommending, but he has reason to believe that's not an effective dose. But he also had some evidence suggesting that in combination with cholinesterase inhibitors, these dangers would be enhanced.

DR. OLANOFF: We're not aware of any such

evidence. In fact, we're not aware of any mechanism to explain that. Frankly, the issue of the dose is something you're evaluating today, so you can qualify that in terms of your sense or concern.

Dr. Olney is well known, has done a lot of neuropathology work. The lesions themselves are named after him. There are a lot of NMDA antagonists that have been under study in humans, many for stroke and head injury. They've all gone through these types of testing, and they've all demonstrated the similar type of profile in terms of species differentiation.

It's in some ways similar to issues. When you start to see findings in other pathology studies, you have to put a face on them in terms of their clinical relevance and that's often done based on a dose ratio, whether it be a carcinogenicity finding, a reproductive finding, whatever. So when you say you don't know the clinical consequences, you also have to interpret it in the context of the multiples that you're dealing with.

I guess Dr. Auer, who came with us, also, who's a neuropathologist, can comment a little further.

DR. AUER: I'm Roland Auer. I'm speaking as both a research neuropathologist in rats who has worked with the Olney lesions and also as a clinical neuropathologist who studies human brain, and I think it's

important not to transfer uncritically these findings from the rodent to the larger brain.

These Olney lesions occur as a result of, we now know, increased metabolism in the focal areas of the brain affected. It appears that the large human brain, with its weight over 1 kilogram, has roughly half the rate of metabolism of the rat brain, and hence this form of hypermetabolic necrosis never reaches the ceiling in the larger brains that you would see in the small rodent brains. There are other examples of hypermetabolic necrosis that occur in rats that we just don't see in humans.

So we believe that this probably can't even occur in humans because it doesn't raise the metabolic rate to the ceiling necessary to produce the hypermetabolic necrosis and kill the neurons and that's why it hasn't been seen in the human studies where amantadine and other NMDA antagonist is given and ketamine has been given to people, and no one has ever seen this lesion in the human brain, this NMDA antagonist-related lesion.

DR. OLANOFF: Just to close, if there are no other questions on this particular issue, Dr. Greenamyre also commented to me that we're not aware that the cholinesterase inhibitor effect has ever been published. So it's hard for us to evaluate that.

I would ask then if Dr. DeKosky could comment on the first part of your question and then followed by Dr. Schneider who will talk to some data that we've been able to generate along with our colleagues from Lundbeck and Merz.

DR. DeKOSKY: This is in response to Dr. Ganguli's first question which was about what she as the country psychiatrist would tell her patients.

I think one of the issues that has struck us over the past 5 to 7 years of experience with the cholinesterase inhibitors was that although we have data from especially a number of the earlier studies that show clear improvement and that the placebo-drug difference is generated by up-regulation of performance on those testings, in fact, when you look at the magnitude of detectable improvements over time, it's very clear that only a relatively small percentage of people who take esterase inhibitors actually get significantly markedly better.

I tell my patients and I suspect most of the clinicians who see lots of Alzheimer patients that it may well be that you'll see a discernible change, but on the whole, we know the populations of people given esterase inhibitors are slowed in their mean progression over time which is exactly the same sorts of effects that we're

seeing with memantine.

If you looked at the S curves, what you can see is that a percentage of people -- and I think it's different for each of them and if you want the specific percentages, I'm sure there's a slide in this massive group that will provide that data. A small number of cases, a small percentage of cases improve over time, as shown by the S curves. But the overall effect of these medications, I believe, just in large part similar to the cholinesterase inhibitors, is a slowing or a symptomatic halting or decline in the manifest progression of symptoms rather than a global increase in cognitive performance or functional performance.

I think it's also useful to comment to Dr. Katz's earlier comment about functional activities in ADLs, that we don't frequently give back the keys to the car, we don't re-entrust the checkbook to people who have lost the ability to do that, but we have great interest in maintaining their function wherever it is and improving it, if we can, and I think that is actually very much like the esterase inhibitors of how we've come to understand them. That's really, I believe, what this medication does.

There are some other important quantitative parallels, though, that Dr. Schneider may want to bring up.

DR. GANGULI: If I could just follow up on

that. When we talk about maintaining function at the level it is and if we're talking about somebody with a Mini-Mental of 5, whether we're doing this patient a service, for example, is there an expectation that we will be prolonging survival?

DR. DeKOSKY: You bring up a different issue from the nature or the circumstance under which these trials are done. There were a couple of surveys of families a number of years ago that asked if you could have even a small improvement or if you could have a stabilization or a slowing of progression, even a minor slowing of progression of disease, would families regard this as something that they thought was positive, and the overwhelming, 85 percent-plus of people surveyed said yes, absolutely, I would like that.

There is a clinical judgment issue about the levels at which you would make a decision that slowing down the progression of this disorder might not be helpful and so forth. One of the issues that I tried to emphasize in my earlier comments was the multi-dimensionality of the nature of cognition.

We teach our residents that the Mini-Mental State Examination which was not devised for Alzheimer's disease assessment, has no executive function measures in it and so forth, is not the entire quantitative cognitive

capacity of mankind and so to characterize somebody as a 5 and therefore they're too low to be assessed, they may have very different aspects of how they do functionally, of how they do socially in interactions with family members. So I think that piece is a clinical judgment very much with respect to when you would make a decision either not to treat, assuming someone presented to you at 5, or when to decrease a medication.

But I think, as some of this discussion earlier has gone, the idea of focusing on one very narrow slice and then saying let's discuss the specifics of the global aspects of the drug to that group, I think, is probably unfair, both to the patients and to the medication.

DR. TARIOT: And Steve, if I could amplify on that a little further, I'm someone whose practice is devoted in part to the treatment of patients with more advanced disease.

If the outcome is the ability to toilet with cuing independently for 6 or 8 months longer, that's very important, to feed independently. These are the sorts of stabilizations that at very advanced stages we're looking for and seeing, although I don't think it's necessary to show those data.

Actually, there's another point that hasn't come up, if the chair will indulge me. There's another

point that I don't think has emerged here that is relevant which is the behavioral impact of this therapy. The MD-02 trial, in particular, showed that incident psychopathology was essentially blunted by administration of active drug versus placebo. Remember that 90 percent of patients with Alzheimer's disease will suffer significant and distressing behavioral and psychological signs and symptoms and that if we can delay their emergence or ameliorate them once present, that is also an aspect of the therapeutic outcome.

So the three domains of relevance which partly overlap are cognition, function and behavior, and if "all we do" is prevent further emergence of distressing and disruptive behaviors, we've also achieved a therapeutic gain and that may be a driver of prolonged autonomy.

DR. KAWAS: I'm sorry. Dr. Tariot, I missed. I sort of blanked out there for a second. Are you telling us there is data showing that this drug affects the emergence of behavioral symptoms in the disease compared to placebo?

DR. TARIOT: Yes. A planned secondary outcome in the MD-02 study was the neuropsychiatric inventory total score, and there's a significant drug-placebo difference in favor of drug at endpoint, largely interpretable as reduced incidence or emergence of psychopathology on drug versus placebo.

DR. KAWAS: Is that data available for us to look at or see?

DR. TARIOT: Yes. If we could pull up the MD-02 secondary outcomes. So if we could show the slide which I have to get oriented to.

So in this case, it's the reverse of what you're used to seeing, Dr. Kawas, with NPI scores. Scores going down would be a beneficial outcome and scores going up reflect emerging psychopathology, and so as would frankly be expected in the natural history of untreated patient, in this case the background is years of donepezil therapy, you're seeing gradually emergent psychopathology assessed with this fairly reliable behavioral scale.

I'll remind you that this is a secondary outcome, but at least at 12 weeks actual average improvement in scores, then by 6 months, a significant drug-placebo difference persisted.

DR. OLANOFF: For the sake of completeness, I should say that in trial 9605, the monotherapy trial, the difference was not statistically significant.

DR. KATZ: Yes. I just want to say this is not an outcome that we have focused on in our review and it may or may not be useful information. It's not replicated, and it's really not the subject of today's discussion, I don't believe.

DR. KAWAS: Thanks for clarifying.

Dr. Ganguli, Dr. Wolinsky, and then hopefully not too many more questions before lunch.

DR. GANGULI: This is just a very brief question to Drs. DeKosky, Schneider and Tariot. Is there a patient with Alzheimer's so severe that you would not recommend using this product? That was really what I was trying to get at, not at a particular Mini-Mental score.

DR. OLANOFF: Dr. Tariot.

DR. TARIOT: I don't think the trials answer that question. So if you want me to render a very personal opinion, I can do that. Is that what I'm being invited to do? Would that be helpful?

We faced the same question with the cholinesterase inhibitors, and so the process that I go through is to involve all the stakeholders. Is there, particularly in advanced disease, an aspect of functioning that, if maintained or improved, would make an important quality of life difference for the patient, and if the answer involving all the stakeholders is yes, we would give it a try.

Is there a point at which I think the outcome is likely to be negative? Sure. For somebody who's bed-bound and contracted and has been mute for a year, I think the outcome is very unlikely to be favorable.

DR. OLANOFF: Dr. DeKosky. No further comment.

DR. WOLINSKY: I have a couple of difficult areas that I'd like to pursue. The first of them is in dealing with a degenerative disease where we're asking patients to take drugs to slow progression and especially if we accept the data that there is a significant effect here in severely affected patients, how would we think -- and maybe this is a question as much for the FDA as it is for the sponsor -- if trials, which I understand are ongoing in mild to moderate disease with the same drug as monotherapy, had no effect?

DR. KATZ: I'm not sure. I suppose you could ask the question if the drugs that are already on the market for mild to moderate were not shown to be effective in moderate to severe, what would we do there? I don't think we'd take them off the market.

So I suppose it's possible that if we believe the data on moderate to severe and we also believe negative data on mild to moderate, one could argue it ought to still be approved for the moderate to severe. We haven't really considered that question yet, though, I have to say.

But one thing I do want to say which is not the subject of your question but is a word you used that everybody's been using which is progression, and this drug might slow progression. I just want to make it clear, we

don't think that these trials were designed to look at that question. Until proven otherwise, we would assume, if we believe that there's substantial evidence of effectiveness, that these studies would have demonstrated a symptomatic effect, and although over time the differences between drug and placebo persist, in and of itself, we don't think that's a marker of progression.

It's particularly important to make that point here because there is some suggestion on the part of some that, based on the mechanism of action, there is a neuroprotective effect. We have no evidence, I don't believe, in humans that the drug is neuroprotective. So I just want to get that out on the table.

DR. WOLINSKY: So that actually brings up the second part of my question, which was whether or not there are data that would bear on the issue of either a delayed start or a delayed stop trial that would allow me to think a little bit more as to whether this is a cosmetic or a therapeutic effect. Well, I have used terms the way I like to use terms, not the way everybody uses them.

DR. OLANOFF: Let me comment on the first question. I think Dr. Katz summarized it well in the sense that this drug, as I indicated for historical reasons, was developed for moderate to severe dementia. The studies ongoing in mild dementia are ongoing. We don't know that

the drug works. We don't know that the drug doesn't work.

Unfortunately, the first study to give us a signal was the most aggressive of the designs and one least expected to show a positive result, and having the ADAS-cog results tells us we couldn't have a positive trial for all practical purposes when the placebo doesn't deteriorate. So we're left without an answer. The only hint of an answer is the fact that we did get some signal in mild to moderate vascular dementia, at least on the ADAS-cog, but that's a remote signal at best.

I think the answer is also in the context as Dr. Katz indicated. If the drug was out on the market for moderate to severe and it didn't work for mild, would you take the drug off the market? Is there a population of interest that's getting a benefit? Would you not make that drug available because you're waiting for results in another population of interest that would also potentially have a benefit? The issue there becomes is the strength of the data adequate for the moderate to severe, at least that's our perspective.

I think the other answer in terms of neuroprotection, I'm not sure there is a common understanding of what would constitute an appropriate trial design to show neuroprotection for any drug, and I know there's a number of trials looking at progression in terms

of looking at the transition from MCI to mild disease, but I'm not aware of any results being reported to suggest that any of them work in that context.

So this is, from a naive background, I think to some degree, that's the Holy Grail for the moment, but I think the study should be done, and I think we will consider such studies with our drug as well.

DR. TEMPLE: There have been a lot of designs discussed to determine whether you're actually making a difference in the disease process. A quick and dirty version, however, is to look and see whether the curves diverge in the kinds of studies you've done, and for the most part, they don't. They look like you get an effect and then the intrinsic decline in function keeps on going and you have parallel but at a slightly better position, which is pretty much what all the cholinesterase inhibitors have done and they also show that when you take the drug away, you get back to where you would have been. You haven't shown that yet but.

DR. KAWAS: Can I just ask before we break for a point of clarification? You made reference to the ADAS-cog data.

DR. OLANOFF: Yes.

DR. KAWAS: Can you recount for me again what I was supposed to learn from that?

DR. OLANOFF: Excuse me. If you remember my historical slide, there were two studies that were performed by Merz in the 1990s in vascular dementia patients. They happened to be mild to moderate vascular dementia patients, and this was prior to the acetylcholinesterase inhibitors kind of jumping into that indication.

It's interesting history again. The basis for that concept was that early on, all the NMDA receptor antagonists were being studied in ischemia. So the thought was, well, if it's going to work in dementia, it may work better in ischemic states of dementia. So they went ahead and did those trials. In those trials, the ADAS-cog was measured, and there was about a 2-point difference in each of those trials which was statistically significant. One was in France, one was in the U.K.

DR. KAWAS: So it was all vascular dementia trials?

DR. OLANOFF: Right. That's entirely correct.

DR. KAWAS: There's not anything from Alzheimer trials that are available?

DR. OLANOFF: That's correct.

DR. KAWAS: Thank you.

Dr. Kieburtz is going to get the last question after which we are going to break for lunch. Be brief.

DR. KIEBURTZ: The exclusion criteria for MD-02 was nursing home placement before baseline and for the other one, monotherapy, was unlikely to require nursing home placement for the entire duration of the trial. Do we know how many people actually ended up in the nursing home in those trials during the conduct of the studies?

DR. OLANOFF: We can talk about 9605 specifically. I'll ask Dr. Schneider to present the data for that.

DR. KIEBURTZ: It doesn't have to be like less than 10, more than 50.

DR. OLANOFF: We'll show you the actual numbers because the analysis was done on this and it was actually published.

DR. SCHNEIDER: Karl, we're waiting for the data to come up. As Larry said, in MD-02, we don't have data on drug-placebo differences in nursing home placement but in 9605, we do. Here is the data using residential status in each column and then across that the rows of the numbers of placebo and memantine patients in institutions, at assisted living facilities in one case, at baseline and then at endpoint. So the numbers go from 13 to 18 in placebo and from 7 to 8 in memantine, and so it also fulfills the criteria that they were not likely to have required placement.

DR. KAWAS: I would like to thank the sponsor Forest and the FDA for a very interesting morning. This committee will be adjourned until 1:30 at which time we'll begin with the open public forum followed by the committee's deliberations.

I'd like to remind the committee members that this is supposed to be a public discussion of the issues and so keep your conversation at lunch quite fun instead of talking about what you've heard.

See you at 1:30.

(Whereupon, at 12:28 p.m., the committee was recessed, to reconvene at 1:30 p.m., this same day.)

AFTERNOON SESSION

(1:40 p.m.)

DR. KAWAS: We're now going to begin with the public hearing. This session of the Advisory Committee of Peripheral and Central Nervous System Drugs is reconvened. I hope you all had a nice lunch.

The rest of the afternoon will be devoted to an open public hearing followed by the committee's discussions, deliberations, and voting on the questions which were given to us by the FDA. The public hearing session should be fairly brief. We have one person we know is speaking, and if anyone else is interested or has prepared something that they would like to present for a few minutes, they should please let us know in the interim.

To begin this session, I'd like to read a paragraph that I did not write relating to disclosure.

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

For this reason, FDA encourages you, underlined, the open public hearing speaker, at the beginning of your written or oral statement to advise the

committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So the first person who's interested in speaking for the public forum is Barry Cooper. Mr. Cooper.

MR. COOPER: Hi. I'm Barry Cooper. In terms of disclosure, when I realized I was going to be speaking in favor of memantine, I sold my small amount of Forest Laboratories stock at a loss, unfortunately.

(Laughter.)

MR. COOPER: But I wonder if I would have made a profit if I would have had to report that as well. Don't know.

I hold a master's degree in health administration from George Washington University and I'm active in the disability management arena. I'm currently

involved in forming the Companion Care Association, a nonprofit organization established to help people with life-altering disabilities lead better lives. Towards that end, we hope to provide family and professional caregivers with new tools to help them perform their important work.

For over six years, my most important job has been to serve as caregiver to my wife Linda. Tragically, she was diagnosed with early onset Alzheimer's disease at the age of 53. Her father had early onset before her. I lost my mother Grace Cooper to Alzheimer's disease last year.

Before importing memantine for personal use for my wife, I consulted with many friends and colleagues who were physicians and scientists, including experts in the field.

On Aricept since diagnosed, my wife has been taking memantine for the past five months. The combination of the two drugs has led to a dramatic improvement in her condition and with no apparent side effects. I personally am convinced that my mother could have benefitted from memantine had it been an option to her, but at the same time, I appreciate the filters that are put into place here to ensure that Linda and I are not outliers on some curve. It's my fervent hope that we're the norm.

I'm going to be speaking to you today reporting

from the front lines. What I've written here is written in the belief that memantine is effective and safe. The public seems to believe that. So I suppose what you're getting here is a slice of what people are feeling out there that are caring for people like Linda.

To quote someone earlier, I heard the term "in the heat of battle", this was really written in the heat of battle with my wife there and having to be dealt with as the computer crashed, et cetera. So I hope you accept it in that manner.

I'd like to share three things with you today as I explain why I believe every month counts in making memantine available to Americans in need.

First, I'm going to talk about how memantine has dramatically improved my wife's quality of life and by extension by life as well, how it's brought back opportunities and pleasures hard to imagine just five months ago. I believe it can do the same for many other Americans in similar circumstances.

Next, I'll talk about how memantine might be able to save overburdened caregivers hundreds of millions of dollars a month, a startling savings for a group of people who have gone into terrible debt as they care for their loved ones. Our national health care reimbursement programs would share in this savings.

I'll close with some observations on Americans forced to import drugs successfully used in Europe for years and about what I believe is a shared responsibility by those who believe in memantine's effectiveness to expedite the process of getting memantine to all Americans who need it.

The quality of life is often overlooked on the macro level but proves to be critically important when making national decisions about health issues, such as the one being considered here. I've seen dementia of the Alzheimer's type slowly slice away perhaps the two people I've most loved in this world. Those who care and love Linda have witnessed a significant, albeit far from miraculous, improvement in cognition and her ability to perform activities of daily living. While performing many ADLs remains a problem to her, others have become happily quite simple for her once again. I'll choose two to report on, but there are others, although not an innumerable number.

It had been a year or so since my wife could put on a seat belt. About a month after taking memantine, she consistently has been putting on her seat belt 99 percent of the time, to the point where once recently when she was in the back of a car that had a seat belt that she wasn't used to, she wouldn't let those people drive away

until they showed her how to use it and she put it on herself.

Linda stopped flushing the toilet quite awhile ago. She now flushes the toilet consistently. Related to that and certainly more important, her personal hygiene in that regard has improved appreciably which has made it simpler for me as a caregiver.

Yes, and let's look at watching television. I had to laugh myself when I heard the discussions here this morning because actually that's really an important thing. I mean if you're not in the world day-to-day, I mean when you watch a woman that you love who used to cry at something or react to something just stare blankly at it and walk away when this is your release for the day, that's critically important. Now I'm not saying that she gets it all but she gets it. There are more times when she gets it, and that's important to her quality of life and it's critically important to me.

Linda's newly-improved cognitive and social skills are exciting to experience. Her day health care center reports that my wife's language skills have improved to the point that she has acquired a new, more highly verbal set of friends, perhaps leaving behind others not benefiting from memantine, perhaps not.

I have been delighted by the occasional return

of her quick wit, of the one-liners Linda has used on me throughout our lives together. One line that stands out is "get rid of the clutter that strangles your faith."

While not completely gone, her inappropriate fits of anger have abated as my wife more clearly understands why she can't always have her own way. She seems to have found a bit more inner peace and her joy of living, which was there before memantine, has been enhanced.

In pre-memantine times, my wife had become a passive observer to conversations. Now to everyone's pleasure, she's increasingly an active participant. Limited in her vocabulary, she compensates with animation and enthusiasm. These are priceless moments regained.

It is my hope that every month saved in getting memantine to Americans will give caregivers an additional month of invaluable glimpses into the people they used to know, glimpses into their very essence. It's my hope that every month saved will find the person inside one month stronger, one month further from being lost forever. Every month can count.

The cost in delay in dollars appears to be more easily measured. Researchers for the phase III memantine versus placebo study provide valuable estimates of how much money memantine can save caregivers. According to them,

the estimates are $824 a month saved in caregiver expenses, including delayed institutionalization.

Now, I'm a systems guy, so I look at that and I say okay, that's almost $10,000 a year. That's real money for caregivers whose difficult lives are often plagued with severe debt. But then again, by these estimates, if you take 20 percent of the 4.5 million people with Alzheimer's -- and that's a liberal 4.5 million, I think it's liberal, but 20 percent perhaps conservative -- we could realize a savings of $742 million a month. That's 900,000 people taking memantine times $824 a month.

If you look at the GAO numbers on people with moderate to severe Alzheimer's disease, you get about 1.25 million referenced for 2000. So that's about 74 percent of those people. So if they took memantine, we're saving three-quarters of a billion dollars a month. That's good news but it's also bad news because every month delayed, if memantine is effective and if those figures are near right, every month delayed means we're losing that three-quarters of a billion dollars.

In conclusion, memantine is widely available and has been in Europe for years but only a select few Americans are using it and hopefully benefiting from it the way Linda and I are. Assuming memantine is effective, that's a national disgrace. Importing memantine from

Europe has proven a daunting and expensive task. Surely there can be a better way to enable the first wave of informed consumers to obtain drugs such as memantine.

But more importantly, it is my hope that when the next promising, safe and uniquely effective drug or procedure becomes available here or abroad, we are able to benefit from it much more quickly. It is a challenge for all to recognize these opportunities as they appear, regardless of whether they come from the NIH, our own drug companies or, as with memantine, from a foreign concern.

For coupled with the responsibility to provide Americans with the world's safest drugs comes the parallel responsibility to move expeditiously when we see an opportunity lost for too long. I look at Gortelmeyer's study in 1992 on memantine and wonder why the NIH hasn't addressed it to this day.

It's now up to this advisory committee, the FDA, and Forest Laboratories to work together to save precious months in getting memantine to Americans in need. Allocating too little staff time to the remainder of this process is clearly a false economy, assuming memantine's efficacy. Protracted negotiations over package inserts harms Alzheimer's disease victims when every month counts. Delaying memantine's roll-out due to competing market objectives is contrary to the public good.

Because of your role as the public's representatives in this matter, I urge each of you who vote for approval, who believe this drug works, as members of this influential committee to personally do what you can to communicate a sense of urgency in your recommendations. Help bring this important drug to America where it is so badly needed.

Thank you.

DR. KAWAS: Thank you, Mr. Cooper. We also received a request to speak from Mr. Leonard Targonski. Is he available in the audience?

(No response.)

DR. KAWAS: Is there any other member of the audience who would like to speak in the public forum?

(No response.)

DR. KAWAS: Thank you very much.

The committee will now turn to deliberations and discussion and voting on the questions for the advisory committee. So the first question which we have been asked to discuss is: has the population for which the use of memantine is proposed been adequately identified in the studies included in this application?

I think rather than just having some cold votes, it would probably be useful for the committee to express their thoughts or questions on this matter and see

where we are. Do I have any takers? Dr. van Belle.

DR. van BELLE: This is a question to the FDA. I don't quite know how this works. Do you review the proposed protocols of the sponsor and approve them? So for example, this was a study aimed to look at moderate to severe dementia. You basically approved that particular objective?

DR. KATZ: Yes, basically. They'll submit a protocol and we have multiple discussions with companies during the course of the development to try and figure out what the right way to go is to get the particular claim they're interested in, yes.

DR. van BELLE: So there was no discussion at all that the mix of severe to moderate had to be at a certain ratio. Basically as they went into a clinical population, there would be a mix sort of naturally occurring and that's the mix that they dealt with.

DR. KATZ: I don't recall the specifics about whether or not we had discussed the proportions. By the way, just to yet again talk about the Latvian study, that was not done under the IND, so we had no role in the design of that trial.

DR. KIEBURTZ: Just from my perspective, the Latvian study, it's clear to me, involves severe Alzheimer's patients. To me, the other two studies, it

isn't clear that there's a significant proportion of severe Alzheimer's disease in those studies. No quibble that there is moderately advanced Alzheimer's disease, but I just remain uncertain as to whether those study populations represent significant fractions of severe Alzheimer's disease.

DR. KAWAS: Actually, yes. I'd like Dr. Katz to comment on that or else I'm going to.

DR. KATZ: Just maybe if you could elaborate on why you think that. I know you talked about it a little bit earlier, but if you could just sort of give us your reasons for coming to that conclusion.

DR. KIEBURTZ: Sure. I'll stick to Alzheimer's disease. Deciding when a disease is severe can be measured as disease-specific phenomenology, like cognitive impairment in this particular circumstance, but really many of the things we hear about in severe disease relate to impairment of activities or daily living, quality of life, global functioning. Those are not phenomenologically driven measures. Those are more generic measures of quality of life activities of daily living that could be impairing any disorder affecting the brain or mobility, arthritis, et cetera.

So, so far, I've seen and we've talked about using a disease-specific phenomology kind of measure for

deciding whether or not people have severe Alzheimer's disease, i.e. the MMSE, and we also heard some other things about the GDS and about the FAST, but the proportion of individuals in these studies who have FAST or GDS scores which are clearly severe in my mind is quite small, probably less than a quarter of the population as best I can deduce. And the information to clearly make that is not either in the information that was supplied or in the discussion that happened today, to my sufficient satisfaction. It may be there, I just haven't gotten it clearly. So I would say the body of evidence from those studies reflecting on severe Alzheimer's disease is in my mind small in the minority of data presented. Let's even say a third.

On the other hand, the Latvian study is clearly in severe and the body of evidence there suggests that it addresses that issue. But I'm not certain that, harking back to your original question, are there two studies that address severe, since I think we're talking about moderate and severe Alzheimer's disease. I'm sort of presaging that question by saying I'm not sure these two populations have a lot of that.

DR. TEMPLE: So are you saying that the diagnosis of severe should not -- this is for the future perhaps -- should not be made on the basis of a single

measurement like the MMSE but should be a more global thing made up of several different measures or what? Because they did meet what people thought was the standard for severe on the Mini-Mental. But you're not persuaded by that.

DR. KIEBURTZ: Maybe it's just the fact that I'm ignorant and everyone knows that an MMSE of 10 is what defines a severe Alzheimer's patient. That's well established, that cutoff?

DR. TEMPLE: Well I have no idea, but probably other people do.

DR. KIEBURTZ: I don't think so. I mean, I think it's a reasonable lower boundary for moderate, but it doesn't mean that moderate doesn't go beyond 10.

DR. TEMPLE: These had to be less than 10.

DR. KIEBURTZ: Right. In Latvia.

DR. TEMPLE: No.

DR. KIEBURTZ: But the others were 5 to 14 or 3 to 14 and certainly for the --

DR. TEMPLE: No. I'm sorry. You're right. I'm referring to the analysis that the --

DR. KIEBURTZ: Oh, yes. I'm sorry.

DR. TEMPLE: About half or roughly half of the patients were below 10 on that score. So it was a mixture of mild -- I mean, by that standard only, which I don't

know what that means but other people probably do, it met somebody's standard for above 10 and below 10 moderate-severe. But I'm just trying to understand.

Are you saying that not all of them were severe which is clearly true by the MMSE or that you didn't think even the ones that were below 10 were severe?

DR. KIEBURTZ: Right. It's not clear to me by the other kind of descriptions of severe Alzheimer's disease that MMSE of less than 10 is sufficient to make that differentiation. Now, there are other things we did talk about, the FAST and the GDS.

I'm trying to address some of the things that Dr. Katz brought up in the general question. Making these differentiations of mild Alzheimer's disease, moderate, severe, are probably generic issues for this advisory board in the future. What about Parkinson's disease or Huntington's disease or ALS? What's severe ALS?

This matters because, as it stands, there's no approved drug for severe Alzheimer's disease. So we're saying this drug meets a unique niche of addressing that issue. There are other drugs that are approved for moderate Alzheimer's disease, but there's something unique and compelling about this body of evidence to suggest that this drug meets that particular niche.

I'm just struggling with, well, if we can

decide to approve a drug for that niche, what is it? It's sort of we know when we see it, but we can't say what it is so much, at least from my perspective. I just haven't gotten my hands around what that means.

DR. KAWAS: Dr. Katz.

DR. KATZ: Yes. What in the Latvian study allows you to conclude that those patients were severe?

DR. KIEBURTZ: That's an interesting question. One part of it is that they're institutionalized. The other is the duration of their dementia is clear. Also, their average scores on things aside from the MMSE were considerably lower than the other populations. I don't know the scale very well, the BGP. But, again, I could apply the same conceptual rigor to what I said about the others and say, well, I'm not really even sure the Latvian ones are severe.

DR. KATZ: Yes. Because I think the most, I guess in some sense, prominent difference that we've mostly heard about between the Latvian study and the U.S. studies is that all the patients were below 10 on the MMSE. I think people are sort of focusing on that and saying, well, therefore these people are severe. But that's just the MMSE, just the same test that you're questioning the validity of in terms of making this diagnosis in the other studies.

So I'm just trying to understand. Given your understanding of the MMSE, independent of the other sort of functional measures in the U.S. studies, just focusing on MMSE score, would you say that in some general understanding, patients below 10 are severely cognitively impaired, if not functionally impaired?

DR. KIEBURTZ: Yes. If you're asking me below 10 is severely cognitively impaired, I'd say yes. But as Dr. DeKosky said in one of his comments, even someone with a 10, regarding is it worthwhile to preserve the level of function of someone who has a low MMSE, not to put words in his mouth, but what I understood him to be saying is don't figure that someone who has an MMSE between 5 and 10 doesn't have a lot going for them. They can still do a lot.

So to decide on that basis that someone is severe, it doesn't seem sufficient. It seems part of it but it doesn't seem sufficient. Maybe this is a generic issue. I'm not trying to here so much talk about memantine but what's a severe Alzheimer's patient. It's funny to parse out. I mean, why not just Alzheimer's disease or moderate Alzheimer's disease? Why specifically moderate to severe?

DR. KAWAS: Dr. Packer.

DR. PACKER: It's interesting that we're

focusing now on the definition in the studies that were prospectively put together. One of the difficulties that I'm having with looking at the data and making the decision is that one of the major studies, although I hear not the critical one of the three that we're supposed to be looking at, is a retrospective classification of patients with Alzheimer's disease. Given all of the difficulties with classification, not that these patients are or aren't severe, but doing something in retrospect to develop or to get approval for a new drug bothers me significantly

I still don't really understand what that Latvian population is. Who are the patients in that group? What were the criteria utilized in Latvia to put someone in a nursing home may be completely different than what we're looking for in the United States. So just that they were in a nursing home and someone in retrospect classified them as severe doesn't give me the same comfort level as if they were prospectively evaluated and classified before they were put in on some criteria.

So I'll tell you from my perspective and I just would like to let the FDA comment on that, that I have trouble with retrospective studies that classify. I just don't know how to put them into the mix as well, especially if I have to put some weight on them to approve a drug in a severe category and that shows up in one of the scales. So

maybe it's only my difficulty, but I have real issues with that.

DR. KAWAS: Before Dr. van Belle, can I ask the FDA? I mean, maybe I was reading this question somewhat differently than many of the comments that are coming.

To my mind, the population was identified by Mini-Mental and it was identified as individuals with 15, 14, whichever cut point you choose in there, and below essentially. Can't the population be defined by score? Does it have to be defined by a word that we argue over whether or not is appropriate for those scores?

DR. KATZ: Well, I think the words are important because all claims are couched in words, and so if the drug is to be approved, we have to write labeling and we have to write an indication for what it's approved for.

So the way the Alzheimer's world has been dealt with so far is to in the claim describe the patients who were studied, and in the drugs that are currently approved, there was a view that those patients were appropriately labeled as mild to moderate. Now the sponsor wants a specific claim, a new claim -- that's why we're here -- to include severe, include the word "severe" because it implies something.

So, yes, I think the words are important, and

we're asking the committee whether or not you think, given the rules that were used to get people into the trial, whether or not it's fair to call those patients severe. That's obviously going to be a judgment. Their cognitive impairment might be severe, but some might feel that their functional status is not severe. It's a personal judgment, but we're trying to get a sense from the committee whether or not you think it would be appropriate to call these patients or to apply the results of these trials to what you think are severe patients.

DR. KAWAS: Dr. Temple.

DR. TEMPLE: This is in part, I think, a religious argument, but it wouldn't be unprecedented to say these people were considered severe on the basis of their Mini-Mental score. In cardiovascular medicine, you grade people by the New York Heart Classification, a somewhat vague but useful classification, and so you grade their degree of heart failure that way. Somebody else could say wait a minute, I don't know their ejection fraction. What kind of ridiculous nonsense is that?

But you commonly define how you do it at the beginning of the study. Now if you look at the definition, you say that's ridiculous, nobody believes that, that's a different question, but there are many cases where you define people that way, and as Russ has been pointing out,

moderate and mild were defined by being above 10 all this time on the Mini-Mental. So there is at least some tradition of doing that.

There are lots of good questions you can ask about whether that's the best way to characterize people. That's a perfectly good question, but this would not be unprecedented.

DR. KAWAS: Dr. van Belle.

DR. van BELLE: The reason I asked my question earlier was there was some understanding as to what the mix had to be between severe and moderate in the protocol and the answer is apparently no. So I think it's very natural how the sponsor went about and got them. They got everybody who had a Mini-Mental less than 15 and some fell out to be 13, some fell out to be 6, and in the Latvian study, they only went for ones with scores less than 10.

So in fairness to the sponsor, I would say that the answer to the first question is yes, they have identified a population and I might have liked to have seen it split half severe and half moderate. That was not the game plan and it's not fair to saddle them with that particular game plan.

DR. TEMPLE: Actually, it was about half and half. If it had been 10 percent/90 and the company wanted severe, we'd be nervous, I would say, but in this case, and

you can look at the individual analyses yourself, it was about half and half, I think. One was slightly more in one direction, the other was slightly more in the other.

DR. KAWAS: Dr. Kieburtz.

DR. KIEBURTZ: Just to respond to Dr. Temple. If it's MMSE scores between 3 and 14 and 5 and 13, whatever it is they were talking about, fine. I don't have any problem. If that's the definition of moderate to severe, okay. That's great. It neither extends above or below. I mean, that's the definition. That's the group of people who were studied.

DR. TEMPLE: Right. Well, labeling always in this division anyway defines, among other things, how patients were entered into the trial, what standard they used, whether it's an ADAS-cog or something else. It commonly gives who the population is by that definition which is always, as you've been saying, debatable but maybe how they were chosen.

DR. KAWAS: Rusty.

DR. KATZ: Just to address the point that Dr. Packer raised as far as the diagnoses of the patients in the Latvian study. I mean some of it, I think, was retrospective but some of it wasn't. I believe the requirement for patients to be below 10 on the MMSE was in the protocol. So those patients had dementia and let's use

the word "severe". They were severely cognitively impaired. The diagnosis of Alzheimer's versus vascular disease was, as I understand it, retrospective or at least that categorization was, at least that's our understanding, but maybe that's not even true.

DR. KAWAS: Dr. Lon Schneider is going to be a cardiac case if we don't let him talk.

(Laughter.)

DR. SCHNEIDER: Just a brief clarification. The analysis based on the division of the Hachinski was prospective in the protocol. It was first at 5 or below and then modified to 4 or below. By the way, each of those analyses did come out. So that was technically a prospective, protocol-defined analysis.

DR. TEMPLE: So then we added our own analysis by looking at the CT scans and then that analysis was done, too. So that was late and if that's the only one you believe in, then I guess you could say it was retrospective, but it was sort of similar to what they tried to do.

DR. PACKER: Well, I don't know if there's a 50 percent prospective/50 percent retrospective study and how you use that as a valid study, and I still don't understand it.

What I also don't really understand, as we're

talking about defining the population and maybe the committee can help me with this, is the logic of mixing this into the severe group and thinking with the subjective rating scale that we are trying to make objective, to believe that the patients who are between the scores of 7, 8, and 9 are anywhere similar to the patients who have scores of 2, 3, and 4 or 2 and 3.

We're creating this category of severe, and from an outsider who doesn't deal with this, I would never accept this kind of a criteria for any studies that I was doing. Mixing in people who couldn't take care of themselves at all and were sitting motionless with patients who couldn't put on a seat belt, I mean I think that you're mixing a lot of different things and we're lumping them into a severe category and we're using the subjective scale.

I don't have an answer how to get out of this. I just find defining the population, mixing different kinds of studies and different kinds of criteria, very confusing.

DR. KAWAS: Does the committee feel ready to vote on this? Yes, Dr. Wolinsky.

DR. WOLINSKY: I want to actually come back a little bit to a question that I raised some hours ago because it seems to me that whether we're talking about moderate or severe and we're having difficulty in figuring

out where those boundaries are, it would seem to me that I would have an enormous problem figuring out how these gradations go from mild to moderate to severe as a clinician. So I'm sure that the population that we're presented data with in large part has Alzheimer's disease and are cognitively and functionally impaired, but I'm not sure exactly how we would expect to let the practitioner know at which point this drug is approved for use.

It seems to me that approving a drug based on the fact it's having some effect always leaves clinicians to use it where it hasn't had that use, and this is where I raise the question about if it didn't behave the way we'd anticipate in mild disease, what would that imply to the FDA in terms of whether or not a drug approved should continue to have that approval.

DR. TEMPLE: Can I try to respond to that? There are two separate questions or possibilities here.

One, which is the one we'd worry about most, is that carrying out a bunch of studies in some severity of Alzheimer's disease and continually showing nothing, that might cause you to wonder whether the trials that look positive got the right answer or whether it was just a peculiar outcome and not supported. So if there was enough negative evidence in another part where you figured, gee, it ought to work in milder disease, that's one thing you

might worry about.

The second possibility is that for entirely mysterious reasons, this is a drug that works only in more severe forms. I mean, it's hard to think of why that would be or how that would be, but you never know till something happens.

I would say, as Russ said before, we wouldn't particularly worry about that. That would be true. You would try to point out in labeling, if you knew it, that it didn't seem to work in people with milder disease, but you don't not approve a drug for something that it's established to be good for because it doesn't work in another group of people that you're afraid doctors might use it in. You'd try to say something in labeling, but you don't deny the thing that has been shown.

So those are really two quite distinct possibilities, I'd say.

DR. KATZ: Just to follow up. There are plenty of examples of drugs that are approved for restricted portions of the population that have the disease in question. Typically, anticonvulsants are initially approved anyway as adjunctive therapy and labeled as such. We don't know if they work by themselves and in the absence of other concomitant anticonvulsants until someone shows that they do, and there's no obligation on the part

of the sponsor to show that they do. If one uses, for example, the adjunctive epilepsy setting as a surrogate for more advanced disease, as most people can be managed with monotherapy, you can say, well, we're really approving drugs for patients with severe epilepsy at the outset, again with no obligation to show it doesn't work as monotherapy.

Similarly, for Parkinson's disease, we approve drugs as monotherapy for Parkinson's disease, in other words, early Parkinson's disease, and if they show it works in more severe patients, they get a claim for late Parkinson's disease as well.

So there's plenty of precedent even within our own division for approving drugs for some restricted sample and with no particular obligation to require that the drug be shown to be effective in the entire universe of patients with a particular named disease.

DR. TEMPLE: One other thought about a question that came up before. There's really a lumping/splitting tension on the question of whether you should try to study as narrow a group of patients as possible or try to include a broader range. Anybody familiar with the cardiovascular area knows about the discussion of large, simple trials where the whole premise is to include everybody and see if you can get an overall effect and then you feel good about

that because you know it applies to everybody.

At the very same time, having established that, people come back and say but how do I know if it works in this group, this group, this group, this group, this group, and the larger and simpler it is, the less capacity you have to answer that question.

So what people sometimes do, I don't believe it's been done here, is they do the trial overall and expect a result overall and then they try to look at the severity grade. So in heart failure trials I described before, you'll always see an analysis of the class 4 heart failure, the class 3, the class 2, along with the overall result. Your expectation is not that you're going to find statistical significance in each of those. You're going to sort of look at the direction and see if you have what looks like a qualitative difference which would be weird.

So in this case, one could at least look at the group with an MMSE of 3 or 3 to 4 or 3 to 5 and then the group from 6 to 8 and see if you have a generally similar direction. Now your power to make that observation is very modest and whether anything would come of it, I don't know, but you can do that sort of thing.

The alternative is to sort of do an infinite number of studies in a group of very narrowly defined groups and most people don't have the patient population or

the money to do it that way. So there is a tension between having a somewhat larger split and being evermore precise about exactly who you're studying and that's a common problem.

DR. PACKER: But my difficulty with that -- and I agree that lumping and splitting can be very difficult, especially when you're using very subjective criteria.

I think there has to be tremendous care taken when you're evaluating a drug or an approach where the best you can probably do is stabilize and not improve. If you are evaluating an approach that can take you from a level 3 to a level 5, then I can see lumping is a very good way of doing it. If you're doing a drug that at best is going to keep you at a level 3 and trying to get from level 3 to level 4 will be almost impossible, also it may be very hard to deteriorate from level 3, then you're adding another area of complexity in this entire analysis. That's why, again, I find that you're right, but I think it's harder when the best you're going to do is stable disease ultimately.

DR. KAWAS: I guess I'll go ahead and make my thoughts apparent here, which is that for me personally, the population has been adequately identified. It's been identified purely on the basis of Mini-Mental, and although I completely understand the issues that are being brought

up and whether or not it should be called severe and what all is certainly an important topic for discussion, but in the tradition in which we've done other drugs, I mean the patient with the Mini-Mental of 10 or 11 also is very, very, very different from the patient with the Mini-Mental of 26 which is essentially the way the cholinesterase drugs were approached.

So my concerns, if I have them, are not so much on the identification of the population, but maybe of some concern to me more instead is that if the bottom rung of that population that's been identified really responded is more the question that I felt the need to focus on.

I think, so that we won't be here until after 5:00, I'm going to probably let those two guys over there, who are going to also become cardiac cases, have a couple of comments and limit it to 60 seconds. So we'll start putting them together, and then perhaps are we ready to go around and do a vote on question 1?

Dr. Ganguli, you can speak first.

DR. GANGULI: If we in this group are having so much difficulty deciding what's severe and what's moderate, if this drug is approved for use and the majority of patients with this condition are not being seen by neurologists or psychiatrists or geriatricians, they're being seen by their primary care doctors, the likelihood

that any of these scales are going to be applied in the standardized way before deciding whether to prescribe something or not is pretty remote.

DR. KAWAS: Can I ask you if you really -- well, my personal impression is that third party payors are going to take care of that. They're going to insist on Mini-Mental in the appropriate range.

DR. GANGULI: Well, in the study that I'm currently doing, the few general practitioners who write anything about mental status testing in the charts write MMSE WNL.

(Laughter.)

DR. KAWAS: Good point, good point. Dr. Katz.

DR. KATZ: Yes. That stands for "we never looked." Right?

(Laughter.)

DR. KAWAS: You didn't even need the floor for that one.

DR. KATZ: Right.

But the problem of whether or not clinicians who will prescribe the drug will be very, very clear about what patients this drug is effective for is, of course, a problem. But that problem probably exists across the board in every disease and certainly in the Alzheimer's world where right now, somebody has to decide if the patient has

mild to moderate Alzheimer's disease. I don't know that they are any better able or worse able to make that distinction than severe. I think what's clear is that the patients identified for these trials, at least by the MMSE criteria, are worse than the patients identified for the previous trials.

DR. KAWAS: Dr. Tariot.

DR. TARIOT: Thank you, Dr. Kawas. As I heard some of this discussion, it was are there patients with severe or advanced dementia included in the trials, and I want to point out, in addition to the Mini-Mental criteria, each trial had more research-useful criteria for staging severity of dementia, and if we could put up the FAST scale.

Just to use the two U.S. trials as an example, while that's coming up, remember that in the 9605 study, all patients had to have a FAST score of 6 or worse. So these are people who you see the kinds of difficulties they were having at this point. If this happened to me, I think my wife would rate my dementia as fairly severe.

In the so-called MD-02 study, roughly 40 percent of patients, so a slightly different proportion or a significantly different proportion, had FAST scores of 6 or worse. So we just want to make the point that these patients were included. They were assessed in a

quantifiable way that's less user-friendly in the trenches.

The third question that has come up is does severity predict outcome which perhaps is a discussion for later, but I would simply point out that the so-called Forest plots that you have in front of you really would suggest, no, there isn't a clear dependency of outcome upon baseline severity.

DR. KAWAS: Dr. Steve Ferris.

DR. FERRIS: Yes. Hi. I'll introduce myself since I haven't spoken before. I'm Dr. Steven Ferris from the Silverstein Institute at NYU School of Medicine and head of the Alzheimer's Center there.

I wanted to follow up on Dr. Temple's comment and actually an analogous comment to Dr. Katz's follow-up to that in terms of focusing on one portion of a disease spectrum to establish efficacy, at least in that portion, and I don't think we have to look outside of Alzheimer's disease, as I think Dr. Katz has just pointed out.

The approved drugs currently are for one segment, mild to moderate, and has anyone split that into mild and moderate separately and questioned whether you could tell the difference and questioned whether you have efficacy separately in those two arbitrary subgroups?

Well, I think data has been looked at and you don't always see efficacy at least a p .05 level in the

mild part of that spectrum when you split it by Mini-Mental State, and there's some published data on that issue. It's probably due to the same problem that you have as you get down to the severe end which is the sensitivity of the instrument to measuring change in the placebo group.

So I think there's ample precedent for this within our own Alzheimer domain and with the existing drugs that are approved for a different portion of the Alzheimer severity continuum.

DR. KAWAS: Thank you.

Dr. Katz.

DR. KATZ: That's a fair point. I don't recall if we looked specifically at the breakdown of either the distribution of patients in the mild to moderate categories or what the actual results were in those strata, however they were defined.

I think the reason to perhaps focus on it a little bit more in this case, although I recognize that it is sort of a retrospective kind of a subgroup look, is that this is different. The claim here is that this does something that the other drugs have not yet been shown to do, that is to say, treat severe patients.

So to me anyway, it makes some sense to at least think about that question perhaps a little bit more than we did in the past. It's possible if there were no

other drugs approved at this moment for Alzheimer's disease of any sort, this was the first drug to come along, we perhaps might not be having this conversation as we perhaps didn't have it in the mild to moderate situation. But it's occurring in a different context, in a different time, where we already have drugs that treat moderate patients, we believe. So now we're being asked to conclude that this actually does something that the other available treatments don't do, and I think that's probably motivating our interest in looking more closely at this particular subset of the subset.

DR. WOLINSKY: But I guess it's that implication that had me asking the questions that I was asking and facing the dilemma that I'm facing because I know these are Alzheimer's disease patients in the main, as well as we can be sure about that. We'll talk about later whether or not there's efficacy, but let's assume that there's efficacy. Why are we making this judgment call about the severity which has some potential implication about either when you use drugs or which drugs potentially are better than other drugs when we actually have no data on that? But there is an implication, if we say this is specifically a subset, that I'm not so sure that I believe the data support.

DR. TEMPLE: There are no direct comparisons

with the other class of drugs. That happens a lot and usually what you do is get credit for studying something that no one ever bothered to study. You can't say you're better than the other guys, but you can say we have evidence in this domain and nobody else does. Believe me, that comes up a lot.

Just sort of speaking philosophically, it's desirable that if you go to the trouble of studying something nobody else studied, you get some ability to make something of it, otherwise no one would bother. So it seems like the right kind of incentive. And we would watch closely to make sure nobody said that we're better than they are in this condition when they don't have any actual comparative data.

I did want to point out, though, that in one of the slides -- they're not numbered, so I can't tell it -- there are data on the effect compared to placebo in people of every severity with an MMSE of 3, 4, 5, 6, 7, so on. Yes, that one. On the SIB, if you wanted to read tea leaves which is the best you can do with these small data sets, it sort of looks like the effect is similar across all levels, and on the ADCS and CIBIC, it's not as clear that you have much of an effect at the very lowest end, although between 5 and 11 you sort of do. So there is some data on that question actually. It's not that there's not.

DR. KAWAS: I think maybe we're ready to vote. Probably the easiest way to do this, to keep a record, is to go around the table, starting with Dr. Packer, and recording the votes on question number 1. Has the population for which the use of memantine is proposed been adequately identified in the studies included in this application?

Dr. Packer.

DR. PACKER: (Off microphone.)

DR. KAWAS: You can feel free to qualify. You have to start with a yes or a no or an abstention, after which you can say anything you want until everyone gets tired of listening.

DR. PACKER: It will be short but they may be tired anyway. I'd say yes, given the limitations, however, of how the studies were put together and sort of the arbitrariness of the scales, but my answer would be yes.

DR. KAWAS: Dr. Kattah.

DR. KATTAH: Yes. I think the population studied was well classified as severe dementia.

DR. KAWAS: Claudia Kawas says yes.

Can I remind you to please speak into the microphone so that it will be recorded on the transcript, also?

DR. WOLINSKY: Yes.

DR. KIEBURTZ: Yes, with a caveat that it's described by MMSE.

DR. van BELLE: Yes.

DR. GANGULI: Yes.

DR. EBERT: Yes, given the fact that it was defined by the MMSE.

DR. KAWAS: So the vote on question 1 was unanimous. Yes, the population has been adequately identified, at least with the MMSE.

Now, we've got the harder questions still ahead of us and it's approaching 3:00. I think it's kind of interesting that several people, except me, seemed to think this meeting might not make it till lunch.

So number 2. Are the designs of the key studies in this application adequate for evaluating the efficacy of memantine for the proposed indication? In particular, are the instruments used to evaluate efficacy appropriate for the patients with moderate to severe Alzheimer's disease?

So the floor is open for any discussion or comments on this topic. I will start out by saying my impression is that the key studies are very relevant here. Assuming the key studies to my mind are MD-02 and 9605, that is, the two studies done in the United States, I think that the designs of those studies were appropriate for

evaluating efficacy for the indication that's proposed.

In my opinion, the Latvian study was designed for another indication essentially, and it may or may not have been adequate for that indication, but it wasn't specifically designed to look at Alzheimer's moderate to severe patients.

In a sense, the instruments question is a different thing to my mind and opens up the question of how we measure this disease, period, in terms of progression. Although I recognize all the limitations of the instruments and I'm familiar with the majority of them, in my opinion, it's about as good as the state of the art is right now.

The Severe Impairment Battery, measurements of function with ADL and the global measure from my personal perspective are reasonably appropriate for the patient group that was studied.

Do we have any comments, thoughts? Dr. Kieburtz.

DR. KIEBURTZ: In general, I agree. The SIB and the ADCS-ADL and the CIBIC-plus all seem like good instruments.

I was a little curious on the 9605, making the choice of a global/global as opposed to a global/phenotype which has been sort of what you've described, Dr. Katz, in the past, a cognitive measure plus some global measure.

Here is a double global measure without cognition as a primary, although the cognition was an important secondary and looked robust in terms of its efficacy.

It's sort of an interesting policy question when you make this shift -- this is another one that you asked us to address specifically -- from mild to moderate to moderate to severe, should cognition leave the venue of a co-primary. It strikes me that the evidence here is that the SIB performs well in this group and cognition is an important part of moderate to severe Alzheimer's disease and it's not clear why in future studies -- I'm not criticizing or commenting on this one in particular -- but that why cognition shouldn't remain an important co-primary, along with some global measure.

DR. KATZ: Well, right. I don't know exactly why it wasn't prospectively designated as a co-primary. We would expect it would. Our view is that it should have been and these studies should have that requirement as well, but our view is that there weren't many specific cognitive measures done in that study, as I recall. The MMSE was and actually wasn't statistically significant. I think we were convinced that the SIB was a reasonable cognitive measure to use in this population and the statistical result was so robust that no matter what sort of an adjustment you could possibly imagine for multiple

comparisons, it still held up. So your point is well taken.

DR. KAWAS: Actually, I want to qualify my statements by saying I think that in terms of design, that was not the best choice. Two measures which are similar in what they're measuring should not be the standard, and I agree with the comments that have just been made. There should be a measure that measures ideally something like cognition and a global measure on top, rather than two global measures.

Dr. Packer.

DR. PACKER: I agree in general to your initial comment. I do worry just as you just said about using two global measures and then getting a chance to cherry-pick the one you think is important if it fits into your population as a positive versus a negative, which is always a risk of doing two global measures.

The other thing I think more, though, is sort of a challenge to this committee in the long term is as newer drugs come up for this indication or similar indications, I'm not sure that these scales are all-encompassing. I think that there is a lot of reason to start thinking about including some kind of scale to talk about what the actual caregiver gets out of the process. Is that an improvement to allow a drug to be licensed?

I think there has to be maybe more emphasis on psychiatric problems in this disease, especially in the severe group, and I just don't think we have hit the correct measures yet. They may be the best ones we have now. They may be the best validated and they are the correct ones for this company to use to get their drug to market, but I'm not comfortable that they're the right ones in the long term, especially if you're going to get into this severe grouping of patients with other needs.

DR. KAWAS: Any other comments or thoughts before we vote on this one?

(No response.)

DR. KAWAS: Now, I assume our vote has to be yes or no. In this case, you're going to hear, I think, even more qualifications than before, but if that's acceptable to you, we'll do it that way. How would you like to handle it?

DR. KATZ: No, no. We're definitely interested in if there's any commentary associated with the vote, but yes, we would like a yes or a no. There are actually, of course, two questions here. If everybody has the same answer to both questions, you can just say yes or no as is applicable and we'll assume it covers the waterfront here.

DR. KAWAS: So should we divide the two questions up and start with the design of the study and

secondly the instruments?

DR. KATZ: I'm sorry?

DR. KAWAS: Would you like us to divide it up into design first round and instrument second round vote?

DR. KATZ: You can. Again, as I say, if most people are going to vote the same way to both questions, if you have that sense, you can just take them together. Fine. You can break them.

DR. KAWAS: I'll try and put them together in the interest of efficiency. Actually, we'll let Dr. Packer start again, but maybe in the next round, just in fair warning, we'll let you be last.

DR. PACKER: Yes. I looked at question 3. I'd much rather be last for question 3.

(Laughter.)

DR. KAWAS: That's what I figured.

DR. PACKER: Thank you very much. Yes and yes for question 2.

DR. KAWAS: Dr. Kattah.

DR. KATTAH: Well, as a general neurologist, I'm most familiar with the Mini-Mental Status Scale score and really much less familiar with all the other measures. So when I analyze these data, I attempt to compare what I know in the Mini-Mental Status and I can visualize the patients and all the other parameters that were looked at.

I think I have come to the conclusion that the design in all three studies was good and that the data that came from that is valid.

DR. KAWAS: A double yes.

That makes me. I basically, as I said before, think that the optimal design should include both the measure of cognition and the measure of global. In fact, one of the studies did not embrace that as its primary outcomes but we did see the data that was retrieved from secondary outcomes on the SIB, which I thought was appropriate.

So overall, it's a very qualified yes, but I say yes the designs were appropriate, and as I said before, yes, I think the instruments represent the state of the art right now, as meager as that may be.

Dr. Wolinsky.

DR. WOLINSKY: Well, as a non-expert in Alzheimer's disease, I have difficulty figuring out which two studies I should look at as key studies, and I'm not sure that I have three key studies. But overall, I think I can get a reasonable gestalt out of these three studies to have an idea of what's going on with this drug in this disorder. So that's the qualification for a yes.

DR. KIEBURTZ: So on the first one, I think 9605 and MD-02 are a yes.

The 9403 I'm not sure is a good design for the indication proposed. It's a good study of dementia. I'm not sure it's a good study for Alzheimer's disease. Some of the benefit of randomization is lost in that it isn't subjects with Alzheimer's disease who are randomized, it's the subjects with dementia who are randomized and the post-randomization choice might dilute the benefit thereof. So I'm not sure. I don't think that, in particular, is a good design for Alzheimer's disease.

The instruments, as I said before, I think are fine, with the caveat that Dr. Kawas noted, and similarly 9403, the cognitive measure there I'm not sure is an adequate cognitive measure.

So I think that in large part translates into a yes, yes, but with some concerns about 9403.

DR. van BELLE: Yes, yes, but with some comments. The design issues have already been mentioned, so I won't repeat those.

With respect to the second issue, I think the instruments probably represent a state of the art at the time the studies were designed and represent the state of the art at this point in time.

But I do think that particularly when we're starting to deal more with severe Alzheimer's, that it can be shown that the information content, for example, in the

Mini-Mental, the maximum information content is about a score of 18, and then it just decreases rapidly after that. So it's just a bad measure to try to characterize severe dementia, and I think the hortatory comment would be that the drug companies and the FDA should be looking at other measures that are going to be more informative and probably more efficient.

DR. GANGULI: Yes and yes. It's easier to say if you just focus on the U.S. studies. I have a lot of concerns about the Latvian study.

DR. EBERT: For the two American studies for design, yes.

As far as the instruments, yes, although I believe that we need to have better consensus on what measures should be used in determining the degree of progression of this disease, and in particular, to evaluate the individual items within each scale to determine which items are most sensitive in identifying progression.

DR. KAWAS: Now comes the stake. Has substantial evidence of the effectiveness of memantine for the proposed indication been demonstrated by the studies included in this application?

DR. KATZ: Claudia, before people comment about it, a number of people have already commented on this, and we used the word "key studies" in the last question. I

think it would be useful for us to know explicitly -- and again a number of people, I think, have said this -- which studies you think are crucial to evidence of effectiveness, if you think that there is evidence of effectiveness. I mean, I'm trying to figure out whether or not there's some flaw in any of the other two studies that you think the Latvian study necessarily fixes or whether people think the Latvian study, if they do, is so problematic as to not really contribute materially to the conclusion. So which studies do you think are key, I guess, is what I'm asking.

DR. KAWAS: I'll start out with my thoughts when I was looking over the information. Essentially, to my mind, the two U.S. studies were the key studies. They were the ones I had the most confidence in the design and the management and carrying out and understood most about the patients and their response.

However, when you only look at those two studies, the CIBIC is not significant, meaning that to my mind, it actually wouldn't qualify as a pivotal study because it was not significant in its primary outcome measure on the global.

However, my recall is that the significance on that was a .06, which made it awfully close. So for my personal thinking, the Latvian study was very useful in overcoming that lack of significance on the CIBIC on the 05

study.

Who else would like to comment or share their thoughts with Dr. Katz? Nobody wants to talk.

DR. WOLINSKY: I think you said it so well.

(Laughter.)

DR. KAWAS: I may never hear that again. I wish I thought he meant it.

(Laughter.)

DR. WOLINSKY: I actually do on this one.

(Laughter.)

DR. KAWAS: Was my answer enough or would you like to hear more? I'll nudge them into answering.

DR. KATZ: No. I think it certainly gets to what we're interested in.

But let me just sort of probe you a little bit more on this point. I know you said the Latvian study is very useful to sort of overcome the .06 on the CIBIC in 9605. If the Latvian study didn't exist and you just had the two U.S. studies -- maybe this is not a fair question, but so what?

(Laughter.)

DR. KATZ: Would you find that there's substantial evidence of effectiveness?

Again, I'll just reiterate that there were two primary outcomes in 9605, one of which was a global, the

CIBIC, and one of which was an ADL, which again we consider would be acceptable as an overall global-type outcome.

I think the p value for the ADL was .022 or something like that anyway, and I guess the protocol said that you have to win on both. I don't really recall. Well, in the other setting, they do. But if one were to Bonferronize, let's say, between the two, even though the protocol didn't call for it -- I think this point was made -- the ADL would still meet the new criterion.

DR. TEMPLE: You don't Bonferronize. Actually you'd probably make an adjustment the other way if you were being fair. If you have to win on two endpoints, it's harder than winning on one endpoint.

DR. KATZ: No, no, no. But the point is they didn't win on two endpoints. So I'm saying an alternative approach would be, well, instead of requiring a win on both, you could say, well, if either one wins, but then you'd have to make an adjustment.

DR. TEMPLE: Well, it's for another time, but there are some people who would say that if you have to win on two endpoints, you should test both of them at some number other than .05.

DR. KATZ: Yes, that is for another time.

DR. TEMPLE: For another time.

(Laughter.)

DR. KATZ: But anyway, after all of that, let's say given the data and the hypothetical circumstance that the Latvian study didn't exist, would the two U.S. studies stand alone?

DR. KAWAS: Does anyone want to talk before I shut the audience up again? Dr. Kieburtz.

DR. KIEBURTZ: Yes, I think so. In ways, I think it would have been easier to not even see the Latvian study from my perspective. I think the two U.S. studies, despite the .06 -- I think Dr. Fisher's point about the informativeness of the missing data in a progressive disorder, the fact that the placebo dropout rate was higher, actually is perhaps an overly-conservative way with an LOCF of handling the placebo group. It's darned close. There are other ways of modeling missing data. They attempted that.

I think, yes, it's not the standard .05 on both of the primaries, but the SIB data is compelling in my view and probably those two studies stand alone.

DR. KAWAS: Dr. Packer.

DR. PACKER: I sort of disagree with the whole premise of trying to evaluate things in a vacuum anyway. That's just not how we do things. I mean, you bring your own knowledge base and you say, well, if you didn't know anything about anything else, how would you evaluate it? I

just don't think that's particularly a fair approach to this.

I am bothered by some of the borderline results. I'm bothered by some of the issues of the scales and how sensitive they really are, but I think that on the whole, there is some suggestion of efficacy, but you can't throw out information when you try to make that kind of interpretation. If it was that easy, then we didn't have to hear any of this dialogue. We could just look at the p values and decide if it was significant or not. So I do object to sort of throwing out the data and trying to evaluate it into a vacuum.

DR. KATZ: Right. I don't think we should throw away data. I'm just trying to assess what weight people give to various aspects of the data. That's really my only goal.

DR. KAWAS: For me personally, I can say I very much believe strongly in determining your design ahead of time, your significance level ahead of time, and all the other measures ahead of time, and I have considerable problem with what was called earlier cherry-picking. We can run 10 trials and get something out of each one that, put together as a composite, would be considered positive.

So for me personally, two studies and if these were the two that were presented to us, one of them failed

to meet its prescribed outcome measures, and I would be having a lot harder time personally.

Are we ready to try and give a vote on this one? No one is even looking at me. So I guess that means we are. Dr. Ebert, would you like to begin? Has the substantial evidence of the effectiveness of memantine for the proposed indication been demonstrated by the studies included in this application?

DR. EBERT: Well, I'm going to vote yes. I believe that overall, if you look at a global picture of the efficacy, it's generally positive in the trends. Certainly, as was mentioned, from the statistical standpoint things look overall very good. Where I have a little less certainty is in the clinical significance of a 10 percent improvement, for example, in a score, but I'm going to defer to the neurologists in the group to help me on that. But by and large, when there was a difference, it appeared to be in the positive direction. So I feel fairly comfortable with that.

DR. GANGULI: I'm going to vote yes.

DR. van BELLE: Yes.

DR. KIEBURTZ: Yes, but as follows; that is, I find the 9605 and the MD-02 to be but not 9403. So my vote would be for subjects who were enrolled in the U.S. studies' entry criteria; that is, a Mini-Mental Status of

either a 3 to 14 or you could argue 5 to 14. The number of subjects enrolled with under 5 is, I think, around or less than 100 and whether that's sufficient efficacy data, or safety data for that matter, to confirm that that's the population that this drug should be approved in. So I would say yes, but with a lower boundary of MMSE to describe the population for whom it's been effective.

DR. WOLINSKY: Yes. I think there's adequate evidence that these drugs have some effect in this patient population.

DR. KAWAS: And my vote is also going to be yes, with the note that I believe this to be a very small effect size personally, but I feel that it's been adequately consistently demonstrated and given the favorable toxicity profile, my vote is yes.

DR. KATTAH: Before I answer that question, I'd like to know from the sponsor if in all three trials, the patients were able to use B2 blockers as needed for agitation. Is that correct? Quetiapine, risperidone?

DR. KAWAS: I believe the question is were antipsychotic agents allowed for treatment in the patients in this trial. Is that the question?

DR. KATTAH: Yes.

DR. OLANOFF: In 9403, no. In 9605, no. In MD-02, yes, but with certain qualifications in terms of

they had to be on stable doses going into the study and then stay on stable doses. They couldn't start while in the study.

DR. KATTAH: Thank you.

DR. KAWAS: Well, then just to clarify, if they were started on the drug, then they were considered a dropout, or if they required a dosage change of their antipsychotic medicine, they were dropped out or what happened?

DR. OLANOFF: No. We continued them on the study. We didn't purposely drop them out of the study, but I think the numbers of patients that switched were tiny. I can get those numbers if you need them. The actual percentages on antipsychotics was small to begin with, about 10 percent in either group.

DR. KATTAH: Thank you. Then the answer will be yes.

DR. PACKER: Although I have to admit I don't find the data compelling and I do worry about different scales being used as showing evidence of efficacy and I'm very unimpressed in the very severe group that we have shown efficacy, with those caveats, I think I'll vote yes, in the generic question.

DR. KAWAS: Are you comfortable with that or do you need any further information? It looks like most of

the audience doesn't seem it wants more information.

(Laughter.)

DR. KAWAS: Yes, Dr. Temple.

DR. TEMPLE: I'm curious about one thing. One of the things that struck me, although it's only true of one study, is that the drug was added to an available therapy that may or may not be effective in people with this severity of disease. Does that strike you as of consequence?

DR. KAWAS: Does that strike us as what?

DR. TEMPLE: As of consequence. This was in the 02 study. This was, I've got to say it right, memantine. I've been saying memantine for a long time. So I've got to overcome that. Was added to Aricept and it's the first study I know of where somebody already on the therapy, that at least in the moderate people we think works, and got added benefit from another drug. That seemed to be of some consequence. I just wondered if anybody thought so.

DR. WOLINSKY: Yes. I think at least I tried to approach that before. I don't think we have a clue that at 2.5 years into treatment with Aricept, that there's any effect whatsoever. So while, if I knew that was true, then I would be overwhelmingly impressed with that data set. Because I have no idea if it's true, it doesn't help me in

my thinking.

DR. TEMPLE: Okay. So they have to do the full factorial next time.

DR. WOLINSKY: Of course. You would make me do it.

(Laughter.)

DR. KAWAS: I think I have personally got more information about the safety of combining those two drugs from that design rather than anything about the efficacy.

Dr. Kieburtz.

DR. KIEBURTZ: In a way, the strongest evidence out of the package is that study. It almost looks like the best situation is to use it is in people who are on donepezil because that was the most unambiguous picture.

DR. KAWAS: Well, actually, if I'm not mistaken, that was the smallest effect size.

DR. KIEBURTZ: Right.

DR. KAWAS: I mean, it went from a small effect size to a much, much, much smaller effect size, yes.

DR. KIEBURTZ: But it had a cognitive and a global outcome which both hit.

DR. KAWAS: Which were significant.

DR. KIEBURTZ: Right.

DR. KAWAS: Yes.

Okay. I think we're ready for the final

question. Has substantial evidence of the safety of memantine for the proposed indication been demonstrated by the studies included in this application? Who would like to make some comments or thoughts? Dr. Packer.

DR. PACKER: I guess maybe I missed it in the presentation. If this is going to be used and used effectively, hopefully it would be used for more than 24 weeks. It's going to be a long-term use. In the slides that you presented, there weren't a whole lot of patients out, a little over 300, greater than 48 weeks.

Could you give me some more comfort level on the long long-term use of this drug? Because if your curves are right and we're right and this is the right thing to do for some patients, they should be on for 2 or 3 years.

DR. OLANOFF: We're going to pull up some data that relates to the ongoing studies just to give you some perspective. Within the studies that were completed and had extension phases, as you're correct, it was a little over 300 patients that were exposed for a year. What's the exact number? 387? Am I getting the numbers correct? Or 287. It's about 300. We'll argue 300 patients that were exposed for a year. Russ can comment, but for purposes of regulatory needs for a chronic use drug, that is a reasonable standard, a reasonable approach to the standard.

But your question is pertinent because the more long-term data, the better in the population that's likely to use a chronic drug.

We'll try to provide you some information from ongoing studies where completing or trying to compile data from other longer-term studies in moderate to severe Alzheimer's disease and are trying to get some duration data. What do we have in terms of at least 6 months or a year? Yes, let's look at at least 6 months and 1 year.

DR. TEMPLE: But that's referring to safety data now?

DR. OLANOFF: Yes, that's correct. Beyond 6 months, they're all open-label.

Again, this is referring to the completed studies. This is inclusive of both open-label and double-blind experience, in the total column, approaching 900 patients at 6 months and at 1 year or 387 patients. I was correct in my first number.

I'm just trying to put some estimates together in my head in terms of the ongoing studies. Do we have any numbers available there? Yes. Total exposure and then any kind of duration data. This is not something we generally compile until the studies themselves are completed, so I apologize for not having them readily available.

But we have effectively two studies of 300 to

400 patients that contributed into one long-term study in moderate to severe and the majority of patients, I think over 80 percent of the patients, went into these long-term studies, if I'm correct, and under those circumstances, we're really looking at now over 500 patients that have gone beyond 6 months in compiling data for another 6 months.

We'll pull this study up. These are just to give you a sense of numbers. 01 is a moderate to severe study. This is just memantine exposure, not just placebo but just memantine. So it shows memantine in the first column. So a 155. We go down the numbers. 10 is a mild to moderate study. 12 is a study in mild to moderate that we talked about earlier. All those three studies went for 6 months.

Two of the studies, 1 and 2, which we showed you as a completed study, contributed to 3. Study 3 then went on and enrolled essentially 230 patients onwards beyond the 6 months' exposure. The actual total enrolled, including the placebo patients, was 475 and typically in these open-label extension studies, we're losing 10-15 percent of patients over time.

So again, I apologize for not having exact numbers in my graphs at this time because we've not opened up the data entirely, but you're looking at effectively 350

or better of patients that have been exposed, in addition to what we showed you today, at 1 year in the 03 study, which is moderate to severe.

In the 11 study, that compiled patients in from the mild to moderate experience, and I believe there's also an extension on 12, and you're looking again at another 100 or plus patients. So we're looking now at probably another 400 or 500 patients at a minimum that are approaching 1 year of therapy, and we have allowed these patients to continue.

In the French experience, patients went on treating for drug for upwards of 2 years or better and we're continuing these patients as well, and we've allowed essentially all patients to stay on trials until the drug is approved.

DR. PACKER: Can I just have a follow-up question to that? I'm reassured that at least you have another cohort of patients, although we've all been burnt when the drugs were approved and then as it got into a large population, you saw complications that we really didn't think about. We lived through the anti-epileptic era with some of those.

I have a concern about how well do you think you actually monitored toxicity in the really severe group, the lower end of the scale, where you have criteria that

you're listing, like headaches and dizziness and things like that. How well do you really think you monitored that, and is that patient population adequately monitored to be sure that it's safe for them?

DR. OLANOFF: Jeff, do you want to comment on that? I'll ask Dr. Jonas to comment. These studies we're showing you today, as well as these ongoing studies, all have systematic data collection procedures. So every time they come in for a visit, they're going through adverse event checklists, and they always have vital signs taken. And at selected visits, they have labs and ECGs done, and that's going to vary by study.

So I'll let Dr. Jonas comment further because this is an important consideration. In fact, it was an interesting comment made by the FDA safety reviewer which is when you're looking at balances between adverse events in placebo patients versus memantine-treated patients, at least in theory, one could argue that if memantine patients are achieving any cognitive benefit, they may be reporting adverse events more often in bias, but I don't think we can rely on that by any means.

I think what we can show you, though, is a split between the moderate and severe patients in terms of adverse event profiles. I'll let Dr. Jonas comment on this.

Another important piece of data, which I think he'll comment on, is neuropathic pain, to draw some similarities in terms of here are patients with unclouded sensoriums in their rate of events they're reporting versus the dementia patients.

Jeff.

DR. JONAS: Thank you. One of the concerns that we had was to see whether patients with different levels of severity had different relative risks for various adverse events, and what we did was we did a post hoc split with an MMSE of 10, greater than or equal to 10, to look to see whether the relative risks differed between patients. As you can see, overall, there were very little differences, whether the patients had an MMSE above or below 10.

In addition, when there were adverse events that might have been construed as being symptoms rather than signs, for example, hallucinations, delusions and such, we also looked into the neuropathic pain population. There, we failed to find any confirmatory signals that there was any systematic, basically under-reporting in the patients who were more severely ill.

So by example with dizziness, we looked to see whether there are other signs, for example, of astigulopathy and so forth, and no examples of that in the

neuropathic pain trial. So we found no evidence of any differential relative risk, whether or not the patients had an MMSE above or below 10.

DR. OLANOFF: Yes. Just to make a comment. At the 20 milligram per day dose, the event rates, especially placebo-corrected event rates or comparisons to placebo for the neuropathic pain, were remarkably similar to what we see in the dementia patients. So it didn't seem to be influenced directly by their cognitive status.

Again I think another crude estimate of adverse event reporting is looking at what percentage of patients overall report an adverse event, independent of that adverse event reporting. Many report multiple adverse events, and the rates we're seeing in these trials, independent of their severity, are running about 70 percent, which is not out of the range of a depression study or in fact what we saw in neuropathic pain, short of increasing the dose.

DR. TARIOT: I'd just like to follow up a little bit from the clinical investigator's perspective because it was one of the things we would have been most worried about.

So in addition to what the patient reports, we're also, of course, interested in caregiver reports of things that look worse, some are different, as well as

things that aren't reported by either, like rates of hospitalization, physiological changes, ECG changes, laboratory changes and so forth. So in the aggregate, there doesn't seem to be a signal anywhere.

I would agree personally that asking a patient with a Mini-Mental of 3 to report dizziness reliably might be a concern. So you have to look at all of these pieces of information.

DR. van BELLE: While the sponsor is here, one question about some of these adverse events, like agitation, that's also measured as a treatment effect, decrease in agitation. How did you deal with these outcomes as either adverse events or treatment effects?

DR. OLANOFF: That's a time-honored question. Because many of the scales we use in just about any disease we study, be it CNS or otherwise -- CNS is probably more complicated -- oftentimes have attributes on the efficacy scales that seem to translate into adverse events. If you're going to ask a patient what their level of suicidality is on a HAMD, is that an adverse event when a score is high is always a time-honored question.

I can say from these trials, however, that the adverse events were simply spontaneously reported adverse events. So they were qualified as events that were signs and symptoms noted either by the patient, the caregiver or

the investigator or the investigator's staff.

We provided you some confidence intervals, but I think it's always difficult to try to do comparisons between groups. You can signals in this trial. For whatever reasons, we seem to have agitation across these trials. It was lower in the memantine group. But we wouldn't go out and claim that that's a source of evidence that there's less agitation. You have to go back and do a structured scale to look at agitation or look at psychometric symptoms.

So the simple answer to your question is that the adverse events were spontaneously reported. They were not checklist items per se, whereas the scales were structured typically, and if there was some crossover, it wasn't intended in terms of trying to report both adverse events and efficacy. It was on the basis of the structured scale and the intent of it.

DR. EBERT: Another question for the sponsor. The dosing of the drug involves titration of the dose and it also involves splitting the dose, giving two doses a day, presumably both because you were trying to minimize some types of adverse effects. What adverse effects were most common if you were to give the drug once a day or if you did not titrate the dose?

DR. OLANOFF: It's a good question. I'm glad

you raised it because I forgot to comment on it earlier, if the question had come up.

I think I've indicated through the history or at least if I didn't make it clear I apologize. The initial selection of a b.i.d. dose really has little or nothing to do with half-life of the drug. You look at the half-life of this drug and you say it's a once-a-day drug. It's arguably a once-every-other-day drug, but it's a long half-life.

So the dose and the titration scheme were based on very early clinical pharmacology studies and some early studies in organic brain syndrome patients which were not definitive but it was kind of a gestalt by Merz in trying to make the best guess of what dose would be best tolerated.

So we carried that forward historically, both the split in the dose and the titration scheme. I think there's better evidence, at least early on in normal volunteers, some very aggressive dosings, like 20 milligrams t.i.d., which clearly wasn't tolerated as well as 5 t.i.d. or 10 t.i.d even. So we would not necessarily start a patient immediately on the dose.

But let me show you what we are doing. I'll call up this slide. Before hopefully the end of this year, we should have the results on this study.

Now, 03 is an open-label study per se, but we did a nested design here where we took patients coming from the double-blind study, either on placebo or memantine -- and this was a substantial number of patients coming into 03 as I indicated -- and without the investigator knowing what group they were coming in from, they were then randomized, and essentially the randomization was determined when they originally entered the trial in the double-blind phase. They were then randomized if they're on placebo to 1 of 4 groups, and memantine to 1 of 2 groups. The intent here was to see if in fact there was any differential adverse event profile based on either a more rapid titration, so a titration in 2 weeks as opposed to 4 weeks, or a once-a-day therapy. This was, I think, a very novel design contributed by one of the scientists who's not here today, so I'll give him credit for that. In memantine, the comparison, was simply twice-a-day versus once-a-day, but it wasn't retitrated because they had already been on memantine coming in.

So what we're going to do again by the end of the year is break the code on this, but I can tell you, based on a blinded analysis of the various groups and as we don't know which group they're in, by looking at adverse event dropouts, on its face there's no difference and they're not particularly high. They're not any different

than our past experience.

So we have some basis to believe at this point that probably a 2-week titration may be acceptable and in fact once-a-day dosing may be acceptable.

I'll give you two other pieces of evidence which I think are pertinent. In the neuropathic pain trials, because the target dose in a substantial number of the patients was 40 milligrams per day and we didn't want to wait forever to get there, we allowed titration at 10 milligrams per week. So essentially patients going to 20 or getting to 20 on their way to 40 got there in 2 weeks, and there was no particular problem in either group getting to 20 in terms of any adverse events or dropouts due to adverse events. If there were problems in terms of adverse events, they tended to occur after the 20 milligram dose. So that's another piece of evidence that perhaps a 2-week titration is acceptable.

Then, finally, I can comment on the MD-12 study which I talked to you earlier today about in mild to moderate disease. We haven't done a full analysis of the safety, but from what we're looking at, the overall dropout rate was about 6 percent due to adverse events. That was a once-daily dose. So in that study, we were dosing with a titration period but 20 milligrams once daily.

DR. KAWAS: Can I just make sure I understand

what you just showed us?

DR. OLANOFF: Please.

DR. KAWAS: Put it back up, if you wouldn't mind.

First of all, all the groups, the lettered groups, are patients who were in randomized trials for dementia. Is that right, or does this include other diseases, like neuropathic pain?

DR. OLANOFF: No, these are all dementia patients.

DR. KAWAS: This is all dementia patients.

You mean overall, the group has not had a particular dropout rate?

DR. OLANOFF: No. If we look at the individual groups without unblinding which group they are, there's no differential dropout rate due to adverse events.

DR. KAWAS: Right. And how far along has this study gone already that you have that?

DR. OLANOFF: We intend to break the code on this information about the end of this year, I believe. One group has actually gone over a year. But the titration period itself takes 4 weeks. Once they get to 4 weeks, they are then maintained on that dose.

DR. KAWAS: Right. And so at least during the titration phase, you're telling us that you didn't see

differential dropout from any of these groups, no matter which schedule they must have been in?

DR. OLANOFF: That's correct. The physicians knew that they were all on memantine at this time, but they didn't know what the titration scheme was, and they didn't know what previous group they were on.

DR. KAWAS: And besides dropout rate not differing, do we know anything else about the AEs in the different groups?

DR. OLANOFF: No, not at this time, because it still remains blinded.

DR. KAWAS: No. And my final question is what's the outcome that you're looking at at the 1 year? What are you trying to learn there?

DR. OLANOFF: This is generally an open-label safety study in general. So we were just continuing patients for safety experience in general, but we'd like to take this data, once it's available and if it supports the case, request the division to consider whether or not different titration schemes could be possible.

DR. KAWAS: I see. Yes.

DR. AZARNOFF: What's the volume of distribution of the drug? Because some people can have trouble because they have high peaks when you give a single dose.

DR. OLANOFF: 10 liters per kilogram. It's a reasonably high volume of distribution.

DR. KAWAS: Yes. Do you have a question or a comment? Oh, we're back to my vote.

On the safety of memantine for the proposed indication, has substantial evidence been demonstrated by the studies included in this application?

So I think we're going to start over at the other end again with Dr. Ebert.

DR. EBERT: I would vote yes, at least for the durations that we were shown on the slides.

DR. GANGULI: I would vote yes, except if there was any further information about the safety of combining cholinesterase inhibitors with memantine, this might not be a bad time to hear about it, just because of the Olney package that came through.

DR. KAWAS: You mean you want to hear from the sponsor if they have anything else to show you on that regard?

DR. GANGULI: Yes.

DR. KAWAS: For the first time, nobody is jumping up. So I think that's where they are. The data we have is what's available.

DR. OLANOFF: We're happy to review that. The data was included in the briefing book where we did a

comparison of the 02 study side-by-side placebo/memantine and the 9605. The point we were making there is although there may be a sporadic adverse event that's different in one study or another versus placebo, there were no consistencies across the two. There is no new data beyond what was in the briefing book.

Unfortunately, the proof perfect arguably, if you believe in Dr. Olney's concept, presumably would be to do autopsies and review data on autopsy, and this wasn't incorporated into the protocol.

DR. DRAKE: Dr. van Belle.

DR. van BELLE: Yes, with the same proviso that I mentioned earlier.

DR. KIEBURTZ: Yes.

DR. WOLINSKY: Yes.

DR. KAWAS: Well, first of all, I want to say that I absolutely take issue with the people I've heard say that these studies demonstrate that memantine is safer than placebo. I am very concerned about the data that has been found in animal models and that data, by the way, is not just neuropath data. I mean, we're talking also about effects on cognition in animals, as well as other toxicity effects or potential effects. But the fact of the matter is we're talking about humans here, and the reason why those things concern me greatly is because humans will be

on these drugs much longer than 6 months.

But the standard is and what's available to us right now shows a good safety and tolerability profile to my mind for the 6 months of data that's available. So I'm voting yes.

DR. KATTAH: Yes.

DR. KAWAS: Dr. Packer.

DR. PACKER: I am still concerned about the long-term use issue as it gets into wider population. I hope that's taken into account if the drug is approved when it gets into labeling, that the statement is made very clear that there is still a lot to be learned about the long-term use.

Also, I'm very worried about information that will come out over time about potential drug interactions, especially in the more severe group as they go on antipsychotics or other medications, and we have minimal data on that, especially since some of your studies excluded those patients from study.

Even given those two caveats, given the parameters of what we're voting on, I'll vote yes, but I have major concerns especially about the drug interactions.

DR. KAWAS: I'd like to make just some overall comments on behalf of the committee. So if I say things that you don't agree with, you need to speak up. But I

think that we just voted on four things and superficially, just like the safety reports, it may look like we are in absolute complete enthusiastic agreement when in fact as these votes were given, it was very apparent that the entire committee has certain concerns, concerns that have to do with all of the areas in which we were asked to vote on, which is just another way of saying I'm glad this is the FDA's job and not this committee's.

But are there any other things that we can discuss or share or talk about or probe that would be of any help to you?

DR. KATZ: I don't think so. I think you've covered pretty much all the issues we were interested in. Thank you.

DR. KAWAS: Well, thank you, and this committee meeting is now adjourned.

(Whereupon, at 3:28 p.m., the committee was recessed, to reconvene at 8:00 a.m., Thursday, September 25, 2003.)