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

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE MEETING

Thursday, October 23, 2008

8:00 a.m.

Hilton Washington, D.C./Silver Spring
8727 Colesville Road
Silver Spring, MD

C O N T E N T S

C O N T E N T S (Continued)

PARTICIPANTS

Larry B. Goldstein, M.D., Acting Chair
LCD Diem-Kieu H. Ngo, Pharm.D., BCPS,
Designated Federal Official

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Larry B. Goldstein, M.D.
Britt Anderson, M.D., Ph.D.
Mark W. Green, Ph.D.
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Ying Lu, Ph.D.
Gregory Holmes, M.D., Ph.D.
Matthew Rizzo, M.D.
Stacy A. Rudnicki, M.D.

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Twyla Bridgwater (Patient Representative)
William E. Bridgwater (Patient Representative)
Elizabeth C. Jones, M.D., M.P.H.
Robert F. Mattrey, M.D.
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PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

Roy E. Twyman, M.D., Industry Representative

GUEST SPEAKERS (Non-Voting)

G. William Rebeck, Ph.D.
Madhav Thambisetty, M.D., Ph.D.

FDA PARTICIPANTS (Non-Voting)

Robert Temple, M.D.
Russell G. Katz, M.D.
Alexander Gorovets, M.D.
Qi Feng, M.D., Ph.D.
CAPT Rafel D. Rieves, M.D.

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. GOLDSTEIN: Welcome to today's meeting. My name is Larry Goldstein, from Duke University, and I am the Acting Chair for this meeting.

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

In the spirit of the Federal Advisory Committee Act and Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting only. We are aware that members of the media are anxious to speak to the FDA about these proceedings, however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded

to please refrain from discussing the meeting topic during breaks or lunch.

Thank you and I hope that everybody will follow those basic rules. So, the topic of today's meeting is going to be discussion of a radiopharmaceutical to aid in the diagnosis or the identification of amyloid in the brain.

Before we move forward what I would like to do is take a minute and have the members of the committee and the FDA representatives that are sitting around the table take a second and introduce themselves. Let me start with Dr. Temple and then we can work our way around.

Introduction of Committee

DR. TEMPLE: I am Bob Temple. I am the Director of the Office of Drug Evaluation I.

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

DR. RIEVES: Dwaine Rieves, Director of the Division of Medical Imaging and Hematology Products.

DR. FENG: Qi Feng, Medical Officer, Division of Medical Imaging and Hematology Products.

DR. RUDNICKI: Stacy Rudnicki, neurologist at the University of Arkansas.

DR. LU: Ying Lu, statistician at the University of California, San Francisco.

DR. MATTREY: Bob Mattrey, professor of radiology at CSD, San Diego.

DR. HERSCOVITCH: Peter Herscovitch, Chief of the Positron Emission Tomography Department at the NIH.

DR. JONES: Elizabeth Jones, Associate Director of Radiology at the Clinical Center, NIH.

DR. ANDERSON: Britt Anderson, I am a neurologist. I am currently at the University of Waterloo.

DR. GOLDSTEIN: Again, I am Larry Goldstein, from Duke University.

DR. NGO: Diem Ngo, FDA, Designated Federal Official.

DR. ROYAL: Henry Royal, nuclear medicine physician, Washington University in St. Louis.

DR. ZEISSMAN: Harvey Zeissman, professor of radiology, Johns Hopkins University.

MR. BRIDGWATER: Bill Bridgwater, Alzheimer's patient and advisor to the FDA.

MS. BRIDGWATER: Twyla Bridgwater, Alzheimer's caregiver and advisor to the FDA.

DR. GREEN: Mark Green, Director of Headache Medicine at Columbia University.

DR. RIZZO: Matthew Rizzo, neurology, engineering and public policy at Iowa, and member of the committee.

DR. JUNG: Lily Jung, neurologist, Swedish Neuroscience Institute in Seattle.

DR. HOLMES: I am Greg Holmes, neurology at Dartmouth Medical School.

DR. TWYMAN: Roy Twyman, I am the industry rep. I am employed by Johnson & Johnson.

DR. GOLDSTEIN: And one semi-late arrival?

DR. GOROVETS: Alex Gorovets, Imaging Division. FDA.

DR. GOLDSTEIN: Thanks you. Just, again, as a reminder for the panel members, if you are wanting to have an opportunity to speak later either try to make me aware of it or my colleague here.

First let's take a very brief overview of the agenda. We have just done the introductions. We will then have some introductory remarks from the FDA to set the stage for today's discussions. We will then have a series of FDA presentations about the topic at hand then a series of

industry presentations, after each of which we will have a few minutes, about ten minutes, for some clarifying questions after each presentation. Then in the afternoon I believe we will turn to public comment and the general discussion.

The thing that is a bit unusual for us on the committee for this meeting in particular, as you will see when we get to them, is that the questions don't require a vote. What we are here to do is to have a discussion and, hopefully, frame the issues for the FDA as well as for the industry sponsors that will be presenting.

Next is the conflict of interest statements.

Conflict of Interest Statement

DR. NGO: Before I begin I would like to remind everyone to turn off their cells phones or put them on silent mode, and pagers as well. I would also like to introduce our press officer, Miss Sandy Walsh. If you are in the room, please stand up. She may be fighting with parking out there.

The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Center for Drug Evaluation

and Research under the authority of the Federal Advisory Committee Act of 1972.

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

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetics Act, FD&C Act, are being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws under 18 USC Section 208(b)(3). Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 208(b)(1) Congress has authorized

FDA to grant waivers to regular government employees who have potential financial conflicts when it is determined that the financial interest is not so substantial as to be likely to affect the integrity of the individual's service to the government.

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

Related to the discussion of today's meeting, members and temporary voting members of this committee who are special and regular government employees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and primary employment.

For today's agenda, the committee will discuss and make recommendations regarding the clinical development of radionuclide imaging products for the detection of amyloid

to assist in the diagnosis of Alzheimer's disease. This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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

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

FDA encourages all other participants to advise

the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. GOLDSTEIN: Thank you. We are now going to proceed to the FDA introductory remarks from Dr. Rieves. Before we do so though, I would like to remind the public observers at the meeting that, while this is an open meeting, public attendees cannot participate except as specifically asked to by the panel. Dr. Rieves?

FDA Introductory Remarks

DR. RIEVES: Good morning.

[Slide]

My name is Dwaine Rieves and, on behalf of our Division of Medical Imaging and Hematology products, I welcome you to our discussion of the clinical development of radionuclide imaging products for the detection of amyloid to assist in the diagnosis of Alzheimer's disease. Before we delve into our specific presentations I would like to highlight a few items to set the stage for our discussion today.

[Slide]

Our discussions today focus upon the diagnostic efficacy considerations for the development of confirmatory,

generally phase 3, clinical studies. In general, the diagnostic effectiveness of imaging products is based upon the establishment of performance characteristics, for example the sensitivity and specificity of the diagnostic imaging agent.

However, these performance characteristics are predicated upon the understanding that the diagnostic information is clinically useful. As noted in our second major bullet here, clinical studies for these products do not necessarily have to establish the clinical usefulness of the information since on occasion the value is already well established or self-evident. For example, the clinical value of imaging detection of a brain hemorrhage is generally well recognized.

However, sometimes the clinical value of the information obtained from diagnostic imaging products is not self-evident. In those situations clinical studies should establish the product's clinical usefulness.

[Slide]

Today our focus is relatively straightforward and is capsulized by these two questions: Specifically, to what extent would a test that detects brain amyloid provide

clinically useful information? Secondly, what are acceptable comparators for a performance characteristics determination?

With respect to the clinical usefulness question, in the absence of a determination that the clinical usefulness is already self-evident, we anticipate that clinical studies would establish the usefulness of the information.

Our second question assumes some clinical value to the amyloid detection claim and relates to the types of information, such as histopathology, that may serve as a standard of truth to establish such performance characteristics as sensitivity and specificity.

[Slide]

This meeting is prompted in large part by requests posed to our Division over the past many months, specifically with respect to the design of phase 3 clinical studies for the detection of brain amyloid. In preparation for today's discussion, we invited the companies who had approached us to submit draft protocol outlines for us to use as pivot points for today's meeting.

Three companies responded and all three are

presenting their outlines briefly today. Of note, all three companies indicated that they desired an initial FDA approval of their products for use in the detection of brain amyloid, an indication that importantly differs from an indication specifically for the diagnosis of Alzheimer's disease. These conceptual differences will be highlighted shortly.

[Slide]

As noted here, we are not focusing today upon any specific product, and we do not anticipate detailed discussion of any specific product, chemistry or supportive animal or clinical data. Indeed, we are not requesting any advice pertaining to any specific regulatory action such as may occur when a committee vets a specific product with respect to approval considerations.

Instead, today we are focusing upon shared perspectives and data from the companies; our existing regulatory expectations for diagnostic radiopharmaceuticals and the various perspectives from our advisory committee members.

[Slide]

Our agenda for today is listed here. In general,

we have all presentations scheduled for this morning and the afternoon reserved for discussion of our specific questions. Firstly, Dr. Alex Gorovets, from our Division, will provide an overview of potential imaging claims. Subsequently, we have two guest speakers. Dr. Madhav Thambisetty will provide a general overview of Alzheimer's disease, followed by Dr. William Rebeck who will briefly discuss amyloid protein and amyloid deposition in the brain.

Then we have a break, followed by presentations from our companies, Avid, Bayer and GE Healthcare. Prior to lunch, Dr. Qi Feng, from our Division, will summarize the questions for the committee. Following lunch we have an open public hearing, followed by general discussion of our topics and questions.

We look forward to these presentations. We appreciate your assistance in addressing basically two very straightforward questions today, and we look forward to the discussions. Thank you, Mr. Chairman.

DR. GOLDSTEIN: Thank you. Let's now turn to the formal FDA presentations. Dr. Gorovets?

Overview of Potential Imaging Claims

DR. GOROVETS: Hi.

[Slide]

My name is Alex Gorovets. I am from the Imaging Division in the Office of New Drugs at CDER, FDA.

[Slide]

In my presentation I will briefly review the regulations that apply to radioactive diagnostic products, as well as our imaging guidances and how they might apply to the development of in vivo diagnostic agents for the detection of cerebral amyloid.

[Slide]

Before we address the regulations, let me remind you what type of agents we are discussing today. These are diagnostic radiopharmaceuticals, each generally consisting of two components. One component is a radionuclide that can be detected in vivo, such as technetium-99, iodine-123, 18F, and the other is a non radioactive component which delivers the radionuclide to a specific area of interest. The non radioactive component may consist of an antibody or a ligand for a specific receptor.

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There are specific regulations that pertain to diagnostic radiopharmaceuticals. They are described in the

Code of Federal Regulations, Part 315. These regulations state that the effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indication for use. Therefore, the statement actually emphasizes two major concepts, the importance of the proposed indication and the need for the test to provide useful clinical information.

[Slide]

The regulation further notes the multiple potential indications that are possible for these products and provides four specific examples, as shown here. A specific indication might relate to structure delineation; functional, physiological or biochemical assessment; disease or pathology detection or assessment; or an indication related to diagnostic or therapeutic patient management.

These examples illustrate the range of potential indications from a claim related to detection of a structure, for example pineal gland, or to a claim related to a specific diagnosis, such as the presence of acute myocardial infarction.

[Slide]

With respect to the actual demonstration of effectiveness, regulations note that the radiopharmaceuticals must provide useful clinical information. The diagnostic performance and usefulness of the diagnostic information are determined by a comparison with a reliable assessment of actual clinical status, as stated in the regulations.

So, the regulations emphasize that the product's diagnostic effectiveness is based upon comparison to a standard with a determination of performance characteristics. The obtained diagnostic information must be clinically useful. These concepts are further discussed in the FDA guidance documents.

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As many of you know, in 2004 FDA published three guidance documents that address the development of medical imaging drugs and biologic products. The first guidance document pertains to safety, which is not the topic for today. The second pertains to clinical indications which, in fact, is our main topic today. The third addresses issues related to study design and analysis.

[Slide]

So, we are going to look at these again. The guidance pertaining to the potential indications for medical imaging products also cites the four general categories of potential indications described in the federal regulations. It goes on to provide specific examples of this type of indication.

For example, an indication pertaining to structure delineation, ability to delineate structure, is exemplified by an image that can distinguish normal from abnormal bronchi or knee cartilage or abnormalities of other tissues.

A disease or pathology detection indication is exemplified, for instance, by a radiopharmaceutical that detects a mass enriched with specific tumor antigens.

A potential functional, physiological, or biochemical assessment indication is exemplified by an image determination of cardiac ejection fraction.

Finally, a diagnostic or therapeutic patient management indication is exemplified in the guidance by an indication pertaining to detection of coronary artery disease.

[Slide]

The guidance notes that determination of

effectiveness of a diagnostic radiopharmaceutical is based upon two major aspects, the test accuracy and test value. The term Aaccuracy@ here applies to its common usage where accuracy is described as simply the quality of being true or correct.

[Slide]

The guidance notes that the accuracy of a diagnostic radiopharmaceutical is determined by a comparison to a truth standard or a test of known reliability. For example, histopathology could be used as a truth standard or a previously approved test could be used as a reference. These reference standards are then used to assess a new product's performance characteristics such as sensitivity and specificity.

The guidance acknowledges that in some situations a truth standard or reference test on reliability is not available and the clinical development program for a new product has to establish the clinical usefulness of the information.

[Slide]

The guidance acknowledges that determination of performance characteristics alone may be sufficient to

establish the clinical value of a new radiopharmaceutical. The guidance notes that information obtained from the new product may already be known to be clinically useful, that is, the clinical value is self-evident. However, the guidance also notes that sometimes the clinical value of the diagnostic information is not well established and in these situations clinical study data should establish the value of the diagnostic information.

The guidance document importantly notesB-the last bullet hereB-that simply generating an image for which the implications to the patient are not understood does not confer benefits to the patient.

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Today we are meeting to discuss the aspects of clinical development programs for radiopharmaceuticals that are proposed for use in the detection of cerebral amyloid. It is important to note that an indication for detection of amyloid could be viewed as uniquely different from a potential indication related to the diagnosis of Alzheimer's disease. In line with our regulations and guidances which I just reviewed, amyloid detection may be viewed as a pathology detection type of claim, whereas, the indication

pertaining to a diagnosis of Alzheimer's disease is a specific diagnostic claim.

Based upon the differences in these types of indications, the standard of truth would vary. In one case the standard of truth would generally be expected to relate to an actual measure of amyloid. In the other case the standard of truth would generally relate to a clinical diagnosis of Alzheimer's.

[Slide]

In relation to an indication for use of a radiopharmaceutical in detection of cerebral amyloid we have two fundamental questions, as outlined in the bullets here. First, is the clinical value of amyloid detection established? If not, then clinical studies would have to establish the clinical usefulness of the diagnostic information. Second, what is the appropriate truth standard or reference test for detection of cerebral amyloid?

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In summary, our regulations and guidances describe a broad variety of potential indications for diagnostic radiopharmaceuticals, including indications that range from identification of normal versus abnormal, all the way to the

establishment of a specific clinical diagnosis.

Our documents note that effectiveness of these products is generally based upon performance characteristics that involves a comparison to a truth standard.

Finally, our documents note that the value of the diagnostic information must be known to be clinically useful or, if it is not self-evident, the clinical value should be established in clinical studies.

Thank you for your attention. I return the podium to the Chairman.

DR. GOLDSTEIN: Thank you, Dr. Gorovets. Next, Dr. Thambisetty-BI hope I am not butchering your nameB-clinical presentation and diagnosis and management of Alzheimer's disease.

Clinical Presentation, Diagnosis and Management of Alzheimer's Disease

DR. THAMBISETTY: Thank you, Mr. Chairman, and thank you, Dr. Rieves for the opportunity to be here this morning.

[Slide]

I am a neurologist and a staff clinician in the intramural program of the National Institute on Aging. I

wear two different hats at the NIA. My main interest is in the development of new imaging biomarkers for neuroinflammation in Alzheimer's disease, as well as to develop biomarkers with neuroimaging biomarkers as well proteum-based approaches to peripheral biomarkers for cognitive decline in Alzheimer's disease.

Dr. Rieves briefed me this morning to wear the hat of a practicing clinical neurologist and present a broad overview of the presentation, diagnosis and management of patients with Alzheimer's disease, which is what I will attempt to do over the course of the next 35-40 minutes.

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So, the outline of my presentation is going to be to discuss very briefly the main clinical features and the natural history of the progression of Alzheimer's disease. We will talk very briefly about the current diagnostic criteria for Alzheimer's disease; briefly touch upon the non-cognitive symptomatology of Alzheimer's disease which is just about as important as the well-recognized and most talked about cognitive symptoms. We will also talk about the diagnostic tools in current practice for Alzheimer's disease, as well as emerging neuroimaging biomarkers for

Alzheimer's disease. We will stop with a very brief look at existing and emerging treatments for Alzheimer's disease. So, we have quite a bit of territory to cover here.

[Slide]

Alzheimer's disease is recognized to be by far the most common of the dementing illnesses, accounting for well over half of all cases of dementia. The remaining causes of dementia can be divided roughly equally into vascular dementia and Lewy body dementia, although some would suggest that that number is considerably higher than the 20 percent, with increasing ability to both detect Lewy body dementia at its clinical stages, as well as to confirm it in autopsy series.

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So, the scope of the problem as far as Alzheimer's disease is concerned is considerable. It affects to date nearly five million Americans, and that number is expected to increase several fold over the next five decades.

In terms of costs, we pay about 25 billion dollars annually in direct costs, a much greater number when you factor in indirect costs that are related to caregiver absenteeism and loss of productivity. So, we are dealing

with a problem of considerable financial implications, and one that is likely to increase dramatically over the next several years.

[Slide]

The clinical features of Alzheimer's disease, of course, were described by ABig Al,@ Alois Alzheimer, more than 100 years ago.

[Slide]

I thought there could be no better way of describing the clinical presentation of Alzheimer's disease than to let Alzheimer speak for himself, as he did more than 100 years ago. This comes from a translation of Alzheimer's paper which was first published in 1907. Alzheimer described this lady here, Auguste D. He was quite intrigued by this 51-year-old lady and he said that the first noticeable symptom of illness in this 51-year-old woman was suspiciousness of her husband, at times believing that people were out to murder her. She started to scream loudly. At times she seemed to have auditory hallucinations.

Right in that little paragraph there are quite striking features of the disease that we now recognize. So,

there is a hint of persecutory delusions; a subtle hint that there was quite a striking change in personality; and there is also the non-cognitive symptomatology of Alzheimer's disease that we now well recognize.

[Slide]

Alzheimer was in many respects the quintessential clinician scientist. He could seamlessly transition from seeing patients at the bedside, make very astute observations about the clinical presentation and diagnosis, and then move effortlessly into the lab and look at light microscope, use silver stains and make very precise descriptions of the pathology of the disease that now bears his name.

So, this is a picture of Alzheimer's initial case records describing the index case of Auguste D. I thought I would also talk about an extract from his case report. He says Auguste D sits in the bed with a helpless expression and he asks her what is your name? And, the answer is Auguste. What is your husband's name? Auguste, I think. Your husband? Ah, my husband. Are you married? To Auguste. Mrs. D? Yes, yes, Auguste D.

So, right here you have at least two features of

Alzheimer's disease that we now recognize. It is a profound disorder of memory. This lady cannot remember who her husband is. There is also a significant impairment in her language abilities. So, here you have a striking example of what neurologists like to call perseveration, a continuous repetition of words that in the context do not really make any sense.

It is very interesting that when Alzheimer first presented this case he did this at a very small meeting of psychiatrists in Germany. It was called the Southwest Association of German Psychiatrists. Interestingly enough, he was really disappointed because at the end of his case presentation there was no question from the audience. They were very confused. The organizers of the meeting, in their infinite wisdom, determined that the case itself was not interesting enough to merit publication in the proceedings of the conference. The only mention that Alzheimer actually presented at this meeting was one line in the local newspaper in Germany. And, I cannot help feeling that even 100 years ago the peer review system was as flawed, temperamental and unpredictable as it is today.

[Slide]

Alzheimer, of course, then went on to describe what we now recognize as the pathological hallmarks of the disease, and described that in the center of an otherwise normal nerve cell there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability. We now recognize that these initial descriptions and silver stain sections of the cortex are, of course, the neurofibrillary pathology that we now recognize as neurofibrillary tangles.

[Slide]

So, the natural history of Alzheimer's disease then is one of gradual, almost imperceptible onset. It has a slow progression that is gradual but not always linear. The duration is typically less than ten years on average from diagnosis to death.

[Slide]

The clinical presentation of Alzheimer's disease is essentially a profound disorder of memory. It is an amnestic disorder. So, loss of memory is the commonest presenting symptom. It initially affects the ability to recall new information. Remote memory then declines as the disease progresses and a close accompanying feature of the

memory disorder is disorientation to time and place.

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Profound disturbances and impairments in language are a well-recognized feature. Reduced conversational output may be the initial presenting symptom, accompanied with word-finding difficulties, reduced vocabulary and then, as the disease progresses, increasing non-fluency and global aphasia in the last stages of the disease.

[Slide]

Apraxia is a term used to denote an inability to carry out previously learned purposeful movements despite normal strength and coordination. This oftentimes results in difficulties that patients describe with handling common everyday objects like utensils and home appliances, leading to significant difficulties with self dressing and hygiene.

[Slide]

Agnosia is a term used to described impaired recognition of sensory stimuli which you cannot attribute to sensory loss or impairment in language. Examples of agnosia that patients with Alzheimer's disease can present with include prosopagnosia, which is inability to recognize familiar faces. This oftentimes is a source of considerable

distress not so much for the patient as for the immediate family and friends. Object agnosia and auditory agnosia can take the form of impaired recognition of either words related to language or non-speech sounds.

[Slide]

Problems with executive dysfunction are, again, a frequent feature of Alzheimer's disease, presenting with a whole host of problems including impairments in problem solving, abstract thinking, reasoning, decision-making and judgment.

[Slide]

Visuospatial dysfunction, on the other hand, can present with problems with driving, getting lost, often in very familiar and previously familiar surroundings, and difficulties with copying figures.

[Slide]

I would like to briefly talk about the non-cognitive symptomatology of Alzheimer's disease. These together come under the umbrella of behavioral and psychological symptoms of dementia, or BPSD for short.

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So, in Alzheimer's disease BPSDs denote symptoms

of disturbed perception, thought content, mood and behavior, and is seen in about half of patients with Alzheimer's disease in some stage of the disease.

[Slide]

The psychological symptoms under this constellation of BPSD symptoms include depression, anxiety, persecutory ideas and visual hallucinations.

[Slide]

The behavioral disturbances, which frequently can be assessed by observing the patient, include examples such as wandering behavior, aggression, screaming and restlessness.

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The importance of the behavioral and psychological symptoms in Alzheimer's disease is that they are a frequent cause, in fact the major cause of carer distress and frequently one that brings the patient to initial attention of the neurologist, the psychiatrist or even the family physician. They are a frequent cause of hospitalization. They contribute considerably to morbidity and mortality in Alzheimer's disease. And, they account for the majority of the costs related to caring for somebody with Alzheimer's

disease.

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This cartoon illustrates the somewhat peculiar relationship that BPSD symptoms have to progression or disease severity. So, the cognitive symptomatology of Alzheimer's disease shows a somewhat uniform decline from the time of onset. The relationship of the behavioral and psychological symptoms is not nearly as clear-cut with disease severity and the passage of time from the onset of initial symptoms.

The causes of BPSD symptoms are multifactorial and we won't have time to discuss these in any great detail, but they form mainly three categories, psychological, biological and social.

Under psychological you have factors like premorbid personality as well as coexisting psychiatric illnesses. There are a whole host of biological substrates that may underlie the causation of the behavioral and psychological symptoms of Alzheimer's disease, including specific brain regions that may be implicated, specific neurotransmitter systems, and genetic predisposition to developing these symptoms. Social factors are equally

important and these are related to the carer input that the patient has access to, as well as the environment in which they are cared for.

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So, I would like to move on to the practical approach in clinical practice to a diagnosis of Alzheimer's disease. The diagnosis rests upon identifying elements suggestive of the disease from the history and physical examination. It is a clinical diagnosis and essentially a diagnosis of exclusion, and exclusion denotes other causes of dementia, and the way you do this is by further laboratory tests and neuroimaging as necessary.

So, the most widely used clinical criteria for a diagnosis of Alzheimer's disease are the NINCDS-ADRDA criteria and the DSM, of the Diagnostic and Statistical Manual of Mental Disorders, edition IV criteria.

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The NINCDS-ADRDA criteria for Alzheimer's disease include demonstration of dementia, or the confirmation of dementia by clinical examination and supported by neuropsychological testing; deficits in two or more areas of cognition; a progressive worsening from the time of onset of

initial symptoms without any disturbance in consciousness. And, the ages of onset are between 40 and 90 years of age. All of these are in a sense in the absence of other systemic or brain diseases that could account for these symptoms.

[Slide]

The diagnosis of probable Alzheimer's disease is supported by progressive deterioration in specific cognitive areas. Examples would include aphasia or apraxia or agnosia, as we briefly touched upon; impaired function and altered behavior; a family history of the disease; normal EEG, neuroimaging or CSF content. So, all of these are supportive of a diagnosis of probable Alzheimer's disease by the NINCDS criteria.

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Other clinical features that are compatible with a diagnosis of probable Alzheimer's disease include a plateau in progression; other neurological features such as gait disorder, myoclonus or abnormal primitive reflexes, especially later on in the course of the disease. Seizures and atrophy on structure neuroimaging modalities are also compatible with the diagnosis of probable Alzheimer's disease.

[Slide]

The features that make diagnosis of probable Alzheimer's disease by NINCDS criteria unlikely include a sudden apoplectic onset of symptoms; focal neurological features; and seizures or gait disturbances early on in the course of the disease.

[Slide]

The NINCDS criteria also recognize a diagnosis of possible Alzheimer's disease, and these are cases with an atypical onset or an atypical course of cognitive decline from the onset of symptoms; focal neurological findings; and coexisting disorders that may themselves produce dementia.

[Slide]

Definite Alzheimer's disease is a diagnosis that includes a clinical diagnosis of probable Alzheimer's disease followed by neuropathological confirmation of the hallmarks that suggest Alzheimer's disease.

[Slide]

The DSM criteria for a clinical diagnosis of Alzheimer's disease include, like the NINCDS criteria, an insidious onset and progressive decline in cognition but with an impairment in social and occupational functioning.

It also includes an impairment in recent memory and either one of aphasia, apraxia, agnosia or executive functioning. This, again, is in the absence of other neurological, psychiatric or systemic illnesses that can cause cognitive decline in the absence of any abnormalities in sensorium.

[Slide]

So, the clinical approach to Alzheimer's disease includes an accurate history, and the history is always obtained from the patient as well as from a reliable informant or caregiver. The clinician is at this stage trying to document a change from prior levels of cognitive performance associated with a decline in functional abilities. You are also looking for personality changes and you want to confirm both an insidious onset of symptoms as well as a gradual progression from that point on.

Cognitive testing in the diagnosis of Alzheimer's disease should include an assessment of multiple domains including memory, language, attention, orientation and executive function.

[Slide]

The neurological examination in Alzheimer's disease is primarily to rule out other conditions that may

be causative in the symptomatology. You are essentially looking for focal deficits which, for instance, may suggest multi infarct dementia or vascular dementia.

Prominent rigidity, tremor and difficulties with movements or slowness of movements early on in the course of the disease would suggest an alternative diagnosis, such as Parkinson's disease or perhaps even Lewy body dementia. Myoclonus and primitive reflexes are often clinical features that are picked up on a neurological exam in later stages of Alzheimer's disease.

The clinician should always be on the lookout in an elderly patient for cognitive impairment to make sure that polypharmacy is not a contributing factor for cognitive decline.

[Slide]

The laboratory evaluation of Alzheimer's disease is, again, mainly to exclude other causes or treatable or reversible dementias. Routine analysis could include complete blood count; a panel of chemistries to exclude electrolyte abnormalities; an assessment of thyroid function and vitamin B12 level.

Depending upon the clinical setting and the index

of suspicion for other causes, these could also include sedimentation rate, syphilis serology, heavy metals screen, chest x-ray, HIV test or an EEG if seizures are thought to be contributing to symptoms.

[Slide]

The role of neuroimaging in Alzheimer's disease to make a clinical diagnosis is somewhat limited. The American Academy of Neurology recommends structural neuroimaging essentially to rule out various other causes for dementia. These include strokes, normal pressure hydrocephalus, space occupying lesions and subdural hematomas. These can be accomplished by a non-contrast CT scan or an MRI scan of the brain.

[Slide]

Structural neuroimaging in particular has taught us a tremendous amount about the temporal profile of neuropathological change in Alzheimer's disease. It is told us that hippocampal atrophy in Alzheimer's disease predicts cognitive decline and is an early event in the disease. These are rates of hippocampal atrophy in young subjects, starting at 30 years and up to 50 years of age, with 0.1 to 0.2 percent atrophy rate per year. That increases to about

0.8 percent in the mid-70s and a further 1.5 to 2 percent in the oldest, between 80-90 years of age.

These numbers for atrophy rates are dramatically higher in subjects with Alzheimer's disease, approaching 4-8 percent a year even in the earliest stages of Alzheimer's disease. More importantly, as far as our ability to diagnose preclinical stages of the disease is concerned, hippocampal atrophy is known to accelerate several years before clinical criteria for diagnosis of Alzheimer's disease are met.

Here is an example of hippocampal atrophy detected by serial MR imaging. This is from a recent article in the British Journal of Radiology. I am not sure this projects well but we have age-matched control subject and a subject with Alzheimer's disease, and each panel is a composite of two MRI scans obtained a year apart.

While there is no change, or literally very little change in the control subject, the areas in red in the subject with Alzheimer's disease indicate areas that have undergone significant loss of tissue volume even in scans spread apart by just one year. You have increases in size of the ventricles at the second time point; small atrophic

hippocampus, as well as the surrounding temporal cortex.

[Slide]

Similar to hippocampal atrophy, whole brain atrophy in Alzheimer's disease is, again, an early event. It is an excellent discriminator between subjects with Alzheimer's disease and age-matched controls; correlates very well with cognitive decline; and has recently been used as an outcome measure in a clinical trial setting with Ab2 immunization trial. Like hippocampal atrophy, whole brain atrophy in Alzheimer's disease is significantly higher compared to age-matched controls.

[Slide]

I am going to briefly touch upon on the role of FDG-PET in the diagnosis of Alzheimer's disease. Reduced metabolism in the posterior cingulate cortex, precuneus and the temporoparietal cortices is recognized to be an early event. It is a good discriminator between cases and controls, as well as in differentiating patterns of hypometabolism between Alzheimer's disease and other dementias such as frontotemporal dementia.

Here, again, is an example of this. You have normal posterior cingulate resting activity in the normal

brain compared to the dramatically reduced posterior cingulate metabolism also associated with an atrophic hippocampus in the subject with Alzheimer's disease.

[Slide]

Our ability to image Alzheimer's disease and to look in a very meaningful manner at in vivo pathology received a tremendous boost with the development of the 11C-labeled Pittsburgh compound B, which binds A-beta with a high sensitivity for A-beta plaques in the brain as well as for vascular amyloid in vivo. In Alzheimer's disease specific binding is observed in the frontal, temporal and parietal association cortices. What is striking, and something that I am sure is going to come up several times during the course of the day, is a characteristic bimodal distribution in control subjects as well as those with mild cognitive impairment when imaged with 11C-PIB.

Here is an example of that phenomenon. You have PIB binding in a healthy control subject at the left; PIB binding in a subject with Alzheimer's disease at the right extreme and here you have two subjects diagnosed clinically as amnestic mild cognitive impairment who show patterns that resemble both the control subject as well as the subject

with Alzheimer's disease.

So, you have this characteristic bimodal distribution in subjects with mild cognitive impairment who have not yet developed disease that looks both like a normal brain as well as a brain with advanced Alzheimer's pathology, raising the question about whether or not PIB is a predictor of subjects at risk for developing late cognitive impairment, or whether or not it might even be a false positive signal in some cases. I am sure that is going to be a subject of deliberation throughout the rest of the day.

[Slide]

There are several other tracers for A-beta that have been developed. A recent fluorinated analog of PIB was recently published by Roe et al., stilbene compounds with 11C tags, fluorinated stilbene compounds, as well as FDDNP which binds to both A-beta and tau, allowing us to image both neurofibrillary pathology as well as A-beta pathology in Alzheimer's disease.

[Slide]

I am going to briefly talk about diagnostic biomarkers in cerebrospinal fluid because these have

attracted considerable attention over the past few years. Major spinal fluid-derived biomarkers are a demonstration of an increase in total tau. This is microtubule, associated protein tau in the CSF, which allows us to diagnose the disease with a sensitivity of 90 percent and specificity of greater than 80 percent. An increase in phospho-tau epitope, again, allowing us to detect disease with a sensitivity and specificity of greater than 80 percent, along with a decrease in A-beta-1-42 with a similar degree of sensitivity and specificity.

What is even more intriguing and important, and possibly relevant to the topic of today's deliberation, is that these CSF-derived biomarkers might predict both progression from healthy controls to mild cognitive impairment, as well as subsequent progression from MCI to full-blown AD.

[Slide]

Treatments for Alzheimer's disease then derive essentially from the cholinergic hypothesis of Alzheimer's disease.

[Slide]

We know that cholinergic neurons are essential for

the maintenance of memory. We know this from a variety of experimental approaches that have given us the same conclusion. So, we know that inhibiting cholinergic function results in cognitive impairment. In animal models lesioning of cholinergic tracts results in abnormalities in learning and memory. Reestablishing these cholinergic rich grafts then restores these deficits. In patients with Alzheimer's disease we know that cholinergic neurons are lost early on. There is decrease in cell markers of cholinergic neurons, like decrease on choline acetyltransferase and significant loss of neurons in the basal forebrain.

[Slide]

Acetylcholine is formed from phosphatidylcholine and acetyl coenzyme A. It is broken enzymatically by acetyl cholinesterase.

[Slide]

Our options to enhance cholinergic function then should derive logically in terms of increasing synthesis of acetylcholine, enhancing its release, preventing its breakdown, or modulating its post-synaptic function.

[Slide]

The major class of compounds approved for treatment of Alzheimer's disease include the acetylcholinesterase inhibitors. These have been approved in both the United States and Europe from 1995 onwards. They are modestly efficacious, producing clearly observable effects on cognition, global change, function and behavior.

[Slide]

I won't go into great detail about randomized controlled trials supporting this, but here is an example of a randomized clinical trial with donepezil, showing that Alzheimer's patients, both on the low as well as the high dose of donepezil, had beneficial effects in terms of cognition measured by the ADAS-Cog scale, whereas subjects who received placebo declined over a 24-week time period.

[Slide]

So, the acetylcholinesterase inhibitors used in clinical practice in Alzheimer's disease include donepezil, galantamine and rivastigmine. The most common side effects are related to their effects on the gastrointestinal system and also problems with sleep are a common feature of the side effect profile.

In terms of their comparable safety and efficacy

profiles, they are all similar. They are approved as first choice in monotherapy for mild Alzheimer's disease, and which specific cholinesterase inhibitor to use is a clinical decision made by the practicing physician, and is made by taking into account its overall tolerability and efficacy.

[Slide]

The newest option in our armamentarium against Alzheimer's disease is memantine, which is a non-competitive NMDA antagonist. It robustly blocks glutamate-induced excitotoxicity which is its proposed mechanism of action as a therapy for Alzheimer's disease. It is approved for the treatment of moderate to severe Alzheimer's disease and may be used in combination with the acetylcholinesterase inhibitors.

[Slide]

I would like to spend the last couple of slides with a sort of perspective on the future as far as emerging treatments for Alzheimer's disease are concerned. There is growing recognition that amyloid is possibly one of the most plausible candidates as far as an emerging treatment is concerned. We are now realistically speaking essentially in the symptom control of palliative stages as far as

addressing disease treatment is concerned.

We really want to be able to intervene much earlier and, ideally, in subjects even before the onset of clinical symptoms, even before functional decline happens. And subjects that possibly we most want to focus on are those at greatest risk, so perhaps subjects with mild cognitive impairment who we know will develop Alzheimer's disease subsequently. We want to, ideally, intervene before the development of substantial neuropathology in the brain, either in the form of tangles or in the form of A-beta plaques. And, I think we are at the stage where we can reasonably or realistically talk about developing such compounds, talking in terms of disease modification and perhaps even secondary prevention of Alzheimer's disease.

[Slide]

I am going to end with this slide that details several promising candidates for disease-modifying treatments in Alzheimer's disease encompassing an entire range from interfering with the amyloid cascade so you have a host of candidates that interfere with APP processing, the beta and gamma secretase inhibitors, those that interfere with the buildup of amyloid plaques in the brain, targeting

amyloid degradation, clearance or its aggregation, a variety of molecules targeting tau, both its phosphorylation as well as its aggregation in the AD brain. Another fairly productive target has been to go after neuroinflammation in the AD brain, specific neurotransmitter pathways, as well as interventions such as hormone replacements, vitamins and cholesterol-lowering medications.

Thank you very much for your attention.

DR. GOLDSTEIN: Thank you. What I would like to do now is go on to our third presentation, by the FDA by Dr. Rebeck, on amyloid and amyloid deposition in the brain. After the three presentations are done, what we will have time for are some clarifying questions if members of the panel have some from all of the FDA presenters.

Amyloid and Amyloid Deposition in the Brain

DR. REBECK: Good morning everyone. It is a pleasure to be here at what I think is a very important meeting and I am glad to be a part of it.

[Slide]

I have been tasked with trying to bring us all up to about the same level of our understanding of amyloid and Alzheimer's disease. One of the things I should say before

I get started though is that one of the things I have learned as a scientist is that the knowledge that I am going to share with you is not necessarily completely concrete. The things that we learn we tend to learn slowly and only over long periods of time. What I think I am going to talk about is the way I think most people in the field of Alzheimer's disease view the disease. But keep in mind that it constantly changes and, as we learn more things, we add to these models that I will be talking about.

[Slide]

So, we have heard this morning about the atrophy that is present in Alzheimer's disease, and that is imaged over here where we have a control brain that is perfectly healthy and then an Alzheimer's disease brain where you can see the gross atrophy, the loss of tissue that is responsible in large part to the symptoms that we see in Alzheimer's disease.

However, microscopically there are two things that we see. One are these things called amyloid plaques and they are made up of a protein called A-beta. They are extracellular accumulations of this A-beta protein into these basically spherical structures. These are two plaques

shown here.

The second neuropathological lesions are these things that are called tangles, or neurofibrillary tangles, and they are made up of a different protein, called tau. They occur not outside of the cells, but they occur inside of neurons and they look like tangled bits of string and so we call them tangles. We saw some of this with the imaging. This is what we see neuropathologically when the brain is examined.

[Slide]

Now, these lesions do not occur everywhere in the brain. This study I am going to talk about is something that was done about 20 years ago where somebody took 40 brains of individuals who died with Alzheimer's disease, either very early Alzheimer's disease or late Alzheimer's disease or anything in between, and they looked for where these plaques and tangles were in those brains after autopsy. At the top here is a distribution of where the tangles were in these various brains, and at the bottom is where the plaques were in these various brains.

I will start with the plaques because it doesn't show very much difference. This is on a scale where red and

yellow are high and blue is low. In these brains, regardless of whether the person had the disease for a long period of time or a short period of time, the brain regions were all more or less equally affected. The frontal cortex, parietal cortex, the temporal cortexB-there were plaques all over the place.

Tangles were a different story. So, some brains only had a few tangles and those tangles were found in the region of the hippocampus. We heard about the hippocampal atrophy in Alzheimer's disease. Since the hippocampus is responsible for allowing us to make new memories, the presence of tangles in this region and these neurons dying with the tangles in them is symptomatically very important.

If there was a brain that was affected in more than just the hippocampal region, generally it was also in other parts of the temporal lobe or, for example, here or other parts of the temporal lobe. If other parts of the brain were affected it would probably have been like the frontal cortex.

There were some parts of the brain that were not affected at all. This is the motor cortex and so it was very rare that somebody had problems in their motor cortex

and, in general, these things line up with the symptoms of Alzheimer's disease that we heard, which have a lot to do with executive function and memory but don't have so much to do with movement and controlling body parts.

So, the tangles show a unique distribution in the brain. Like I said, this is all deduced from studies of postmortem brain tissue, 40 Alzheimer's patients and, like I said, this was done about 10 years ago by Steve Arnold.

[Slide]

So, plaques and tangles are the two lesions in Alzheimer's disease. I am going to talk mostly about the plaques and I will explain to you why the focus is on these plaques in just a minute.

[Slide]

When you look at the brains of people with Alzheimer's disease you see a lot of plaques. So, this is the cortex and it has been immunostained for A-beta and all of these little black dots throughout the cortex are plaques. This is the region of the brain where all the neuronal cell bodies are and a great deal of that part of the brain is now replaced by plaques. So, where does this A-beta come from?

[Slide]

Somebody 25 years ago, Klemmer and Wong, purified the plaques and they sequenced what was in them and they came up with this protein that we know refer to as A-beta. A-beta is this protein here. It is about 40 or 42 amino acid long, and this is the amino acid sequence from this D down to this A.

Then, when we look for where the A-beta actually comes from, it is part of a larger protein that is called APP, for amyloid precursor protein. So, the amyloid precursor protein is a protein that sticks in the membrane of the cell. It has a big portion of it outside the cell and a little portion of it inside the cell. In this region what has to happen is that a protease has to cut the APP right there, and then another protease has to cut the APP right there, and that frees up the A-beta. Then the A-beta can go on to form these plaques, and I will talk about that for a few minutes.

The protease that cuts APP right here is called beta secretase and the protease that cuts APP right there is called gamma secretase, and there are drug programs going on to find inhibitors of beta secretase and inhibitors of gamma

secretase as potential treatments in Alzheimer's disease.

I should just point out for sake of completeness that there is another protease, called alpha secretase, that will cut APP right in the middle of this A-beta sequence and so alpha secretase would prevent the production of A-beta.

[Slide]

This was our state of knowledge 20 years ago, and soon after cloning APP and identifying it as a source of A-beta what geneticists started to discover is that mutations in APP could cause Alzheimer's disease. This is an extremely important piece of information. Inheritance of just a mutation in this gene will cause the entire disease. It will cause plaques. It will cause tangles. It will cause dementia. It will cause atrophy. Just a single mutation in the APP gene will cause Alzheimer's disease. It is rare. There are only very few families in the world with these mutations but as an example of the importance of APP, these families have taught us a great deal.

So, this is just part of the normal sequence of APP here, and the amino acids that have been drawn in red denote mutations that have been identified that cause Alzheimer's disease. So, this mutation here is called the

Swedish mutation. People who have inherited that mutation will get Alzheimer's disease and they will get it early in their lives. There are mutations down here called the London mutation. There are mutations within the A-beta sequence called the Dutch mutation or the Iowa mutation. Inheritance of these things will lead to accumulation of A-beta in the brains of these people and will cause disease.

I should also point out that APP is a gene on chromosome 21 and in individuals who have trisomic 21, three copies of chromosome 21, people with Down syndrome, will develop Alzheimer's disease. So, if you look at the brain of an individual with Down syndrome late in life, in their 50s, they will have all the symptoms, all the signs of Alzheimer's disease that I have mentioned up till now, plaques, tangles, atrophy. There are also families that have a genetic duplication of APP on one of their chromosomes. They will also get Alzheimer's disease. So, all of these things link changes to APP and changes to A-beta with development of Alzheimer's disease.

[Slide]

So, this has led to this model of development of Alzheimer's disease. Let me just take a moment to go

through this. We have a timeline down here and what I am trying to show is the progression of the neuropathology over time. In normal aging there is a low level of A-beta. We all have A-beta floating around, some small amount, in our brains right now. There are no tangles, and you have a normal number of neurons and synapses.

Then, at some point the amount of A-beta starts to accumulate in the brain in these deposits that I have shown you. But this is occurring probably in a prodromal state so before any symptoms are seen we start to have an accumulation of A-beta. At some point the number of tangles starts to rise as well. The longer you have the disease the more tangles you accumulate. So, we see a rise in the number of tangles and, as the tangles are rising, the number of synapses and the number of neurons are declining. So, these are, of course, the symptomatic stages of Alzheimer's disease.

The early stage is called mild cognitive impairment when there is only a little bit of loss of synapses and a few tangles. But even at this point there is a lot of A-beta that has already accumulated. For example, there are plenty of stories of people who had just a little

bit of impairment and then died of some cause, like a heart attack, and when you look at the brain there are often very large amounts of amyloid there even though there wasn't a great deal of symptoms.

[Slide]

So, this has led basically to this model of Alzheimer's disease that I have been trying to develop here, and that is, you have changes in APP that lead to an accumulation of A-beta. And, APP mutations can drive that, duplication of the APP gene can drive that. There are other mutations that cause Alzheimer's disease in these genes called presenilins and they are known to be part of the gamma secretase cleavage of APP and they can drive the accumulation of A-beta.

Then, the rest of the disease goes downstream of that. So, downstream you have tangles. You have inflammation, oxidative stress, death of neurons. And, this is what we heard a few minutes ago referred to as the amyloid cascade hypothesis. It probably should be described more as the A-beta cascade hypothesis because from now on I am going to start talking about what is the difference between A-beta and amyloid because they are different

things.

[Slide]

This is an immunostain of a brain for A-beta. These are the plaques that I talked about. Now, one of the things about a picture like this of a brain of somebody with Alzheimer's disease is that not all the A-beta is exactly the thing. So, you can see some things that look very large and dense, and this would be your typical idea of a plaque. But you also have A-beta that is deposited around blood vessels so the blood vessels that are coursing through the brain, providing oxygen and sugar for the neurons, they can accumulate amyloid around them and that is called amyloid angiopathy. You see several examples of it here.

There are also other kinds of deposits of A-beta that occur in a brain that are not dense but are kind of more diffuse. This might be sort of a diffuse plaque up here. Over here we might have more of a diffuse plaque. So, not all these deposits look exactly the same and one of the differences is that some of these deposits are amyloid and some of them are not. So, what do I mean by amyloid?

[Slide]

Amyloid means that something stains with a

specific dye. So, here we have an immunostain of a plaque, of a dense core, senile plaque. So, this is all A-beta right here. Now, this plaque has been stained with a different die, called thioflavin S. They look the same. So, in this case this A-beta, here, is amyloid because it stains with this dye. But, as I said, not all A-beta deposits stain with these dyes. So, these dyes don't only just stain A-beta deposits, they stain other things that are amyloid. For example that amyloid angiopathy that I talked about with the A-beta in the blood vessels, they will also stain with thioflavin S. So, the A-beta in those deposits will stain with this dye.

[Slide]

But neurofibrillary tangles will also stain with this dye. Now, remember that neurofibrillary tangles are made up of a completely different protein than A-beta. They are made up of this protein called tau. But when they are stained with this dye, this amyloid-staining dye, thioflavin S, they are also recognized. So, these dyes are not recognizing A-beta, they are recognizing something else. So, what are they recognizing?

Well, in order to talk about that we have to go

into the structure of A-beta just a little bit. Amyloid is a protein that has a beta-sheet confirmation, and a lot of different proteins can have a beta-sheet confirmation. So, what exactly is that?

This is a diagram of an amyloid that is being formed. In this case what we have is a protein that is folding up on itself and it has these sheets next to each other, these beta-sheets. Her is one protein and then it forms this beta-sheet and then the next protein forms a beta-sheet and it combines with that first protein. Then the next protein does the same thing, and the next protein does the same thing, and the next protein does the same thing. And, as these proteins accumulate they end up forming a fibril.

We heard about fibrils in the last talk and there is an electron micrograph here of fibrils of a protein that accumulate into these long fibril structures. But this is an amyloid and, as I said, it doesn't matter exactly what this protein is but if it forms this kind of tertiary structure where it has a beta-sheet bound on itself it can bind these dyes. So, there is a number of these dyes and that is certainly something you all are going to be talking

about this morning. But in the lab we use things called Congo red and thioflavin S and methyl violet.

[Slide]

So, these dyes seem to stick in between these layers of beta-sheets. So, these proteins have these beta-sheets that leave a little space in between the layers and the dyes seem to fit into those spaces there.

There is a little bit of discussion still about how exactly the various dyes could be identifying these amyloids, and I should point out that in the lab when we do these experiments the immunostains that I showed you are all very nice and clear, and you have nice pictures of the plaques and then there is not much background. Thioflavin S, not so much. So, the plaques are stronger but the background is harder to see. So, there is actually some evidence that these stains actually bind to other places as well.

One thing that is interesting is that in vitro studies when you are making these proteins that form these fibrils the introduction of these dyes can actually lead to the prevention of the fibril formation. So, there is some evidence that the presence of these amyloid-staining dyes

actually interferes with the production of the amyloid itself.

[Slide]

In the case of A-beta, there is a lot of research that goes into exactly what the molecular steps are that take the A-beta from being a normal protein that is present in our brains to being a form that ends up making this amyloid and forming the plaques or the amyloid angiopathy that I talked about.

This is just a sequence of the amino acids of A-beta up here, the primary sequence. Then, this is in a recent review from David Teplow's lab where individual A-beta molecules will form their beta-sheets and then aggregate in a way that forms some sort of a structure that then can form a polymer that ends up looking like the fibril that we have talked about.

So, here is kind of a more detailed explanation of that, where normally the protein is unstructured so it doesn't have any of this tertiary structure that I talked about. But occasionally it will go into this beta-sheet formation and then, once that occurs, it can start to form these higher order complexes that end up with things like

protofibrils and fibrils, and these are the things that will be staining with the amyloid dyes.

[Slide]

One thing I want to stress is, again, when we are talking about amyloid we are not talking about A-beta; we are talking about a different thing altogether. There are a lot of proteins that have been identified that are amyloids. Some of them are in the brain. Some of them are not in the brain. So, in the brain we have A-beta and it can be in plaques or blood vessels. And, we have tau that ends up in these neurofibrillary tangles.

But there are other things that will form amyloids. None of them are nearly as common as Alzheimer's disease or, even if they are common, for example alpha-synuclein in Parkinson's disease, the number of lesions are many orders of magnitude fewer than the plaques that I showed you in an Alzheimer's brain. So, if you remember, when we looked at those plaques they were all over the cortex. But the lesions in Parkinson's disease are much fewer and show a different distribution in the brain.

But there are a lot of different proteins, some in Huntington's disease, prion proteins, which I will talk

about for just a few minutes, which are in these prion diseases, other rare forms of amyloids, cystatin C or amyloid of the British or Danish type.

There are also amyloids that form in other tissues. So, you can get amyloidosis in heart tissue or liver or kidneys, and there is a bunch of different proteins that will be responsible for those amyloids forming in those different tissues. I have just listed some of them here but, again, I just want to stress that the term amyloid means more than A-beta.

[Slide]

I just want to take one of those as an example. This is a prion protein which causes a disease that in its familial and sporadic form is mostly called Creutzfeldt-Jacob disease. But this is the protein in its normal confirmation and it has a certain structure and these things are called alpha helices. But it can take on a confirmation that has a lot of beta-sheet character, and that is drawn here in these blue arrows, and that is where the amyloid dye would be binding.

[Slide]

These are very rare diseases but they are actually

infectious person to person and so we pay attention to them. You can stain for the prion protein. This is in the cerebellum. You can see in this case that there is a distribution of prion protein that looks a little bit similar to the distribution of amyloid, in a different region of the brain, different clinical symptoms but the same deposition of a protein and that protein will stain with, in this case, thioflavin S, an amyloid-staining dye.

[Slide]

As I said, the distribution of these lesions is very different in different forms of the disease, fatal familial insomnia or Creutzfeldt-Jakob disease, but I just wanted to underscore the idea that we are talking about amyloid binding and not A-beta binding molecules.

[Slide]

I hope I have brought everybody up to speed on where we need to be in order to understand the neuropathology of Alzheimer's disease. We have plaques and we have tangles. Plaques are made up of A-beta and tangles are made up of tau. The accumulation of A-beta seems to be a primary event in Alzheimer's disease, by which I mean that it occurs early and it seems to affect everything downstream

of that accumulation.

These deposits that are so prevalent in Alzheimer's disease can be detected not only with A-beta antibodies but can be detected with amyloid binding molecules. But there are other proteins that form amyloids. Thank you.

Clarifying Question

DR. GOLDSTEIN: Thank you. We now have 15 minutes for the panel to ask any clarifying questions they may have from the presenters from the FDA. Yes, Dr. Green?

DR. GREEN: I would like to have a better understanding of the prevalence of the amyloid angiopathic changes in different age groups and how they correlate, or do they, with the progression of Alzheimer's.

DR. REBECK: So, this amyloid angiopathy in Alzheimer's disease is very common so you see a lot of it in probably 30 percent of Alzheimer's cases. It has not been correlated with symptoms, with the normal symptoms of Alzheimer's disease. Occasionally those blood vessels will break and cause hemorrhagic strokes. So, those, of course, have the symptoms that are associated with hemorrhagic strokes. But it is very common in Alzheimer's disease.

When I say 25-30 percent, that means a lot of amyloid angiopathy in those cases. In the other ones there is less and in a small fraction there is probably no amyloid angiopathy.

DR. GREEN: Thank you.

DR. GOLDSTEIN: Dr. Rudnicki?

DR. RUDNICKI: It is my understanding though that you can have amyloid angiopathy and not Alzheimer's. Is that not correct?

DR. REBECK: Yes, amyloid angiopathy can be diagnosed completely on its own. Those individuals generally show up with symptoms of a hemorrhagic stroke as opposed to Alzheimer's disease which, as we heard about, has a more insidious onset.

DR. GOLDSTEIN: Dr. Royal?

DR. ROYAL: My question is also for Dr. Rebeck. Thank you very much, by the way, for that presentation. As a non-neurologist I really appreciated it. Since amyloid beta comes from APP, is there a reduction of APP in the brain when you have Alzheimer's disease, and does APP have a function?

DR. REBECK: Presumably APP has a function. But,

remarkably, after 20 years of research we are still not clear on that. APP seems to be induced under times of damage so probably what is happening is you end up with a negative feedback loop where you get the A-beta starting to accumulate. That causes damage. Cells respond to that by making more APP. That leads to more A-beta production and you go down into a bad spiral.

DR. GOLDSTEIN: Dr. Rizzo?

DR. RIZZO: We saw a slide that seemed to show biphasic distribution of disease or signal in patients with mild cognitive impairment. How does that pattern change with range of severity of illness, from mild cognitive impairment all the way to severe Alzheimer's disease?

DR. THAMBISETTY: I don't think we know for sure. I am not entirely confident that we know enough about PIB retention with the 11C compound to be able to draw robust conclusions about relationship PIB retention and disease severity. So, the bimodal distribution is something that I have been very intrigued by, both in healthy controls as well as in subjects with mild cognitive impairment.

DR. RIZZO: Does it suggest or support a lack of a dose response relationship between the findings and the

disease?

DR. THAMBISETTY: It could; it could. And, it also hints towards suggesting that the signal that we are seeing may either be a false positive in terms of its relationship with the disease, or it could suggest that subjects who haven't yet developed Alzheimer's disease but are either health controls or subjects with mild cognitive impairment may, in fact, be identified by 11C PIB as those most at risk for developing the disease. But I am not entirely sure at this stage we have enough data to be able to draw meaningful conclusions between PIB signal and disease severity.

DR. RIZZO: Dr. Goldstein, may I ask a second question?

DR. GOLDSTEIN: Sure.

DR. RIZZO: Is there any evidence as yet that early diagnosis of cognitive decline results in a better outcome?

DR. THAMBISETTY: It is a great question. Intuitively it could make sense to think that that was the case. So, we know that pathology, both fibrillary pathology as well as plaque pathology and neuroimaging correlates such as hippocampal atrophy or whole brain atrophy are very early events in the disease and predate the onset of clinical

symptoms and cognitive decline. So, intuitively it would suggest that targeting those early stages before clinical symptom onset is probably a viable approach.

DR. RIZZO: Thank you.

DR. GOLDSTEIN: To clarify I think the point a little more, that slide that Dr. Rebeck showed on a temporal course of AD in that prodromal stage there is an exponential increase in A-beta. That is what your cartoon slide showed, that it doesn't correlate at all with disease severity or with degree of cognitive impairment. That seemed to correlate much more with neurofibrillary tangles. So, it is sort of two different issues. One is a potential marker for the diagnosis of the disease, but not necessarily a marker for disease progression or severity of disease. Am I getting that right from that slide?

DR. REBECK: Yes, so I think this falls into the category of interpretation of data that not necessarily everybody would agree with. For example, if you look in transgenic models of Alzheimer's disease the amount of amyloid continues to accumulate in these mice. The older they get, the more you see.

This data is mostly drawn from autopsy data where

a large number of people were looked at and somebody took patients who only had the disease for a very short period of time, and some people who had had it for 15 or 20 years, and everyone in between, and looked at the levels of the number of plaques in those individuals. The levels didn't show any sort of increase over time.

Now, with tangles that was not true. You could count tangles, and the longer somebody had it or the worse their symptoms were, the more tangles they had.

There are people who have taken brains of people with Alzheimer's disease and ground them up and tried to measure the A-beta in the ground up plaque, and they say the longer you have had the disease the more A-beta we see in those brains.

So, those two pieces of data don't quite fit together. It could be that there is more A-beta in individual plaques, like they just get packed a little bit tighter. But that is the kind of information that we don't have and, honestly, the reason we don't have it is because there is no way of imaging A-beta deposits until autopsy. So, if there were, that would be an enormous boon for research into that area.

DR. GOLDSTEIN: Dr. Twyman?

DR. TWYMAN: I have a question around the histopathological diagnosis for Alzheimer's disease in that the identification of the plaques provides the definitive diagnosis. So, what types of stains are used for that diagnosis? Are these dyes used or are there more specific stains such as A-beta specific antibodies, or otherwise, used in that definitive diagnosis?

DR. REBECK: The first thing I want to say, which I should have mentioned and I think we have both alluded to, is that Alzheimer's disease diagnosis depends on both plaques and tangles. So, if somebody is demented and their brain is analyzed and you only see tangles, it is not Alzheimer's disease. So, unless both things are seen it will not be diagnosed as Alzheimer's disease.

Secondly, there are several different kinds of dyes that are used routinely. I showed you some examples of the antibody stains. There are silver stains which are pretty nonspecific and they will identify plaques and tangles. Then routinely people do use amyloid stains like Congo red.

DR. TWYMAN: So, the routine methodology is using

these dyes, these types of dyes?

DR. REBECK: The routine methodology, it varies depending on the sophistication of the lab. So, antibodies require a little bit more sophistication and so routinely if there were a lab that was not going to do antibody staining they would probably do a silver stain and a Congo red stain. There are probably only two or three stains that would be done on brain tissue and those would be among them.

DR. GOLDSTEIN: Thank you. Dr. Herscovitch?

DR. HERSCOVITCH: I guess I have a question for each speaker. Clinically, how good is the clinical diagnosis, even at the research level, between Alzheimer's disease and what appears to be the second most common dementing illness, dementia with Lewy bodies? The question pathologically is how commonly is amyloid found in other dementing diseases, particularly dementia with Lewy bodies?

DR. THAMBISETTY: Thanks, Dr. Herscovitch. I think it depends upon where the diagnosis is made and where the patient presents. So, in tertiary referral centers I think the sensitivity and specificity for clinical diagnosis with the established NINCDS criteria approach is 89-90 percent. It is a lot less in the community.

As far as Lewy body dementia is concerned, I think more recent series with autopsy confirmation have suggested that it is a lot more prevalent than we have recognized over the last, say, 10 or 15 years. I think we will see with greater refinement of both the clinical methods to diagnose Lewy body dementia, as well as with larger series with autopsy confirmation, we will see that number rise even more than the 20 percent that I showed on the slide.

DR. GOLDSTEIN: Dr. Rebeck?

DR. REBECK: From a neuropathological standpoint, it is extremely common to see both pathologies, the diffuse Lewy body staining in the presence of the amyloid staining. The diffuse Lewy body staining is much smaller. I mean, there are many fewer Lewy bodies. They are inside of cells. There are just not that many of them. But biologically there is going to be a connection between the accumulation of plaques and the accumulation of these Lewy bodies. We just don't know what that is. And, somebody knows the exact numbers of how often you see Lewy bodies in Alzheimer's disease and how often you see Alzheimer's disease with Lewy body dementia. I just don't know the numbers.

DR. GOLDSTEIN: A followup?

DR. HERSCOVITCH: Just to clarify, in dementia with Lewy bodies what is the amyloid burden, especially in comparison with somebody who has pure Alzheimer's disease?

DR. REBECK: Oh, it is probably 100-fold less. So, it is an accumulation of this alpha-synuclein protein in these small Lewy bodies and in Lewy neurites, but it is kind of hard to see so when you look at a brain an experienced neuropathologist will say, oh, there's a Lewy body. Then you look around, oh, there's a Lewy body. Whereas, you know, I can see amyloid deposition. I mean, anybody and their brother can see amyloid deposition in Alzheimer's disease.

DR. GOLDSTEIN: Mr. Bridgwater?

MR. BRIDGWATER: Yes, I believe it was Dr. Gorovets that mentioned, on slide 12, titled Adetection of amyloid vs. Alzheimer's disease diagnosis,@ and we said that amyloid detection is a pathology indication of Alzheimer's disease as a specific diagnosis. The inference is that amyloid alone is not an Alzheimer's diagnosis. My question would be that holistically we know that the symptoms that present themselves that we spoke about this morning, the neuropsychological testing, and the scans that can be

performed holistically under the skillful observation of a neuropsychological professional can determine Alzheimer's disease.

Would it be the inference of this committee at some point that we would concur that these imaging techniques are appropriate for one component of defining Alzheimer's disease, and make them part of a recommended regimen so that insurance carriers would be encouraged to reimburse patients to get them and increase the early detection rate for individuals that are currently unable to do so?

DR. GOLDSTEIN: Well, I think that is an important question but that is a downline question. That is where we would end up once it is determined that this is the correct thing to do, and I guess that is what the real topic is for today, to provide guidance for these companies because they are looking to develop this as a potential marker for disease. Dr. Holmes had a question I believe.

DR. HOLMES: Yes, just a follow-up on Dr. Twyman's question about pathology and definitive diagnosis. Are you saying that, say, you do a brain biopsy frontal lobe and you get plaques, but not tangles, in a patient that has clinical

symptomatology of Alzheimer's that would not be good enough for the diagnosis? I was just wondering if you could use brain biopsies. If you miss the tangles, could you make the diagnosis?

DR. REBECK: No, you need both pathologies to make the diagnosis. That doesn't mean that they might have Alzheimer's disease and you might not be able to see the tangles until a person dies and you can autopsy the whole brain and say, oh yes, in the hippocampus there has tangles, we just didn't see it in this little bit of biopsy that we looked at. So, they might have Alzheimer's disease but you just couldn't say definitively that that is what it was.

DR. GOLDSTEIN: I am going to go three minutes into our break. We have I think four more questions so these have to be relatively rapid and, hopefully, relatively rapid responses. Dr. Lu first.

DR. LU: I have a question about pathological measurement for the amyloid burden. Is there any quantitative measurement for severity, and how do you summarize that severity?

DR. REBECK: You can count the area of the brain that is covered with plaques and that can range between a

couple of percent and up to maybe 10 or 12 percent of the grey matter that is covered by plaques. So, that is kind of the basis level of trying to measure amyloid burden.

DR. GOLDSTEIN: Dr. Mattrey?

DR. MATTREY: I have two questions for a non-neurologist, just a little bit for my education, is there a cause effect between the A-beta or tau and Alzheimer's disease or is it just a surrogate marker of the disease?

The second question is do you need the entire brain to make a diagnosis of the pathology, given the regional distribution, and what is your sensitivity and specificity assuming that the pathology is always the gold standard but we don't know if it really gold? I mean, you are rendering statistical opinions.

DR. REBECK: Part of the diagnosis pathologically requires that you look at different brain regions. So, there is staging of Alzheimer's disease, stages 1, 2, 3, 4, 5, 6, and that largely depends on where exactly you see tangles. So, if you see tangles only around the hippocampal region that would be an earlier stage. But if you see tangles, you know, in six different regions in the brain that would be a late stage. Then the diagnostic accuracy is

I think generally around 85 percent. Is that the question you were asking in terms of neuropathology?

DR. GOLDSTEIN: Let me speak as a clinician quickly. Part of this is circular. If you have a patient without dementia and the pathologist sees plaques and tangles they won't make a diagnosis of Alzheimer's disease. They will say there are plaques and tangles pathologically. If you have a patient that fulfills a clinical diagnosis of Alzheimer's disease and the pathologist doesn't see plaques and tangles, then they say, you know, it is not Alzheimer's disease. So, part of this is a bit circular. Dr. Katz?

DR. KATZ: Actually, my question was the same as the first question that we heard just before, which is a question of causality. You talked about the mutations causing, if that is the right word, Alzheimer's, certainly with mutations in the precursor protein the amyloid test of hypothesis and A-beta being the primary event, that is to say, basically responsible or causative for the subsequent downstream effects.

Does it follow logically or inexorably from the fact that patients with a particular mutation develop Alzheimer's disease that A-beta is the primary cause? Maybe

you could just talk briefly about other competing hypotheses or how well accepted you think in the field A-beta as the causative agent really is at this point.

DR. REBECK: So, I think in science, like in a lot of things, you get attention for taking stands that aren't well accepted. You are viewed as a maverick, to use a word that we hear a lot these days. That doesn't necessarily mean that you are right.

DR. GOLDSTEIN: Be careful, this is Washington.

DR. REBECK: Exactly. I think with Alzheimer's disease, like with a lot of diseases, you can get there different ways. So, you know, with heart disease you can apply cholesterol or high blood pressure or bad genes and they will all end up with some sort of heart disease. I think the same will be true of Alzheimer's disease, but I think the general view is that all these outside influences will affect A-beta metabolism.

Now, it might not necessarily be these plaques that I was talking about. It might be some of the smaller aggregates that we in the field call oligomers which are shown to be toxic to cells. So, there are different ways that you can promote formation of these oligomers and that

can cause Alzheimer's disease.

Some people think that if you interrupt the formation of tangles you will actually be treating Alzheimer's disease, and I don't disagree with that at all. I think you will have the A-beta forming these oligomers or plaques. That will be causing damage. Those cells might be starting to die. But if you can prevent them from dying you haven't done anything to the A-beta, but if you are preventing those neurons from dying you are preventing the disease, which is the symptoms.

So, there are other ways to attack it. Now, I do think that the plaques are a necessary cause of the disease. There are diseases that only have tangles. They get formed in different brain regions than I showed you for Alzheimer's disease so they have different symptoms but those are different diseases, frontotemporal dementia and progressive supranuclear palsy, much rarer.

DR. GOLDSTEIN: I am told by my handler here that we can do one more question and then we will just take a ten-minute break so we can start at 10:05 and resume.

I have one question based on this one slide. It is a really nice pie diagram where things look awfully

clear. The problem we have as clinicians is that this Aain't@ life. For example, we now know that this should probably be a big ven diagram with tremendous overlaps between Alzheimer's disease and vascular dementia. The majority of patients or a large number of patients probably have mixed dementias. This is a bit artificial and I think that is also part of the issue that we are going to need to be dealing with. I just wanted you to clarify this and then we will take our break.

DR. THAMBISETTY: I couldn't agree more with you. That pie diagram would be, I guess, a pathologist's nice and clean view of various disease phenotypes which is completely different to what a practicing clinician would see out in the community or even in a tertiary referral center.

I think it brings out the point that I guess is inherent in your question. We need more robust biomarkers that we could possibly employ as a patient walks into the clinician's office to be able to better characterize and phenotype these various syndromes. And, until that happens I think such divisions based purely on pathology in small series will be completely artificial. I completely agree with you.

DR. GOLDSTEIN: Very good. I think we all went back to medical school here for the morning. We will take a ten-minute break. We will start again promptly at 10:05. Thank you.

(Brief recess)

DR. GOLDSTEIN: We can resume. The next section is a series of talks from the industry sponsors. The first is from Avid Radiopharmaceuticals.

Avid Radiopharmaceuticals

Introduction and Development Overview of 18F-AV-45

DR. SKOVRONSKY: Thank you, Mr. Chairman. It is a pleasure to be here. Members of the advisory committee, ladies and gentlemen, good morning.

[Slide]

My name is Daniel Skovronsky. I am the Chief Executive Officer at Avid Radiopharmaceuticals, a company which I founded four years ago because I, like all of us in this room, recognized the major public health crisis that is Alzheimer's disease, and a hope that some day we will be able to provide definitive information about the presence or absence of Alzheimer's pathology to the millions of Americans who are suffering from memory loss.

Today we are one step closer to achieving that objective. We meet here today to talk about how to translate amyloid imaging from the fascinating, exciting research tool to become a widely available, well validated resource for the doctors who are on the frontlines of managing Alzheimer's disease.

Before I begin with my prepared slides I want to take a moment to thank the FDA, both the Divisions of Medical Imaging Drugs and Neurology Products, for their strong support and for their visionary outlook in hosting this meeting today. This advisory committee meeting represents a pivotal opportunity to advance the field of both Alzheimer's and molecular imaging and I am very much appreciative of that.

[Slide]

In our 30 minutes I will spend the first 10 minutes introducing our development plan and giving you a bit of history on the AV-45 data that we have collected. I will then turn it over to my colleague, Dr. Clark, who will talk about the clinical utility of amyloid imaging and potential reference standards for amyloid imaging. Finally, I will wrap up with our specific development plan and our

phase 3 proposal.

[Slide]

As we heard this morning, Alzheimer's disease is a clinicopathologic disease entity. Like many other human diseases, it is defined only by the presence of both clinical findings and neuropathology findings. One of the key neuropathologic findings is the amyloid plaque. We heard already about the great strides we have made in understanding what amyloid plaque means over the last 25 years.

Even more impressive perhaps is what we still don't know about what amyloid plaque means. So, we base our development plan and we base our clinical utility upon the bedrock of our knowledge of amyloid plaque. That is, it is a required component for diagnosis of Alzheimer's disease. If you don't have amyloid plaque you don't have Alzheimer's disease. It is a sine qua non and based solely on that we can build everything else.

So, because amyloid plaque is a sine qua non for diagnosis of Alzheimer's disease, the clinical diagnoses ante mortem can only be made with a level of certainty called probable Alzheimer's diseaseB-you probably have it.

Definitive diagnosis is only possible post mortem today when we can see the amyloid plaques and the neurofibrillary tangles.

[Slide]

This is 18F-AV-45. This is our amyloid imaging agent. I show you one set of images here. 18F-AV-45 was developed to be specific for the beta amyloid pathology. It doesn't bind to any of those other types of amyloids we heard about, synuclein, tau etc. It is specific in vitro for the amyloid plaque pathology.

Here you can see the scan from a probable Alzheimer's patient, clinically diagnosed with probable AD and you can see the dramatic retention of the tracer in all the brain regions, frontal cortex, precuneus, posterior cingulate, where we know there is amyloid plaque deposition based on autopsy studies. You can see in the cerebellum, a region which is not affected by amyloid deposits in Alzheimer's disease, that there is no tracer retention.

Similarly, in this cognitively normal elderly control subject we have very little tracer retention, shown in the blue color. We hypothesize that there is no amyloid pathology in this subject. This is a ten-minute scan

conducted with our agent 18F-AV-45.

Therefore, we believe that 18F-AV-45 provides information about the presence or absence of the amyloid pathology in the brain. It is our goal to prove this through phase 3 trials.

[Slide]

We have demonstrated this through a number of preclinical and nonclinical studies. The target of 18F-AV-45 is the amyloid plaque pathology. Our indication, therefore, is straightforward. It is imaging that amyloid pathology. And, what is the clinical utility of imaging amyloid pathology? Why do we want to do this? Well, as I said, amyloid pathology is the sine qua non of Alzheimer's disease. If you don't have amyloid pathology you don't have Alzheimer's disease.

So, this can be used. If we have a reliable marker of amyloid pathology it can be used to exclude the diagnosis in patients who have a negative scan. How do we prove that we have a reliable marker of amyloid pathology? There is only one gold standard established for amyloid pathology. As we have heard, it is the histopathological examination of the brain at autopsy. That is how we know

whether or not there is amyloid plaque pathology and that is what we need to correlate our imaging studies with.

[Slide]

So, our proposed indication: AV-45 is indicated for imaging that amyloid pathology to aid in the evaluation of patients, and the clinical utility, as I said at our first NDA submission, should be that patients who don't have significant brain amyloid do not have Alzheimer's disease.

In addition, there is a second clinical utility. Amyloid imaging might be used as a biomarker for anti-amyloid therapy trials and we will talk more about how that might happen to be demonstrated in the future by additional clinical trials and perhaps we can do something about positive scans. We hypothesize that if you have brain amyloid you have an increased likelihood of having Alzheimer's today or perhaps developing Alzheimer's in the future. We don't know that as a fact today. It will take additional well-controlled studies to prove this clinical utility.

[Slide]

So, 18F-AV-45 represents a culmination of ten years of research and development. It started in the lab

with Prof. Hank Kung at the University of Pennsylvania, and over the last decade we have synthesized and tested thousands of compounds. Hundreds have gone into mice, and 12 different amyloid imaging ligands have gone into human trials under exploratory FDA IND trials to select the best agent for imaging plaques. Based on those trials we selected 18F-AV-45 as the agent that had the best pharmacokinetics, the best signal-to-noise properties to proceed to full development.

[Slide]

You see here the timeline of that development. Since selection in 2007 we have advanced it through five clinical trials, two phase 1 trials, two phase 1/2A trials looking at dose ranging, test-retest reproducibility, and a phase 2B trial looking at preselected populations of Alzheimer's mild impairment in cognitive intact individuals. To date, we have studied 284 subjects as of today. All of these subjects have been studied under IND using standardized methods for drug production, standardized methods for imaging and standardized methods for data analysis, all conducted under our IND.

[Slide]

These are examples of the data. You can see there are some patients who are clearly negative, no significant uptake of cortical AV-45. Some patients are clearly positive, lots of uptake of AV-45. Then there is a spectrum of pathology, patients having increasing amounts of 18F-AV-45 uptake. We have to understand what these scans relate to in terms of what is actually happening in the brains of these subjects.

[Slide]

The technical performance of the tracer is excellent. You can see this is a test-retest reliability study. Here is an Alzheimer's subject imaged, lots of uptake, and we sent them home and brought them back a week later and imaged them again. The images are almost exactly the same qualitatively and quantitatively. There is a unique fingerprint of amyloid in each subject that we can reproduce over time when we bring them back and image them.

The reproducibility data shows the variability is in the range of 3-5 percent and the test-retest correlation coefficient is exceedingly high. This is a very reliable, reproducible metric.

[Slide]

Based on that, we can perform quantitation studies and here you see data from approximately 60 subjects, conducted at 15 different sites in the United States, looking at how does the tracer quantitate in cognitively normal individuals versus subjects who have a clinical diagnosis of probable AD. Certainly, you see the cognitively normal subjects have a lot less signal in their brain than the probable AD subjects. But here are some people who are cognitively normal who are creeping up there. They have more and more signal in their brain. Do these patients have pre-symptomatic Alzheimer's? Do they have a brain full of amyloid plaques? We don't know yet but we would look forward to doing studies where we can definitively assess that.

The Alzheimer's subjects are all quite high, with the exception of two, two out of 22, about 10 percent of our probably Alzheimer's subjects had negative scans with no uptake and they looked like controls. We would hypothesize that this is the 10-20 percent that we would expect to be misdiagnosed as false positives on the clinical diagnosis. We would set out to prove that these subjects have no

amyloid in their brain. That has to be proven through well-controlled clinical trials.

So, in addition to the data set I show you here, we have just completed enrollment in our 180 subject phase 2B trial that is now finished, comparing imaging to clinical diagnosis in preselected populations and the analysis of this data is ongoing. In total, our clinical data base is now growing to be quite extensive using 18F-AV-45 in well-controlled trials in healthy elderly, Alzheimer's and MCI patients.

[Slide]

All of our production of our compound has been unified under a single CMC package, with single product quality standards in all of our IND clinical trials, and we are doing this across the country. You can see we have a nationwide manufacturing distribution network for this compound. It is being used in more than 30 sites around the country today, and this sets the stage. This enables us to now move forward into large phase 3 trials and move this agent towards approval.

Now I will hand it over to my colleague, Dr. Clark, to talk about clinical utility and reference

standards.

Clinical Utility and Reference Standard

for Amyloid Imaging

DR. CLARK: Good morning. I am a clinical neurologist and for the past 23 years all of my clinical activity has been focused on the evaluation and care of patients with late-life cognitive impairment, for the first period, at Duke University at their Alzheimer's disease research center and then later at Penn's Alzheimer's research center.

My clinical focus over the past 15 years has been on the development and evaluation of biomarkers used to detect the presence of Alzheimer's disease in patients. It is from this perspective that I would like to share with you my thoughts on the two questions before the committee today. Those questions are what is the clinical utility of detecting amyloid in the brains of patients with late-life cognitive impairment? Second, what is the appropriate reference standard to use when you are trying to determine if what you are detecting truly is tightly linked with the pathology of the disease?

[Slide]

I want to start with just a couple of clinical truisms. The first is that clinicians take better care of patients when they get the diagnosis correct. The second is that it is in general better to identify disease early than late. The third is that a clinical diagnosis will almost always be more reliable when it is grounded on the pathology that causes that disease. Then, the fourth is simply that when you get the clinical diagnosis correct all the things flow from that, your management of the patient, your selection of drugs, your treatment decisions. The information that you give patients and families about the disease is more likely to be correct and more likely to be appropriate for the patient.

However, a skeptic might say why do you really care about whether you diagnose Alzheimer's disease or diagnose it correctly? I would just point out this one metric. Currently there is an extraordinary amount of time and effort that is expended attempting to determine what is causing symptoms of dementia in patients approaching the latter part of their life. In part it is driven, of course, from the clinician's desire to help patients, but it is also driven from the awareness in the public and the awareness

from the public health standpoint that this is a growing problem and that getting the diagnosis changes the way you manage these patients; allows them to become involved in decision-making early in the course when they can still do that; and helps the families plan for future care. Well, how well do clinicians do in making this diagnosis?

[Slide]

As we have heard today, Alzheimer's disease is by far and away the most common cause for late-life dementia but it is not the only cause. As has been mentioned already, almost 25 percent of patients with late-life cognitive impairment do not have Alzheimer's disease as the responsible pathology.

How well can clinicians separate patients into these two broad groups? Well, this is data from Penn. So, our expert group of clinical diagnosticians, which includes geriatricians, neurologists and geriatric psychiatrists, has an overall accuracy rate of only 78 percent, not much different than any expert center, when saying that they think a patient has a diagnosis of Alzheimer's disease that is actually what the pathologist will find.

Most importantly, the false-positive rate, giving

a patient a diagnosis of Alzheimer's disease when there is no Alzheimer's pathology there, at least at Penn, is 17 percent, not a trivial number when you consider that there are up to five million patients currently in the United States carrying a clinical diagnosis of Alzheimer's disease. That actually translates into a false-positive diagnostic rate of about 580,000 patients. So, that is not trivial. This accuracy rate is well within the range that is published in multiple series, going from 10-35 percent.

[Slide]

Well, how would amyloid imaging help? This is just briefly a clinical diagnostic algorithm. Patients present to a clinic and generally get a brief cognitive assessment if they have signs and symptoms that there might be a problem. If the cognitive assessment indicates there is no change, no further evaluation is needed. If there is a suggestion that there is cognitive change, then they generally move to a more extensive evaluation where the clinician's main job is to detect Alzheimer's disease and separate them from this category compared to a non-Alzheimer category.

How well do clinicians do this? As I pointed out

on the other slide, they are wrong 17 percent of the time. They are accurate 83 percent of the time, and it is this 17 percent that amyloid imaging has the potential to move out of this category and into this category which is where they really belong. In addition, there is always a muddled category in the middle where the clinician is not quite sure whether they have Alzheimer's disease or not based on their clinical phenotype. Alzheimer's imaging indicating that there is no amyloid in the brain would certainly suggest that they most likely belong in this category, not in this category.

[Slide]

So, how can amyloid imaging lead to better patient management? Well, a negative amyloid scan indicating no amyloid pathology, no Alzheimer's disease as the most likely diagnosis. Positive imaging would suggest that there was amyloid in the brain and, therefore, amyloid pathology was likely and Alzheimer's disease could be the most likely correct clinical diagnosis. So, amyloid imaging can help rule out Alzheimer's in those patients who are cognitively impaired and in patients where a clinical diagnosis is uncertain but their cognitive impairment is not.

[Slide]

But that is not the only utility for amyloid imaging. As this slide points out, there is a driving need to develop pathologically-targeted, disease-modifying therapies and amyloid imaging can play a tremendous role to increase the efficiency of these trials and improve the ability to make the appropriate decision at the phase 2 level by helping with patient selection. In a disease-modifying trial you want the patient who has the disease in the treatment trial so that the target is there.

Amyloid imaging can exclude inappropriate participation from patients who don't have amyloid in their brain and help identify those who should be in the trial. At first this would operate, of course, best with patients who have clinical diagnosis of Alzheimer's disease, but the field is moving towards developing therapies earlier in the pathological cascade so a second horizon would be those individuals with mild cognitive impairment where a clinical diagnosis of Alzheimer's pathology is much less certain.

Then, if you extend your vision all the way out you could and, hopefully, at some point we will be able to identify pathological amyloid in individuals who have not

yet reached the symptomatic stage. This is really where you want to be if you are going to truly envision a world free of Alzheimer's disease. You need to have patients identified at this point so they can participate in primary prevention trials and identify what we need to do to prevent the expression of the disease, not simply slow it down. Amyloid imaging, of course, would also operate as a treatment efficacy biomarker within the arena of clinical trials.

[Slide]

Well, how about the issue of what is an appropriate reference standard? I want to start off again with just a couple of general truths. Reference standards should provide direct information about the target of interest. They should be well standardized and standardization should be based on well-controlled, standardized clinical trials.

They should be validated against the truth standard. The truth standard here is amyloid pathology. They should be independent of the test agent. They should be generally available to the drug development community and they should be FDA approved or FDA validated as a measure of

truth for the pathology you are trying to image.

[Slide]

Well, what are the appropriate reference standards or what are the candidate reference standards? Well, this is just a list of six candidate reference standards.

[Slide]

Clinical diagnosis, its great strength is that it is widely available and it is pretty cheap. We all just don't make that much money. But its weakness is that they are not that good. It has limited diagnostic accuracy.

[Slide]

MRI, good regional definition of atrophy but it has overlap with non-Alzheimer dementing disorders. It is good for controls versus Alzheimer's but too much overlap with the other dementing disorders and, of course, it hasn't been validated against amyloid histopathology.

[Slide]

FDG-PET, good spatial information on hypometabolism, but it doesn't image amyloid and that is your target, and it has not been validated against amyloid.

[Slide]

11C-PIB, well, there is a growing research database concerning 11C-PIB. It certainly does image amyloid but this database has been constructed without using standard IND, standard research protocols. Primarily they are investigator-initiated protocols and, of course, it hasn't been validated, adequately at least, against amyloid histopathology. There have been a number of case reports that report on pathological finding on patients who have been imaged previously with 11C-PIB, and they are certainly very encouraging but they don't really answer the two critical questions, and that is, what is the prevalence of the absence of amyloid in patients with 11C-PIB negative and what is the prevalence of pathological amyloid sufficient for a diagnosis of Alzheimer's disease in those individuals that are 11C-PIB positive?

[Slide]

What about CSF biomarkers? Well, there is extensive data available for them and they are linked to the pathology, as we heard earlier. This is spinal fluid beta amyloid and spinal fluid tau. The main problem is the overlap between diagnostic groups in the CSF biomarker field. Controls versus Alzheimer's is very good. Controls

versus other neurodegenerative cognitively impairing diseases, not so good. Of course, they haven't been validated against histopathology.

[Slide]

I will just show you one slide about the overlap issue. This is very recent data using the best technical methods for detecting beta-amyloid, xMAP Luminex, and you can see in this group of controls the overlap with the group of Alzheimer's disease. There is plenty of separation between the means but multiple overlap between the actual values at the individual patient level. For diagnostic accuracy that is a big problem because your diagnosis is at the patient level, not the group level.

[Slide]

What about histopathology? It certainly defines the disease and it defines the presence of amyloid. It has good spatial correlation to imaging possibilities because you can detect where the amyloid is in the brain and you can correlate that with where the amyloid retention or where the ligand retention is in the image. Its main problem? Well, it requires an autopsy, not a trivial issue. But these studies have been done in the past, pathological correlation

studies. This is imaging to pathology.

[Slide]

It has been done. And, this is just three examples, an FDG PET correlated with Alzheimer's disease; a SPECT scan series correlated with the presence of Lewy body pathology; and an MRI showing correlation with vascular pathology. What is the problem? Well, one of the problems is the interval. This is a progressive neurodegenerative disease. It is dynamic. You would want the correlation to be in the shortest time frame possible and the only way to do that is to design a prospective trial to accomplish that goal.

[Slide]

Now I want to turn it back over to Dan, who will tell you how we plan to do that.

Development Plan Proposal

DR. SKOVRONSKY: Thank you.

[Slide]

As you have heard, our development proposal is to conduct a prospective autopsy study. So, what do we mean by this? This will be a phase 3 study where we image elderly individuals who consented to brain donation studies and we

follow the patients for up to a year to obtain autopsy validation.

So, the imaging will be read by blinded readers, just as is conventionally done. The autopsy will be read by an expert neuropathologist, using established criteria for neuropathologic evaluation, and that will be our reference standard for the clinical trial.

Our study population, it is important to note, will include a diverse range of subjects. We will have subjects who are cognitively normal. We will have subjects who are mildly impaired. We will have subjects who clinically have probable Alzheimer's disease. The goal in having this diverse population is to have an autopsy population that has a wide range of amyloid pathology so that we can understand how our tracer performs in patients who have no amyloid, in patients who have a little bit of amyloid, and in patients who have a lot amyloid. We need to have all of these groups.

[Slide]

Maybe before I get into the details of exactly how we conduct the study, I want to address the question of feasibility. Is it really feasible to carry out an autopsy

study? You have seen that past ones have taken a long time. Well, I think today we can benefit from a tremendous investment that has been made over the last two decades in Alzheimer's disease research. There are Alzheimer's disease centers funded by the NIH all over the country that are now doing large numbers of autopsy studies. They are following cohorts of cognitively normal individuals as well as Alzheimer's individuals and following them to autopsy.

There are thousands and thousands of elderly individuals who have altruistically agreed to be in these programs and when they die they come to autopsy. All we need to do is go out to these centers, image the patients and then follow them to autopsy. At certain centers, if you are on this list about 20-30 percent of these patients might come to autopsy in a given year.

So, if we can target those subjects and perhaps enrich for those subjects a little bit by imaging just a few hundred subjects, which is what we have accomplished in the last few months, if we can image just a few hundred subjects we will have a significant number of image to autopsy correlations in just one year. So, this is readily doable.

Image evaluation metrics will be standard metrics.

We will have a qualitative read as well as a quantitative read, and we will correlate the imaging evaluation to the autopsy evaluation. We know how to do this. We have a hundred years of experience, starting from Alzheimer, doing autopsies and understanding how to measure the pathology in the brain. It is the established standard and it is also the established standard for definitive diagnosis of Alzheimer's.

So, our key outcome variable is the negative predictive value. If you have a negative scan what is the likelihood that you actually don't have Alzheimer's? If that is our indication that needs to be our statistical test. That needs to be what we prove in this prospective autopsy study. And, we are not talking about a couple of case reports or anecdotal studies. This is a prospectively defined, well-controlled series of autopsy study patients so we can compare imaging to histopathology.

[Slide]

Why do we want to do this? To be clear, we probably don't need it to say you are negative. We probably don't need it to say you are positive with symptoms. These aren't the hard patients. If you have Alzheimer's disease

clinically and a scan like this we have reasonable confidence that this is positive. But when we want to look at patients who are in here, who are in the spectrum of pathology, how do you know how to read these studies? Does a patient who has some signalB-are they positive? Are they negative? Where is the cutoff in relation to the cutoff for histopathology? There is only one way that I know of to answer this question, and that is to do the prospective autopsy validation study.

[Slide]

And, we can do this with a small number of subjects. We are talking maybe 30-50 subjects to get statistical power here and validate 18F-AV-45 against the autopsy, and perhaps each of these dots would represent a different subject, amyloid burden versus imaging outcome.

[Slide]

How does this plan work with the regulatory guidance? Well, in fact, the regulatory guidance, as you heard this morning, clearly states that a pathology indication is a valid indication to go after but it needs to be supported by a clinical trial design that supports that indication. If the indication is imaging pathology the

clinical trial design and the reference standard should speak back to that. That is why we select histopathology, one of the FDA suggested truth standards for any imaging agent.

[Slide]

In addition to our pivotal autopsy study, which is our pivotal phase 3 study, we have supportive studies in cognitively impaired populations. I told you about our phase 2B study in 180 subjects.

We have a study that will soon begin in patients presenting for first evaluation of cognitive impairment. We certainly don't have a reference standard in those patients but we want to understand how our tracer performs. We are also looking in well-defined populations of Alzheimer's and frontotemporal dementia, again, to add to our database and understanding of the agent.

We are also involved today in treatment trials, trials with therapeutics, for example Eli Lilly's gamma-secretase inhibitor where we image patients and then they are followed in the treatment trial. This will add to our database over time as more and more of these studies are conducted.

[Slide]

So, to summarize our proposal, our initial approval should be based on a phase 3 autopsy study with a limited number of subjects and to follow them to autopsy. Based on that, there will be immediate benefits to the medical community.

First and foremost, exclude patients who have a negative scan from having Alzheimer's disease. If we can prove that we really are imaging amyloid and we understand the sensitivity of the test we should be able to make this statement.

Second, we will have a biomarker that can now be available, widely available to many, many therapeutic companies to develop disease-modifying therapeutics. This is what we need. But we can't do that until the tracer is first validated against its target.

Post-approval, we don't stop here. Avid commits to the agency, commits to you to continue to study this tracer. We want to understand not just what a negative scan means but what does a positive scan mean. Now we are talking about a long-term, longitudinal study in hundreds, if not thousands, of patients following what does a positive

amyloid scan mean for healthy controls. We can do that to establish the prognostic utility of the scan, but also to enable prevention trials.

[Slide]

So, if we look at this, and this is our last slide here, what are the horizons of amyloid imaging? Well, the field is based on a strong foundation. It goes back ten years of preclinical data, or academic-based research studies, and I hope that Bill Klunk will have time to talk about some of the work that he did as one of the founding fathers of this field to establish this foundation that we can now build upon.

The investment has been made. The next step is multi-center trials in well-established clinical populations. I have shown you we have done that. The next step is the autopsy studies. We can do this. It only takes about a year to validate imaging using the histopathology reference standards.

Then we propose that at that level we will have adequate scientific certainty to establish a correlation between what we image and what is present in the pathology. Of course, that is our indication. That is the study to

support the indication.

But we don't stop there. In fact, we started these other studies, longitudinal studies in mildly impaired patients. We are doing that today, following those patients today, and therapeutic biomarker trials.

Today we have to discuss where we put the threshold for NDA approval. We suggest it should be here. I think we look forward to getting a response and feedback from the community so that we can further accelerate this development so that we can move towards having a biomarker available to help therapeutic companies develop truly disease-modifying drugs for Alzheimer's disease. Thank you very much.

Clarifying Questions to Presenters

DR. GOLDSTEIN: We have five minutes for the committee if they have just clarifying questions. Remember, we are not discussing the purpose of the meeting right now, just clarifying questions based on the presentation. Dr. Katz?

DR. KATZ: Yes, just a quick question for Dr. Clark. Seventeen percent of patients who were diagnosed with Alzheimer's didn't have Alzheimer's disease. Did that

depend on severity of the symptoms when they were seen?

DR. CLARK: No, it didn't. We have actually spent a lot of time trying to figure out why we made those mistakes. So, there are two points that are relevant to the answer to your question.

The first is that these were based, of course, on the diagnosis the last time they were seen. So, we were weighting everything in favor of the clinician and it turns out that that diagnosis doesn't change very much. It changes about 3-4 percent from the first diagnosis they are given to the last. So, it isn't that there is something unusual, that the patients are floating back and forth between various clinical diagnoses and they simply happened to end up with a diagnosis of Alzheimer's disease when they die.

The second thing is that we have been unable to detect anything that is particularly unusual about them. I mean, you would initially think, well, they were all the ones that we started off saying had possible Alzheimer's disease because we really weren't quite certain because, you know, there were other complicating factors. But that is not the case. They look exactly like the other 87 percent

from the clinical perspective where we got it right. As a neurologist, I hate to admit that.

DR. ZEISSMAN: You mentioned that you had done a power analysis to determine the number of autopsy subjects that needed to be done. Can you give a little bit of detail? Your lower number of subjects there was 30, which sounds a little bit low to me and I am wondering what the power analysis allows you to predict that you would be able to diagnose.

DR. SKOVRONSKY: It is a great question. Thank you. It is a question we don't have a definitive answer for. In fact, we have proposed already to the agency that our autopsy study should be conducted as a front-running phase 2/3 study so the first cohort of subjects that come to autopsy will be used to finalize the sample size calculations by understanding exactly what is the correlation between imaging and pathology.

Based on our assumptions about having an excellent negative predictive value, i.e., those negative patients really don't have plaques, it could be done in a small sample size. But based on the results of that first front-running cohort we will be able to finalize those

calculations.

DR. GOLDSTEIN: Dr. Rudnicki?

DR. RUDNICKI: An extension of the question from Dr. Katz, what did those 17 percent of the patient have on autopsy?

DR. CLARK: Actually, I don't know if I have the slide with me to actually give you those numbers, but basically I would say that they were fairly distributed amongst the categories that are prevalent for late-life dementia. So, the most common is that they end up with frontotemporal dementia. That actually makes up about 20 percent of patients who walk through the door at the University of Pennsylvania.

The other patients were misdiagnosed. Occasionally there is no pathology seen, and that continues to be a mystery. It is at least about half a percent of all patients presenting with cognitive impairment. We probably just don't have the right dyes, I have always assumed, as I keep telling our pathologists.

The others, I think there is one case of PSP; a couple of cases that qualified as Lewy body dementia which we define as cortical synuclein aggregation. As we heard

this morning, there is lots of mix between the pathologies for the various neurodegenerative diseases, but we have a pretty narrow definition for dementia with Lewy bodies.

So, you know, they fall through the spectrum and it just points out that the brain is pretty pleomorphic in the way it falls apart and clinicians aren't that good at definitively deciding what that pathological process is while they are still alive.

DR. GOLDSTEIN: Dr. Clark, just one quick question from me and then we will go on. The 17 percent number is in an expert Alzheimer's disease memory disorders clinic. What is the accuracy rate by neurologists in general practice, and what is the accuracy rate by family physicians and internists? Because that is what this supposedly is going to be used for if it is going to be used for clinical utility.

DR. CLARK: Sorry, I wish I could give you definitive answers. I think the closest is really the community-based study reported from the University of Washington basically using the Seattle Group Health Plan. There, their false diagnostic rate, based on those patients who come to autopsy so there are always a whole lot of

caveats on this, is about 20 percent.

Now, this is a group health plan cohort which is drawn from the community, and they are seen by clinicians but the clinician team that was part of that publication that saw all those patients was two geriatricians and one neurologist. So, I wouldn't exactly call that non-expert. But that is what the rate is. So, we presume that in the general community the rate is even higher than that. But part of that, of course, is driven by the need and the time and the resources that those community physicians have.

DR. GOLDSTEIN: We have four more panel members that want to ask. Again, just quick, clarifying questions. Dr. Lu?

DR. LU: You mentioned the primary endpoint will be the negative predictive value. So, you have a cross-sectional study. The negative predictive value depends on prevalence so how do you adjust for that?

DR. SKOVRONSKY: Yes, that is correct, but we think that is the appropriate clinical metric because that is what the clinicians will use when they try to decide how to evaluate an amyloid brain scan. Certainly, I think we would welcome further discussion about exactly how to craft the

statistical package, but it is our impression that that is the most appropriate if we want the clinical utility of the test to be to rule out Alzheimer's disease. But if we are going to use that metric it is important that we have a diverse population and that is why we designed the study that way.

DR. GOLDSTEIN: Dr. Temple?

DR. TEMPLE: I think the last question was making the point that maybe you should be looking at sensitivity and specificity, and then you figure out who to apply it to, to find out about negative predictive value.

But I had a different question. I understand the role of a test like this and choosing people to put into a trial. I don't have any question about that. But you are assuming that figuring out what those 17 people had that wasn't AD is somehow very important to something about them. Can you elaborate that a little bit? I mean, they are demented. What difference does it make what you call it? This is a non-neurologist asking.

DR. CLARK: Right. I mean, I may be too old-fashioned, but I think that there is clinical utility in providing an accurate diagnosis for patients and for their

families. Alzheimer's diseaseB-sure, they all become demented. I mean, it is progressive; it is lethal; and they all end up in the same place, curled up on the bed. But the path that they take to get there differs from the path that a frontotemporal dementia patient takes to get there, and the time course differs.

Alzheimer's disease has a very broad survivability time course. Mean survival is seven years; 8 percent of them within 15 years. Then there is a small percent that can live 23 years. That doesn't happen in frontotemporal dementia. It doesn't happen in dementia with Lewy bodies, as far as we know. Families and patients need to know there is a difference between those two things.

And, currently, at least if you are doing it on label, there is therapy available for Alzheimer's disease. Sure, it is not the most robust therapy, and sure you can't always tell or even often tell whether a patient is on therapy or not, but there are two points to remember and, you know, this is clinical research studies. The first is that when you look at longitudinal studies, this is placebo-controlled patients treated for a year, the ones at the end of the yearB-this is Alzheimer's disease now, were always

performing better, who were treated, than the ones on placebo.

So, if you didn't care whether you were performing better or not then, fine, you could say it doesn't make any difference. But most individuals do care or at least they think they should care and the families certainly care.

The second thing is that Rachelle Duty[?] just published a study showing that survival is increased in patients who were treated with the anticholinesterase medications. Now, in deference to my dear friend Rachelle, there are lots of problems with that sort of design, dropouts and all sorts of things. She adjusted for everything she possibly could but she still came up with about a two-year difference, and I don't think that that was all chance and differential dropout. So, there is benefit to treatment. Treatment should depend on disease diagnosis.

DR. GOLDSTEIN: Thank you. I know that we have panel members additionally that had questions but we are going to need to move on. What we will do is we will take your questions at the beginning of the afternoon discussion session. Please, again, as we are asking questions and as we are getting responses, try to keep them as succinct as

possible. We have a lot to cover.

Thank you. Next we are going to go on to the presenters from Bayer Healthcare. Dr. Anant I think is the first presenter.

Bayer HealthCare Pharmaceuticals

Introduction and Bayer Position

[Slide]

MS. ANANT: Mr. Chairman, my name is Madhu Anant and I am here representing Bayer HealthCare Pharmaceuticals. Bayer thanks the FDA, both the Medical Imaging Division and the PCNS Division, for giving us this opportunity to present an industry position on the clinical development of molecular imaging agents that assist in the diagnosis of Alzheimer's disease.

Bayer, as you may or may not know, has a long-standing history in developing medical diagnostic imaging agents. You have heard from prior presentations that diagnosis of Alzheimer's disease is a clinical challenge. The options today for the diagnosis of dementia, AD in particular, are an important, yet remain an unmet clinical need.

[Slide]

As you saw from prior presentations, a definite diagnosis of Alzheimer's disease requires histopathology, that is, beta-amyloid plaque deposition in the brain. There are currently no diagnostic tools widely available that permit noninvasive, in vivo visualization of this underlying pathology. Bayer is, therefore, pursuing the development of a fluorine-18-labeled tracer, known as BAY 94-9172, previously known as AV1/ZK, to detect beta-amyloid. We have completed phase 1 proof of mechanism studies and are currently in global phase 2 clinical development.

[Slide]

The goal of our development is to confirm that beta-amyloid can be reliably detected. Since the knowledge about the presence of beta-amyloid is clinically meaningful, our phase 3 study that we will presented today is designed to pursue the indication that BAY 94-9172 can detect beta-amyloid plaque deposition in the brain and, thereby, assist the physician in the diagnosis, that is, exclusion or detection, of Alzheimer's disease.

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Therefore, our presentation today covers three key topics that were prior communicated by the FDA to us. Our

phase 3 design is focused on these three key topics which will cover the clinical usefulness, standard of truth, and study population.

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Here is the outline of our presentation. The clinical usefulness of imaging beta-amyloid will be presented by Dr. Ken Marek. Dr. Ken Marek is a clinical consultant to Bayer. The clinical program which addresses the appropriate standard of truth and a proposed phase 3 study design will be presented by Dr. Cornelia Reininger, of Bayer HealthCare Pharmaceuticals. I now invite Dr. Ken Marek.

Clinical Utility

DR. MAREK: Thank you very much.

[Slide]

It is certainly a pleasure to be here to be able to contribute to this very important meeting. Let me just start for one moment by way of disclosures and biases. I am a clinical neurologist. I have had three decades of experience in clinical neurology and neurodegenerative disorders, and have a particular interest and experience in developing imaging biomarkers for neurodegenerative

disorders. I am the president of the Institute for Neurodegenerative Disorders, in New Haven; clinical professor of neurology at Yale University; and co-founder of Molecular Neuroimaging.

This morning I would like to review with you the clinical usefulness of imaging beta-amyloid pathology. My discussion is going to be I think highlighting some of the same issues that you have already heard from Dr. Clark, and I think probably throughout the day we are going to be discussing similar issues, highlighting different concerns related to those issues. Certainly, the best sort of reason or example for clinical utility of beta-amyloid relates to its ability to assist in the differential diagnosis of Alzheimer's disease.

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So, I think what I would like to do in the next ten minutes or so is simply very briefly review the current diagnostic criteria for Alzheimer's disease; an array of new potential tools that have been developed to assist in that diagnosis; focus for a moment on amyloid as a target for pathology; and then, again, focus on the clinical implications of imaging beta-amyloid pathology.

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You have seen this already. I want to, again, just emphasize that the definitive diagnosis of Alzheimer's disease really requires both pathologic and clinical data. The definite diagnosis does require the presence, as illustrated in this slide, of plaques and tangles. Of course, the clinical diagnosis, as we have heard already, is based on comprehensive clinical and neuropsychiatric exam, medical history, medical imaging, and so forth, and is really based on two well-accepted diagnostic criteria.

[Slide]

We have also heard that it is not so easy to diagnose Alzheimer's disease for the clinician. Certainly, there are many patients in whom this may be clear but many in whom it is unclear, particularly early in the disease and particularly those with atypical symptoms.

This slide provides a meta-analysis comparing a number of studies that have compared clinical diagnosis with post mortem findings. You can see that the mean sensitivity in this compilation is about 81 percent, specificity 70 percent. This generally was from centers with considerable experience, not out in the community where, again as was

suggested, this number might be lower.

There also is quite a lot of variance among the centers, but I would emphasize that really specificity was often suboptimal, often lower at the expense of sensitivity. Clearly, this underscores the need for tools that can increase overall diagnostic accuracy.

[Slide]

Since the original criteria, the NINCDS criteria, were proposed, of course, we have learned a great deal. Additional diagnostic tools, many of which were already detailed by Dr. Clark, are under investigation-BCSF biomarkers, volumetric MRI, FDG-PET, of course, beta-amyloid PET, the topic of today's discussion.

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In some ways the current criteria have fallen behind the science. This was I think perhaps best articulated by Dubois et al., in 2007, and it has been suggested that revisions be made to these criteria, taking advantage of these newer tools. Among the tools beta-amyloid-targeted imaging is really the only method that can delineate the underlying pathology.

[Slide]

Again, I am going to review this quite quickly. This was detailed in the earlier discussions this morning very elegantly, but to make the point that, as indicated in this slide from a paper by Braak and colleagues, amyloid deposition occurs early in Alzheimer's disease and then spreads widely into the cortex. It is a hallmark of Alzheimer's disease, present really in every Alzheimer's disease patient. It can be used perhaps to help us to differentiate between dementias, particularly dementias such as frontotemporal dementia. But it is also important to note that it does occur in healthy elderly individuals, perhaps in as high as 25, 30 percent of people over the age of 70.

[Slide]

Now, can we detect amyloid in vivo, in life? That is really the goal that is facing us today. We have heard already about AV-45. BAY 94-9172 is another example of an agent that can detect amyloid. There is evidence from preclinical data for high affinity selective binding in vitro to beta-amyloid in human postmortem tissue; ex vivo beta-amyloid plaque labeling in transgenic mice models; and, of course, evidence in clinical trials as well showing

differences in cortical uptake in subjects with AD compared to healthy subjects.

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This is an example of a typical BAY 94-9172 image. You can see that there is robust uptake in the frontal and temporal parietal regions. You can see as well in the elderly control subject uptake which really represents non-specific activity in white matter and co-registry MR and there really isn't a great deal of uptake that one would see in cortical regions. So, this is reasonably easily interpretable. It is important. This is hot spot imaging so you can see robust uptake that is evident and you can, of course, use that, as indicated in this slide, for registration with MR for structural correlation.

[Slide]

So, that is all well and good. We can potentially image amyloid. Is this useful in any way? Again, I would make the statement that I think imaging the pathology of AD is in, and of itself, useful for the clinician who is particularly faced with a decision with a difficult patient whether that patient may or may not have Alzheimer's disease, and trying to determine really the cause of their

dementia. Having that window into the pathology can be extraordinarily useful.

I think that it provides valuable information as well to enhance our understanding of disease mechanism and, as was emphasized in the previous set of talks, I think it is particularly valuable to be able to have the absence of pathology making a diagnosis of AD unlikely. So, I would suggest that it is both valuable to have the information that you do not have amyloid, as well as whether you do have amyloid, to help you, to assist in that diagnosis.

[Slide]

Let me show you a couple of examples of why that might be true in trying to distinguish between AD and frontotemporal dementia. Again, clinical AD can mimic frontotemporal dementia. The treatment and prognosis, as was just mentioned, is quite different. Here again, a negative scan can essentially exclude Alzheimer's disease, making frontotemporal dementia much more likely.

[Slide]

Perhaps a bigger issue that occurs in clinical practice in the community is trying to distinguish AD from cognitive changes associated with depression. Again,

treatment and prognosis differ considerably in these two entities. Differential diagnosis may be quite difficult for even an experienced physician and, again, a negative scan can assist in making a diagnosis of dementia much less likely, making a diagnosis of depression much more likely.

[Slide]

But in addition to this kind of existing clinical usefulness, or perhaps using the terminology that was used before in addition to the fact that it may be self-evident that imaging beta-amyloid pathology is of value, I think there are other values that may come as we learn more about amyloid imaging.

I think these are of particular value for patients, physicians and caregivers. It will help physicians to expedite referrals to specialty clinics and may decrease time to diagnosis and treatment. Is that valuable? I think it may be valuable. We heard just a moment ago that early therapy may be helpful in reducing long-term disability. I think early therapy in many respects makes sense when you have a progressive neurodegenerative disorder. Importantly, it avoids inappropriate therapy for those who may not have the

diagnosis, again, preventing the cost of these medications as well as adverse side effects. Of course, it provides additional certainty for family members, planning, and reduction of anxiety.

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Again, as was discussed in the previous set of talks, I think the future potential is really where things get very exciting and I think that amyloid imaging has the potential of really assisting in the prediction of those individuals who may progress from MCI to AD. As was indicated in the talks this morning, this is a particularly vexing problem and, again, amyloid imaging has the potential of really addressing that problem directly.

Finally, it supports the development of beta-amyloid-targeted therapies. Again, as was discussed, there are numerous therapies that are under development and, indeed, right now amyloid imaging is being used to assist in the development of those therapies and I think it would assist in two ways. One is to try to identify who would best be in those clinical trials to ensure that the sample is, indeed, as accurately set up as possible, and also as an outcome measure to understand whether these therapies might

change amyloid beta pathology.

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So, I am going to close with this kind of general perspective. A similar slide was shown earlier today. Just to point out the magnitude of the problem, there are about five million people with AD in the U.S. This number is expected to increase to as high as 16 million. If 10-20 percent of AD subjects are clinically misdiagnosed in the community, I think a very conservative estimate, the potential of a PET scan that can identify amyloid pathology is clearly a very substantial clinical value.

I am going to stop there and give this over to Connie Reininger who is going to talk about the selected standard of truth and the phase 3 development program. Thanks very much.

Phase 3 Study DesignB-Standard of Truth

[Slide]

DR. REININGER: Thank you, Ken, for elucidating the clinical utility, and thank you to the previous speakers for doing that as well. The previous speakers have taken most of the introductory words out of my mouth so I will proceed that it is a great pleasure for me today to present the

clinical development program for Bayer HealthCare, the phase 3 program.

[Slide]

Within the presentation I will cover our proposed standard of truth, the indication, go into the major components of the phase 3 trial, which will include the choice of the primary and the secondary efficacy populations, the methodology involved in the establishment of the standard of truth and in the PET visual assessment. I will conclude with a study flow chart that will diagram the sequence of events.

[Slide]

Now, as we have heard this morning, the appropriate choice of the standard of truth is crucial for a pivotal phase 3 program and we have given a lot of thought to the choice of an appropriate standard of truth in our phase 3 trial. We have seen some of the principles that have guided the others in their choice of a standard of truth. These principles have guided us in our present decision and the fact that the standard of truth must be prospectively validated; that the standard of truth should be widely available; and that it should not include any test

results obtained with the medical imaging agent or an agent similar to the medical imaging agent under investigation.

[Slide]

Now, we have heard that the definitive diagnosis, in addition to the clinical diagnosis of probable AD, does require histopathological verification. Although we recognize most assuredly that histopathology is very important, postmortem autopsy is generally not feasible in the setting of a larger phase 3 global clinical trial. By that, I mean a trial of the size of 400-600 subjects, which will not only guarantee the validation of the efficacy, the effectiveness of the agent, but also provide an adequate safety database on which to submit for approval.

We also felt that no other single test that is currently available meets the clinical criteria for a standard of truth. Instead-Band this is also stated in the guidelinesB-an appropriate combination of validated tests may be used as a surrogate standard if known to provide a good approximation of the disease state. In our case, we have chosen the clinical diagnosis as a surrogate standard of truth for our phase 3 clinical trial.

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Now, we have heard a lot about the clinical diagnosis this morning, and in the phase 3 trial our clinical diagnosis, of course, will be based on standardized, comprehensive clinical and neuropsychiatric evaluation which will include, of course, medical history, psychometric cognitive testing, laboratory values and structural MRI, and the diagnosis will be based on the widely accepted, validated clinical criteria.

In view of the limitations of the clinical diagnosis when established by one physician on site at an investigative center, and the fact that the consensus panel approach has been proven to be able to increase the sensitivity and the specificity of the clinical diagnosis to above 90 percent, in our phase 3 trial we intend to use a consensus panel to establish the clinical diagnosis as the standard of truth. Of course, all of the members of the consensus panel will be experts in the field of differential diagnosis of dementia.

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Our proposed indication revolves around the known fact that has been discussed this morning, that beta-amyloid plaque deposition is one of the major hallmarks of

Alzheimer's disease and that the absence of beta-amyloid does make Alzheimer's disease highly unlikely.

Thus, our indication is a pathology detection indication that states that on the basis of presence or absence of tracer uptake, the PET tracer can detect beta-amyloid plaque deposition in the brain. The qualitative sentence is based on the fact that we realize that this diagnostic tool, as all other diagnostic tools and biomarkers, will not serve as a stand-alone in the establishment of a clinical diagnosis but, rather, serve as a clinical diagnostic imaging adjunct to increase the overall diagnostic accuracy of the clinical diagnosis. Thus, we state in our qualifying sentence the PET image findings can assist the physician in the diagnosis, that is, the exclusion/detection, of Alzheimer's disease.

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The phase 3 trial that we have planned will be an open-label, multi-center, single dose trial to determine the diagnostic efficacy in approximately 450-600 subjects. The primary efficacy populationB-I will go into why that is in a minuteB-will consist of probably Alzheimer's disease subjects compared to healthy non-demented individuals. A

secondary efficacy population will include other dementia subtypes such as frontotemporal lobe dementia, Lewy body dementia and vascular dementia.

An important assumption that we will be validating in the course of this trial, of course, is that the uptake of tracer in our PET images does reflect amyloid beta deposition.

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To do this we need a very well characterized population for the calculation of the primary efficacy endpoints. Thus, as positive controls we will be using individuals with a high probability of tracer uptake. By the very nature of their disease that will be probably Alzheimer's disease subjects for a calculation of sensitivity.

For negative controls we will be using individuals with low probability of tracer uptake, so squeaky clean, very non-demented, healthy volunteers and, of course, the recruitment of these will be a major challenge in the phase 3. The healthy volunteers will be used for calculation of specificity.

[Slide]

For statistical demonstration of our endpoints, the co-primary efficacy parameters will be the sensitivity and specificity of the independent visual assessment in differentiating between subjects with known probable Alzheimer's disease and healthy volunteers.

Major secondary endpoints, that I won't go into in detail, will include sensitivity and specificity calculation of both voxel based and volume of interest based quantitative analysis, whereby we will be building threshold values and normative databases to assist our physicians with a more detailed analysis of parameters in intermediate cases in the real world when the tracer is approved and used in clinical routine. We will also be performing a descriptive analysis of tracer uptake pattern in the brain in other dementia subtypes.

[Slide]

A bit on the methodology so that this is a bit more understandable, for determination of diagnostic efficacy the following components will be compared: We will compare the visual assessment of the PET scan results to the standard of truth diagnosis. The visual assessment of the scans will be performed as part of an independent blinded

read. This is a standard procedure in imaging trials. And, the standard of truth diagnosis, as mentioned, will be performed by a consensus panel of experts in the field of dementia.

We know that in order to achieve diagnostic efficacy the quality of both the image data in the clinical trials as well as the clinical data must be absolutely perfect, or as close to perfect as possible. Thus, not only the three independent nuclear physicians but also the consensus panel members will be trained and validated before the initiation of the respective sessions involved in the efficacy evaluation.

[Slide]

I would like to touch very briefly on the visual assessment procedure that we will be using for this study. The tracer uptake, the degree of tracer uptake in predefined cortical brain regions will be analyzed by the blinded readers. Based on total regional scores, the scans will be binarily categorized into a negative scan and a positive scan, and I would like to highlight that this procedure is being fine-tuned and validated as part of our global phase 2 program.

[Slide]

Here is an example of a positive scan and a negative scan so that the advisory committee can see basically what we mean by that. We have seen the scans earlier. We have seen that they are easily interpretable. We have seen that the majority of the scans are either positive or negative. By a positive scan we meanB-and this is represented by the regions of orange and yellow in the cortex of the brainB-that there is a mass of uptake of the tracer in the cortical region compared to a negative scan in which this cortical uptake is restricted to the white matter region, and the region of the cortex, visualized here in this image as dark blue, is free of tracer uptake.

Now, these scans stem from proof of mechanism, a second proof of mechanism study that is performed and was recently presented at the SNM, and correlate to an Alzheimer's subject in the case of the positive scan and a healthy volunteer in the case of the negative scan.

[Slide]

Briefly, I would like to go into the sequence of events in the phase 3 trial. As mentioned, we will be recruiting both healthy volunteers and dementia subjects.

These subjects will be recruited by a dementia expert and on-site physician that will recruit these subjects. The physician does not necessarily have to be a neurologist or a psychiatrist but can also, of course, be a geriatrician or a GP that has a broad knowledge in the differential diagnosis of Alzheimer's disease and other dementias.

The subjects recruited into the trial will undergo extensive clinical and neuropsychiatric evaluation. The physician will determine the eligibility of the subject into the trial based on inclusion and exclusion criteria, and establish an on-site diagnosis. The subject will go on to having a PET scan. All of the clinical, neuropsychiatric and MR imaging data will go onto the consensus panel of experts.

I should note at this time that the consensus panel, of course, will not have knowledge of the results of the 18F team amyloid-targeted PET scan. The PET scans will undergo a blinded read. They will be binarily categorized into either a positive or negative scan.

In parallel, consensus diagnoses will be established. According to diagnosis, these subjects will be put into the primary efficacy population or secondary

efficacy population. Probable AD subjects and healthy volunteers will go into calculation of the co-primary efficacy endpoints; the other dementia subtypes into the secondary efficacy calculation.

[Slide]

To conclude, and this I think has been mentioned again and again this morning, we believe that PET imaging, because it does provide a noninvasive tool for in vivo visualization, is in itself useful. That is our premise. We also believe that our suggested standard of truth, because it is a validated, verified research standard, does provide an adequate surrogate for histopathology; provides the best approximation of the disease state; and, because the disease state does involve the presence of beta-amyloid, it is the best surrogate of beta-amyloid pathology within the constraints of phase 3 clinical development.

Further, the phase 3 trial does facilitate a rigorous verification of diagnostic effectiveness, diagnostic efficacy, thus supporting the proposed indication.

[Slide]

Now, we firmly believe, because of the usefulness

of knowing whether or not amyloid exists in the brain, that PET amyloid imaging will increase the understanding of the disease mechanisms in dementia, many of which are still unknown. And, we would like to contribute, of course, to the body of knowledge around amyloid and amyloid imaging in dementia. Thus, after we achieve our initial claim and validate the tracer on the basis of a detection indication, a detection of pathology indicationB-first things first, then, of course we will be looking at the diagnostic efficacy of the tracer and its efficacy in predicting the conversion of mild cognitive impairment to Alzheimer's disease, and also its value in disease progression, that is, therapy monitoring trials.

With that, I would like to conclude and thank you all very much for your attention.

DR. GOLDSTEIN: We only have five minutes for questions and we have a number of committee members. Unless what you have to present is critical, I would like to be able to get the committee to talk. Go ahead.

Clarifying Questions to Presenters

DR. ZEISSMAN: Thank you. Imaging certainly isn't binary in interpretation and I wonder why you don't choose

criteria for interpretation of scans that is more similar to your consensus panel.

DR. REININGER: The true/false categorization is the only statistical means of calculating the sensitivity and specificity of the tracer. By that, I mean that we are equating a positive scan with the presence of Alzheimer's disease and a negative scan with the absence of Alzheimer's disease.

DR. GOLDSTEIN: Dr. Mattrey?

DR. MATTREY: I have a question regarding the potential use of clinical data as the standard of proof. So, we heard that it is at best 80 percent sensitive and 20 percent false positive, or thereabouts. Right? If then your scan, let's say, is negative how would you dealB-in other words, you are using the clinical as the standard of truth. You are going to have crossover. First, you are going to be, at best, as good as the clinical, which is not very good so we hear. The second is that you will not truly know what is your true false positive and false negative. Are some of these patients going to go to autopsy so that you actually confirm the clinical diagnosis? I mean, where does the follow-up end?

DR. REININGER: There was more than one question in that question so I will answer the question of follow-up. Of course, the follow-up is being considered as part of our development program.

With respect to the clinical diagnosis, I did highlight the fact that we will be using an adjudication committee, a consensus panel of experts, and this approach has been shown by numerous authors in neurodegenerative dementia trials to increase the level of sensitivity and specificity to above 90 percent.

DR. GOLDSTEIN: Thank you. That is going to be probably a good portion of what we are going to be talking about this afternoon. Dr. Herscovitch?

DR. HERSCOVITCH: Just following up on Dr. Mattrey's question, not only issues with regard to diagnosis in patients presenting with dementia, but Dr. Marek pointed out, and perhaps he can provide more information about the presence of amyloid in healthy volunteers which will have a great impact on your specificity calculations. What roughly is the prevalence of amyloid by decade in the 60s, 70s and 80s in your healthy volunteers? I am told that can be quite substantial.

DR. MAREK: Yes, that is a very important point and I think that clearly we don't know the answer fully but it does seem to increase with age. It seems to be particularly relevant, say, after age 70 and it can be as high at that point as perhaps 25 percent. There have been various series that have had some differing information. So, we would expect it to be an important issue as individuals are older and it would have to be considered when one is considering the sensitivity in the study, absolutely.

DR. GOLDSTEIN: Dr. Lu?

DR. LU: Yes, I have a question about your negative control population that you mentioned will be super healthy and there is not any sign of dementia. So, what is relevant for the clinical application for that particular specificity or in terms of differentiation diagnosis?

DR. REININGER: The major purpose of the primary efficacy calculation is to validate that the tracer can do what we say it does, and that is to detect amyloid beta in the brain. The way that we feel is best to do this is by choosing a well characterized subject population and verifying and validating that tracer so that it can be used to answer all of the questions that the medical community

still has in a widespread manner.

DR. GOLDSTEIN: Well, this should make for an interesting discussion this afternoon. Dr. Jung?

DR. JUNG: Given the prolonged survival of Alzheimer's patients, what is the role of serial scans and serial neuropsychological testing? Just because someone has a negative scan initially doesn't mean that over time someone that you think may have mild cognitive impairment or even someone who you think is normal neurologically won't progress in the elderly population.

DR. REININGER: You know, that is a very important question. On the last slide I did address the fact that we will be looking into mild cognitive impairment and the ability of a positive scan to predict conversion. But that will be after we validate the tracer for the detection of pathology indication.

DR. GOLDSTEIN: Dr. Katz?

DR. KATZ: You can't ever do better than the results with your standard of care or, you know, the standard of truth in this case. So, you are limited in how well your test will perform by that. But you are trying to get a claim for, I guess, in a sense aiding in the diagnosis

of Alzheimer's disease. So, how does it actually aid? Is it intended to replace some of the tests that people typically do to diagnose Alzheimer's disease? Because if you can do just as well with the standard approach to diagnosing as you do with your test, what does it add or what does it replace?

DR. MAREK: Yes, I think this is really the crux of the matter. That is a great question, and the issue I think is that the goal here is to establish that this is a marker for the pathology in this very cohort in this study. But in the real world it will aid in the diagnosis because, indeed, as we have discussed, as individuals are diagnosed in the community their diagnostic capabilities would likely not be as good as the consensus panel that we would be using in this particular study. So, it would assist in that way. It would assist as one goes out in the community.

DR. GOLDSTEIN: Again, a great discussion. Unfortunately, the clock ticks on. I know that we have two other committee members who wanted to ask questions. As in the first portion, please hold them and we will get to them first at the beginning of the afternoon, if that is okay.

Next is GE Healthcare, Dr. Brooks.

GE Healthcare

Product Introduction, Proposed Indication and Clinical Development Plan for GE-067

DR. BROOKS: Thank you. Like Ken Marek, I am a practicing neurologist. I am based at Imperial College, in London, and see Alzheimer patients. But I also help direct the clinical neurology program for GE Healthcare.

[Slide]

What I would like to do in my opening talk is introduce you to the product GE-067, and also talk about our proposed indication and clinical development plan.

[Slide]

So, the rationale for developing GE-067 was very clear. As you can see on the left here, we have thioflavin-T which is a benzothiazol and is well known as a histopathological stain for showing amyloid plaques in postmortem slices from Alzheimer patients and other dementias.

Unlike thioflavin-S, which you saw earlier in the presentation, thioflavin-T has actually a very low affinity for neuritic blocks and synuclein so it is primarily a selective amyloid marker, and certainly in the microgram

quantities that we are using it does not stain intracellular tangles or synuclein.

The problem with thioflavin-T is that it is a polar molecule and so it does not cross the blood-brain barrier. So, the chemists under Chet Mathis at Pittsburgh produced a neutral version of this thioflavin, which they called PIB, Pittsburgh Compound B, and they labeled that with carbon-11, and this gets taken up very well into the brain. It binds to beta-sheet amyloid with nanomolar affinity and now 11C-PIB PET is being used really as the standard for imaging amyloid in dementia across the world.

There are many centers in the U.S., Europe, Japan and Australia, all using 11C-PIB. We estimate more than 40 sites in 2,000 subjects have been imaged with this agent and, indeed, it is part of the ADNI protocol which is running at the moment. This should in time generate a great deal of postmortem data which can be compared with the 11C-PIB database that is being assembled by ADNI.

Now, the problem with the carbon-11 version of PIB is that, of course, it is only available locally at the center that is making it. It has a half-life of 20 minutes. However, if you label it with fluorine-18, which is what

GE-067 is, then it has a two-hour half-life and it allows you to distribute it from centers to neighboring PET centers.

Here you see scans in an Alzheimer's patient where there is clear uptake of GE-067 in the cortical areas, compared to an age-matched control where the cortical signal is normal and the main uptake is in the white matter here, so a clear discrimination of Alzheimer's from normal.

[Slide]

So, the indication we are going for is rather similar to the one that you heard from the presentation from Avid. We want to use it purely for the detection of beta-amyloid. We are not using it specifically as a diagnostic tracer. We simply want to be able to categorize patients or subjects as beta-amyloid positive or beta-amyloid negative with this tracer, independent of the actual clinical diagnosis.

Now, clearly, it can be very helpful in management. As people pointed out, if you believe someone to have Alzheimer's and they do not show increased GE-067 uptake it is unlikely that that is the true diagnosis. But also, if you haveB-and this is the problem in most people's

clinicsB-MCI patients where they just have some memory loss but no other features of Alzheimer's you can help to compartmentalize them into those that are amyloid positive and those that are amyloid negative.

[Slide]

So, we are simply advocating a trial to establish that GE-067 is a valid way of detecting amyloid in the brain. Clearly, one can go on and do further steps in the life cycle. Typically, one would have diagnostic progression and therapy monitoring indications. In fact, we feel the greatest utility of this tracer will be in categorizing MCI. We know from 11C-PIB studies that MCIs who are amyloid positive progress far more rapidly than those who are found to be amyloid negative. So, it is a good prognostic marker.

Also, as has been discussed, if therapies come through that are actually useful in clearing amyloids--secretase blockers, immunotherapies--then, of course, we can use GE-067 for proof of mechanism and to show efficacy of the anti-amyloid therapies.

[Slide]

We have done three trials to date with GE-067.

The first two were done with the carbon-11 version since this is much easier to synthesize than the 18F tracer. In this first trial we took 10 Alzheimer patients based on DMS IV criteria and 10 healthy volunteers.

Here you see examples of scans with the 11C-labeled GE-067, again, showing clear discrimination between amyloid-positive and amyloid-negative subjects. The majority of Alzheimer cases showed scans like this and the volunteers like that, though there were a couple of outliers falling into opposite clusters.

As a group, here you see the uptake ratios in the target regions relative to cerebellum. You can see that there is significantly increased GE-067 uptake in the frontal and cingulate areas in these Alzheimer patients compared to the normal group.

We then followed these patients for a year and, in fact, saw no significant change in their amyloid load whether they be Alzheimer or normal subjects. This, in effect, gave us test-retest data for this tracer and across different cortical regions it panned out at about 5-7 percent variability on test-retest using the data from these two trials.

[Slide]

The third study is with the 18F version, the version that we intend to develop and launch. Here, again, you see an 18F scan of an Alzheimer patient and a healthy volunteer, showing clear visual discrimination of the two patterns of uptake.

So, the purpose of this trial is, first of all, to establish the dosimetry of the tracer and we found that in 6 subjects, giving 185 mecabacarals[?], which is the recommended injection dose, there was radiation dosimetry of around 6 milli c. volts which is acceptable to most licensing authorities.

We then took subjects to understand the brain kinetic modeling of this trace. We scanned a group of Alzheimer and normal subjects over four hours, and we estimate that the best snapshot window would be 80 minutes after tracer injection. So, we did a third group of subjects 80 minutes after tracer injection.

[Slide]

We found, as you might expect, that the Alzheimer patients mainly congregated in the amyloid-positive grouping, shown here with red circles, whereas the healthy

volunteers, the unfilled circles, remained the amyloid-negative, though there were one or two outliers in either group. So, again, the main finding of this trial was that there was clear clustering of data in amyloid positive and amyloid negative with a separation between the two ranges.

[Slide]

So, what we wish to do now is an open-label study to show that GE-067 is an effective tool to detect amyloid, and to do this we simply want to estimate the metric as our primary objective. We want to find and define as closely as we can the range of GE-067 binding in Alzheimer's or probably Alzheimer's and in normals, and we want to see whether those patients who have amnestic MCI, defined according to the Peterson criteria, fall into one or other of the normal and Alzheimer clusters, or whether there is a continuum of uptake. And, our prediction would be that they will cluster into one or other group based on 11C-PIB PET data that is emerging.

As secondary objectives we want to see how robust the tracer is. We already have a hint that the test-retest data is around the five percent mark for variability but we want to firm that up by doing further test-retest studies in

Alzheimer's disease. We also want to have blinded visual readers with a panel of readers. We want to check that each reader gets the same result when he looks at a scan and that there is consistency across the readers, and we will compare blinded readers against quantitation.

We also want to show concordance between GE-067 and 11C-PIB, and that is because we do actually believe that 11C-PIB can be justified as a valid standard of truth, and we will go into that a little later. Also, we want to establish that the tracer is safe to use.

[Slide]

So, the trial we are advocating is a relatively small and straightforward one to develop tracer metrics. So, a group of Alzheimer patients will have both GE-067 and 11C-PIB to compare uptake with the two tracers. Another group of Alzheimer patients will have test-retest studies with GE-067. Amnestic MCI patients will be scanned with both these tracers to demonstrate concordance between them and show that they cluster either into an Alzheimer or a normal group.

Normals will comprise two groups, a young set of normals, where we are not expecting to see any amyloid, and

an older set where there may, indeed, be some amyloid and some of them may cluster into the amyloid-positive group in practice.

[Slide]

So, why do we believe 11C-PIB may be a valuable standard of truth? Well, in order to be a standard of truth one has to show there is a clear correlation with pathology. One has to show that we have established valid methods of quantitating 11C-PIB binding. We have to show, like GE-067, there is a clear difference between abnormal and normal ranges for this tracer, and we have to show that the results are reproducible.

[Slide]

I would like to invite Dr. Klunk, who is professor of psychiatry and neurology at Pittsburgh, to come up now and discuss why 11C-PIB may well be a valid standard of truth for our studies.

Data to Support 11C-PIB as a Standard of Truth

DR. KLUNK: Thank you for the opportunity to speak today.

[Slide]

By way of introduction, David already mentioned my

academic interest, but by way of disclosure, though I am not an employee of GE Healthcare, I am a party to the license agreement so, therefore, have a financial interest.

[Slide]

First let me talk about correlation with pathology, and let me say we are doing this. We agree that histopathology has to be a part of the validation of these agents. We are doing it. It is easy to say; it is very tough to do. We have done nearly 300 subjects in Pittsburgh since 2003. Three Alzheimer's disease patients have come to autopsy; zero cognitively normal controls. There have been a number of subjects scanned in ADNI over the past few years. I know of no subjects that have been PIB'd and have come to autopsy. So, it is difficult to gather a lot of these cases. We will continue to gather these as they present.

[Slide]

This was the first case reported in the literature. It was by colleagues Backskai and Dr. Johnson. It is an elderly gentleman who died with dementia with Lewy body as his clinical diagnosis. As we know, 80 percent of them have some amyloid pathology, as did this gentleman. He

had a positive PIB scan in life. This can be quantified. I will go into this in a minute. The postmortem histopathology was quantified. The amyloid was quantified biochemically and there was a good correlation.

[Slide]

I will go through this quickly because I want to spend most time on the case we did here, in Pittsburgh. This is one of our three Alzheimer's cases, the only one in the paper.

We had available to us a whole tissue slab that is in the same plane as we use for imaging. We carefully dissected 25 regions of interest from this tissue slab. We could then correspond them to areas of the MR scan that was done ten months before the autopsy, at the time of the PIB scan and, of course, these two scans are co-registered so we could overlay this on the PIB scan and we could then do the postmortem histopathology in a variety of methods and we could directly compare high, medium and low levels of pathology to the in vivo imaging.

[Slide]

Here you will see some of that. So, this is a postmortem PIB scan. This is antibody specific for A-beta.

I have just moved those plaques over. You can see the spatial correspondence. So, it is not very surprising that if we compare this to an in vivo measure, the distribution-volume ratio of this subject, we see a very nice correlation with postmortem plaque load percent area and the same with PIB.

However, this is not true for all Alzheimer's pathology. We heard about tangles today. At reasonably low doses we don't see any tangle staining with PIB like we do plaques. Not surprisingly, we see no correlation between an antibody specific for tangles in in vivo PIB retention.

[Slide]

But really the crux of it is if we are talking A-beta detection, what is the amount of A-beta in this tissue and how does that correspond to the in vivo measurement? Total A-beta here was measured with an ELISA with an antibody specific for A-beta. I should mention that of that total A-beta in an AD brain about 95 percent is insoluble fibrillar material. Similar to what Dr. Skovronsky hypothesized, this is real data now. You see a nice correlation, very statistically significant between the in vivo measure and the actual content of A-beta postmortem.

Really, you know, it is the content, not the percent area, that I think is critical.

[Slide]

Here is a biopsy study done in Finland, looking at ten patients that were shunted for suspected normal pressure hydrocephalus. Many patients were shunted. Ten of them were brought in for PIB scans, five of which looked like this and had essentially no amyloid, five of which, on this very small percentage of the brain needle biopsy, had substantial amounts of amyloid. All ten received PIB scans.

Of the five that had no tracer amyloid, all five were PIB negative. And, I will tell you how we are talking about positive and negative quantitatively in just a minute. The three that had both clear antibody-designated plaques but also silver stain that Dr. Rebeck mentioned had lots of plaques. All three of them were in the positive range. But of the two that had antibody identifiable plaques but really very few of these cord plaques by silver stain, one was positive, one was not. So there remain questions in this field.

[Slide]

I want to talk about these metrics now and the

distinct differences. In cognitively normal controls this is the challenge. I will show you that it is easy to show the difference between Alzheimer's patients and cognitively normal controls. But you see a continuous distribution. It is a continuous measure, and it is skewed. And, if I show you these images this person will look just like an AD patient. So, how do you distinguish what is positive and what is negative, and how can you do that objectively?

[Slide]

Well, there are several approaches we have taken. This is just one that is easy to describe. You can do standard box and whisker plots. For those of you who have forgotten your statistics, let me remind you that the bottom of the box designates the first quartile; the top of the box the third quartile. The whisker is called the upper inner fence. Anything above that upper inner fence is statistically defined as a mild outlier.

So, what we did iteratively is we stripped off the mild outliers, recalculated box and whisker plots, had a few mild outliers left, stripped them off, and by the third iteration had no more outliers, and then our upper inner fence was chosen as our cutoff. I am just showing it to you

here on the data.

[Slide]

The open circles are cases that fell below the cutoff in each of these seven brain areas, anterior cingulate, frontal, lateral, temporal occipital, occipital parietal, precuneus. The filled circles are cognitively normal controls that fell above the cutoff in at least one brain area. So, you will see some of them below in some of these brain areas but they fell above in one brain area. That is how we were objectively classifying cases as positive or negative.

[Slide]

If you throw on the AD cases you will see in several brain areas that all of the AD casesB-in most of the brain areas all of the AD cases are positive. Here in lateral temporal there is not even any overlap. I have cut off some of the AD cases. I will expand the scale and show the real difference in this data. But also this slide shows you an important check of negative. The highest probability of somebody being amyloid negative is when they are young. Even if they are going to have Alzheimer's disease they don't have the pathology yet.

[Slide]

Based on how old I am in any given year, I define young as less than 55 now. But these are the black circles, and all of them, comfortingly, fall below the cutoffs. There are only about eight of them here.

Robustness, we mentioned that. One measure of that is the Cohen's effect size. That is the measure of the difference between the means normalized to the pooled standard deviation. A big effect is something larger than 1. If we now take all of these controls, the filled red circles and the open ones, whether they are positive or negative, and compare them to the AD cases we see huge Cohen effect sizes in all of these brain areas. If we now just compare what we call amyloid negative, the beta-negative cases, to the AD, they are huger, bigger.

[Slide]

You can do this visually too. So, we presented five readers, after one session of saying this is how you read positive and negative, with three slices, axial, sagittal and coronal PIB scans, along with the MRs, and said rate them positive or negative. Then we took the consensus of the five readers.

This is the objective method I just showed you. Red is positive; 62 controls and a bunch of AD cases, about 25 here. The raters rated all of these objectively classified positives as positives but there was discordance in five cases where the raters rated positive where the objective measure rated negative. But 92 percent concordance in the controlsB-that is tough; the ADs are easy. Everybody sees them as positive and they are grossly positive by the objective measures.

[Slide]

What about reproducibility? We have heard test-retest. I won't go into this. These are a variety of different pharmacokinetic methods to analyze the same data. This is probably the most representative of what we have done in the study, about five percent at a single site, this is in Pittsburgh, within 21 days.

I don't expect you to read this. These are 14 studies, and the point here is that across the world when people look at Alzheimer's patients and controls they see pretty much the same range. There are a few controls that are up in the AD range. There are frequently a few AD cases that are down in the control range. But it is very

consistent across the world.

So, we believe we are beginning to correlate with pathology. We will continue to do this as these very difficult to acquire cases become available. We have established methods to measure uptake and we have talked about how we define positive and negative, not just saying the words.

We have shown a distinct difference between the normal and abnormal ranges and I showed some data on reproducibility and robustness. On availability, I would just like to say as an academic member of the University of Pittsburgh, we have been very successful in making 11C-PIB available throughout the world to other academic centers. So, it is a choice and I will leave it at that.

I would like to introduce the next speaker, Dr. Keith Johnson who is a neurologist at Harvard and a clinician investigator at the Alzheimer's Disease Research Center. He has over a decade of experience in neurodegenerative imaging and has become an expert over the years in PIB imaging, and he is actually the founding organizer of the human amyloid imaging conference that is now entering its third year.

Clinical Utility for Amyloid Imaging

DR. JOHNSON: Thank you very much, Bill.

[Slide]

My purpose is to describe and illustrate with some specific examples my take on the utility of amyloid imaging. I know that a lot of this has been covered and I will try to be very brief, but I want to put in context the discussion that we have been having with a couple of specific examples.

In my view, the utility, as has been mentioned previously by several speakers, lies in the ability to detect or exclude the presence of beta-amyloid pathology, and potentially to rationalize the use of treatment where the underlying pathology cannot be predicted on the basis of available data.

[Slide]

This is a patient of mine who was 70 years old when I first saw him. He presented with anxiety. There was a mild sleep disorder. He had some benzodiazepine dependence and forgetfulness. On neuropsychological testing, he was found to fit criteria for mild cognitive impairment. This was difficult. His IQ was 130. He was a

very intelligent man. And, his concern was clouded by a number of other issues that were present in the clinical history. The family was worried. They wanted to know what is going on. Imagine yourself in this position.

As part of the research protocol, he underwent FDG imaging which showed some equivocal changes in a non-specific distribution. His amyloid image is shown here with abundant take up in the frontal lobe. At follow-up, most importantly, after I saw him for over a year and a half, he clearly had progressed and he now satisfied criteria for Alzheimer's disease and he was started on acetylcholinesterase therapy.

So, this is an example of MCI in which the findings on amyloid imaging could have gone either way. We know that a substantial fraction of these people do not have amyloid in the brain and do not, therefore, have a high likelihood of progressing to Alzheimer's disease. In contrast, the findings here, in my view, place this man in a much higher risk group for developing Alzheimer's disease and that information, to me anyway, seems to offer some clinical utility.

[Slide]

As has been mentioned, the conversion of MCI to Alzheimer's disease has been studied in the context of PIB image findings in this study from the Karolinska. The subjects in the open circles are those who did not convert. You will notice that in the MCI group here, all of those enclosed circles, the ones that did convert were PIB positive. That is, they are above this basically arbitrarily chosen cutoff of 1.5. So, to reiterate, 7 out of these 21 converted to Alzheimer's disease over 8 months. So, the observation illustrated in the previous case seems to be borne out at least in this preliminary series. We are all, of course, hoping for more data as greater lengths of follow-up are able to be observed.

[Slide]

The next case is the opposite situation in which a man who was 68 years of age presented with memory impairments. His referring physician was convinced that this represented Alzheimer's disease. He was winding down his orthopedic surgery practice and there was a great deal of issue about whether his memory impairments portended a much more grave prognosis or whether, in fact, this was a benign memory problem associated with his age or other

factors.

He participated in a research study and the FDG suggested that, in fact, there might be more abnormalities in the frontal lobes, raising the possibility of a frontotemporal lobe degeneration instead of an amyloid beta-based pathology. So, the PIB, shown here, was really able to help us understand that it is actually very unlikely that this clinical syndrome was due to the presence of beta-amyloid.

In fact, over three years of follow-up his illness evolved to a much more typical picture of frontotemporal disease with severe language impairments, trouble with comportment, in addition to his memory impairment.

[Slide]

I will just present very briefly a couple of other cases. It is frequently encountered in the clinic that patients will have word-finding difficulty, trouble speaking, slowness and hesitation, and occasionally accompanied by comprehension difficulty. They are referred in a setting of a diagnosis of possible Alzheimer's disease to have an FDG scan which shows perisylvian left hemisphere hypometabolism consistent with the language impairments that

they are suffering.

The problem is this is a very difficult issue in the field because half of these people don't have amyloid as the basis for their disease. They have something else. In this gentleman we were able to demonstrate that his disorder was one of those in which amyloid-beta seems to be the underlying pathology.

[Slide]

Finally, there is this case of a woman with similar presentation in some ways, with word-finding difficulty, who became much worse and had a basically normal FDG study. In her circumstance the difficulty was, again, a situation where the underlying pathology could have been frontotemporal lobe degeneration of a particular subtype that presents with semantic dementia or it could have been Alzheimer's disease. In her situation progression occurred and over subsequent follow-up she had a much more typical evolution of symptoms of Alzheimer's disease.

So, this is meant to be just to illustrate and perhaps raise in the appropriate context some of the issues that surround the evaluation of these individuals and how the amyloid images could actually be quite useful.

[Slide]

In summary then, we think that the utility is actually to perform a role similar in life to that of a postmortem analysis by demonstrating the presence or absence of the pathology, and to use this to guide management along with other tools that are available. Thanks very much.

Clarifying Questions to Presenters

DR. GOLDSTEIN: Clarifying questions from the committee? Dr. Holmes?

DR. HOLMES: Dr. Klunk, a question on the PIB from the study that was just published, you mentioned that it may be that PIB doesn't bind to all forms of beta-amyloid. Could you just clarify that?

DR. KLUNK: No, I didn't mention that. I said there was one case that was amyloid positive that wasn't PIB positive. But I do agree with the statement. In transgenic mice we have a difficult time of imaging them because they have 1/550th the number of PIB binding sites with the kind of amyloid we find the human brain has. So, there probably will be different forms of amyloid that may not be easily distinguishable histologically that these probes, PIB being one example, can distinguish between tertiary structures.

DR. GOLDSTEIN: Dr. Mattrey, you have a question?

DR. MATTREY: I actually have two questions. If your PIB data seems to be so accurate and yet it is based on clinical since very few have come to pathology, can we assume it is only 80 percent?

DR. KLUNK: You might have noticed that 100 percent of our 30-some Alzheimer's patients are positive by our definition. These are cases enrolled in the study that we felt were prototypical AD cases with a high degree of certainty. At our Alzheimer's center we have a diagnosis of Alzheimer's disease, atypical presentation or atypical course. Those go into a different study. Several of those are negative.

But, remember, this is a tertiary referral center. Our accuracy rate with clinical diagnosis at entry, not at last evaluation but at entry to autopsy, is sitting right around 95 percent in our setting. We don't need this to diagnose a classic AD case in most cases in a tertiary center. In the community it is a completely different story. I think that is what we are trying to do, to even those two out.

DR. MATTREY: And if PIB is in the nanomolar

sensitivity range, what is the 18F G-067's?

DR. KLUNK: I don't have that data in here, but the KIs are nearly identical. It is actually a little better. It is around three nanomolar but usually measures around four nanomolar. But that is within the error of the pharmacology.

DR. GOLDSTEIN: Any other clarifying questions from the committee? Dr. Lu?

DR. LU: Just a question about the AL-03. Do you have PIB data too for that plot?

DR. BROOKS: No, that was not done with the comparator, which is why we are planning to do that with the current study. You have done that, haven't you?

DR. KLUNK: We have done that in Pittsburgh on three subjects, actually four, and I can show you that data this afternoon if you like.

DR. LU: Yes, it is very interesting about the outliers and what PIB would show in the outlier setting.

DR. GOLDSTEIN: Dr. Rudnicki?

DR. RUDNICKI: Regarding your two sets of controls, younger and older, are you just going to compare those two or are you going to use younger controls to compare to your

demented patients who, by your definition, are older?

DR. BROOKS: Well, we want to establish that a proportion of the elderly controls have the same uptake as the young controls, which is likely, and then they can, in principle, be combined and then there will be some outliers in the elderly controls who fall into the Alzheimer type range. So, we can combine them in principle if that is statistically identical.

DR. GOLDSTEIN; Dr. Rizzo?

DR. RIZZO: If we think about imaging for beta-amyloid, is that any more sensitive or specific than CSF measures of beta-amyloid for detecting the presence or absence of disease?

DR. BROOKS: Well, we have not so far done the same things in the same series but, based on what has been published, the imaging appears to be more sensitive and specific. You know, the CSF beta 42 levels do look very good.

[Slide]

DR. KLUNK: This is the data behind the correlation of 11C-PIB GE-067 done on the same day sequentially.

DR. BROOKS: I don't know what the practice is in

the U.S., but we don't routinely do CSF studies on all our Alzheimer's and ethical committees are not that keen on it unless you can justify it.

DR. GOLDSTEIN: Very good. Well, I want to thank all of the industry presenters. Again, we should have a very interesting discussion this afternoon. I am going to invite Dr. Feng, from the FDA, to provide a summary and some considerations as we think about this.

FDA Summary and Considerations

DR. FENG: Hi, good morning.

[Slide]

My name is Qi Feng and I am a medical officer in the Division of Medical Imaging and Hematology Products in FDA. I am going to restate a few points to present our question to the panel for discussion this afternoon.

[Slide]

The major types of potential indication for medical imaging agents can generally be grouped into four categories, outlined here on this slide. Companies have requested that FDA consider approval of their diagnostic radiopharmaceutical specifically for the indication related to the detection of amyloid within the brain the indication

which can group within the category that contains pathology detection indications.

[Slide]

As previously noted, the FDA asked companies to supply the draft indication statement and outline for the phase 3 clinical studies that would help establish the efficacy of the company's diagnostic products. In general, the supplied draft outlines are very limited to summaries and we wish to outline the three major aspects here: The patient eligibility criteria, the standard of truth, and the study's primary endpoint.

[Slide]

Avid has proposed that their product is indicated for PET imaging of amyloid plaque pathology in the brain to aid in the evaluation of patients with signs or symptoms of cognitive impairment.

[Slide]

Avid proposed a phase 3 study that compares PET imaging findings with autopsy findings. Specifically, the company proposed to recruit patients with life expectancy of six months or less. At least one-third of their patients will have a diagnosis of Alzheimer's disease or mild

cognitive impairment and all the patients will participate in the brain donation program.

The standard of truth is the autopsy finding of the extent of amyloid deposition. The primary endpoint is correspondence between the scan findings of low cortical amyloid and autopsy evaluation of plaque burden within the subset of the patients who die within 12 months of their scan. In general, we consider this proposal as reasonable although we have a concern about the feasibility of completing the study.

[Slide]

Bayer's proposed indication notes that the product can detect amyloid-beta plaque deposition in the brain and, thereby, assist clinicians in the diagnosis of either detection or exclusion of Alzheimer's disease.

[Slide]

The Bayer proposed a phase 3 clinical study that compares PET imaging findings to clinical diagnosis. Specifically, the study will enroll healthy volunteers and a variety of patients with cognitive impairment. The proposed standard of truth is presence or absence of a clinical diagnosis for probably Alzheimer's disease based upon the

expert panel consensus.

The primary endpoint is sensitivity and specificity within the subset of patients who are assessed as either healthy or diagnosed with probably Alzheimer's disease.

We are particularly concerned about this type of study design because a clinical diagnosis may not be a fully reliable marker for amyloid, especially among the patients who may have amyloid in the absence of a diagnosis of Alzheimer's disease.

[Slide]

As shown here, in this slide, GE Healthcare proposed that their product is useful for the detection of beta-amyloid deposits in the brain.

[Slide]

GE proposed a clinical study in which patients will undergo scanning with both the investigational agent as well as the 11C Pittsburgh compound agent. Specifically, the study will enroll healthy volunteers and patients with mild cognitive impairment or clinically diagnosed Alzheimer's disease.

The standard of truth is investigation of the

reference imaging agent, 11C Pittsburgh compound. The primary endpoint is to compare imaging findings between the 11C Pittsburgh compound and the study imaging agent.

In general, this approach might be a reasonable one if sufficient data are available to verify the use of 11C Pittsburgh compound as an indicator for amyloid.

[Slide]

The clinical value of amyloid detection is the focus of our questions. As noted here on this slide, the clinical value of diagnostic information should either be self-evident, such that diagnostic efficacy studies do not need to establish the value, or if the clinical value is not self-evident, then the clinical study should establish the value of the information. With this in mind, we propose our two major questions.

[Slide]

Our first question is to what extent, if any, would an indication for use of an in vivo diagnostic agent for detection of cerebral amyloid provide useful clinical information?

If the general response is one of no value, then we anticipate the company would need to conduct studies that

establish the clinical value of the information. If the response answer is generally yes, then we move on to our next question.

[Slide]

Our second question relates to the development of the performance characteristics. Specifically, if an in vivo diagnostic agent is clinically useful in detection of cerebral amyloid, what should be the standard of truth of a phase 3 clinical trial study?

[Slide]

Our final request today relates to consideration beyond our first two questions, specifically, we request that the advisory committee comment on the strengths and weaknesses of the clinical trial proposal supplied by the companies, with special consideration of patient populations, the standard of truth and the primary endpoints.

Thank you for your attention, and we are looking forward to the extensive discussion this afternoon.

DR. GOLDSTEIN: We are going to take our lunch break now. Because we are breaking a bit early, we are going to try to get back a little early so that we can have

more time for discussion. It is coming up on 12:15 so we will come back at 1:15 when we reconvene in this room in an hour.

Please remember, if you are going out, to take everything with you because this room is going to be secured by the FDA so you won't be able to get back in here until the room opens up again. Also remember, panel members, very important, we have no discussions about this amongst ourselves or with anybody else while on break. All the discussions we have, have to be on the record. So, talk about football; talk about Duke basketball; talk about whatever else you want, just not this.

[Whereupon, at 12:15 p.m., the proceedings were recessed for lunch, to reconvene at 1:15 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. GOLDSTEIN: We are ready to reconvene. Good afternoon. I hope everybody is having their postprandial sugar rush now.

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

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

Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not

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

The FDA and this committee place great importance on this open public hearing process, the insights and comments provided to help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair, me, and thank you for your cooperation.

So, for this open public hearing portion we have, I believe, three speakers that will be speaking. They will each have ten minutes. They will get a one-minute warning before their ten minutes are up. We will then allow the panel to have a few minutes to ask any clarifying questions. So, our first speaker I think is Bill Theis, I believe.

DR. THEIS: Thank you, Larry, and thank you to the committee for giving me this time. I would like to compliment the committee on calling this meeting. I think the timing is really appropriate.

But even more, I would like to compliment the committee on their wisdom because they have identified me as number one, and I am going to try to live up to that really elevated status.

The reason that I think we were invited to talk had more to do with the fact that we are regarded as the voice of the Alzheimer public and we try to be as effective as we can in that. In that context, the public has very little interest in the details of what happens in meetings like this. Their major interest is progress and we certainly share that.

But on the topic of amyloid imaging, the Association has been involved for a number of years and, in fact, I think is the first organization to invest heavily in basic research in amyloid imaging and continues on to fund the amyloid imaging add-on to the ADNI study with the single biggest grant the Association has ever given.

So, in terms of conflict of interest, I don't have

any company affiliation or any stock ownership, but remain enthusiastic for the technology involved in amyloid imaging.

I think that this is a very important area for a couple of reasons. It is going to likely have long-term clinical utility, but we probably aren't going to know that clinical utility the first day that we are able to use these kinds of diagnostics. But we are at a point where we are beginning to see really important clinical studies, both drug trials and longitudinal studies, that will be highly dependent on amyloid imaging as part of the data that they collect.

We heard from Dwaine Rieves at an earlier meeting this week that for a test to be recognized in a trial setting it needs to be broadly applicable. So, I don't have a particular favorite in this race, but I think it is very important that we come to closure around some of the decisions. We have heard a number of recommendations for how we would do a phase 3 trial and I am not going to embarrass myself or the Association by trying to weigh in on that because I am not enough of an expert. But there are plenty of experts around and I have great faith in their ability to arm wrestle through what the proper design is.

The one thing that I think is key is that we have to have better ways of identifying people with Alzheimer's disease, better ways of treating people with Alzheimer's disease, because the public health imperative is just immense and if we don't get that done fairly quickly we are going to end up bankrupting our medical care system.

So, in talking to the committee, the one thing that I really want to emphasize is that I think you should be as careful as you need to be. You should be as rigorous as you need to be, but you should also have a distinct sense of urgency and get to the end of this discussion because if we come back three years from now and are having the same discussion with no new data we will have failed in our mission to help the American public.

With that, I would be happy to take questions.

DR. GOLDSTEIN: Any committee questions for Dr. Theis?

[No response]

DR. GOLDSTEIN: Thank you. The next speaker?

DR. BUDD: Good afternoon, everybody. My name is Samantha Budd. In terms of conflict of interest, I am a full-time employee of AstraZeneca, today representing

AstraZeneca.

I would like to thank the members of the advisory committee, as well as the FDA, for allowing us to comment on the very important topic of beta-amyloid imaging radioligands for the diagnosis of Alzheimer's disease.

I have just a few slides to show you today in the spirit of sharing information and forwarding the advancement of science in the field.

So, the aim of AstraZeneca as a pharmaceutical company is to bring effective new medicines to patients. As we have heard this morning, there are approximately some five million Americans that are diagnosed with Alzheimer's today. I don't know if we really heard that this is actually a terrible disease that impacts the patients, their caregivers and society with both emotional as well as financial impacts. It is an issue that is not going to go away and, indeed, as we become older the number of patients are set to double in the coming years.

At AstraZeneca we recognize the importance of this problem and the benefits that biomarkers may bring to Alzheimer's disease. We have heard comments regarding how biomarkers may enable us to measure the effectiveness of

therapeutic intervention and that is our ultimate aim, as well as providing definitive diagnosis. Very importantly, as treatments become available that may slow or even stop the disease, early diagnosis is expected to enable the efficacy of those treatments. It is also towards improving the knowledge on disease pathophysiology, and to monitor disease progression.

The presence and detection of amyloid, as we have heard this morning, is currently postmortem diagnostic criteria, and is well believed by the field and by many pharmaceutical companies to have a central role in disease pathophysiology. There are a large number of therapeutic trials focusing on this.

The characteristics of a good biomarker for diagnosis of disease have previously been established, but with regard to Alzheimer's disease, we believe that an ideal PET ligand is one that has high sensitivity and specificity for beta-amyloid detection, as well as high contrast. By high contrast, I mean signal to noise ratio.

It should also be possible to detect low levels and changes of amyloid and amyloid burden. These ligands should have properties supporting quantification and ease of

use. Here we refer to reversible binding to amyloid, as well as binding kinetics suitable for reliable quantification, and something I haven't heard mentioned this morning is with regard to short imaging times. We believe it is quite important to reduce or to improve the comfort of patients undergoing this type of procedure.

It is also important with regard to good reproducibility, such that these ligands give reliable measurements in repeated situations. Finally, it is very important that these ligands are safe to use for patients and people who are using them, and that there is ease of distribution across medical centers. For early diagnosis and differentiation of neurodegenerative diseases we also believe high specificity is needed.

The kind of process that you would use to improve upon the properties of a ligand is shown in this kind of scheme, and tests include things such as iterative medicinal and synthetic chemistry, as well as improving binding properties and assessment of binding to amyloid forms, as well as showing and testing for selectivity and specificity in animal, human and patient brain.

This takes several years and at AstraZeneca we

have, indeed, understood the importance of this approach and since 2003 we have tested thousands of compounds towards this end. We have today one 11C and one 18F ligand that I would like to share a little bit of information about with you.

The 11C ligand we call AZD2184. It is an improved 11C amyloid PET ligand in that its preclinical properties have high specificity, high affinity and rapid reversible binding to amyloid. This translates in the Alzheimer patient brain, and here you can see a picture, to very high contrast. That is, low background in regions that you would not associate with amyloid plaques, as well as binding in regions where you would expect amyloid plaques.

Moreover, the specific binding peaks are achieved in under 30 minutes towards that short imaging aim that I discussed. Finally, you can see on the graph on the right two superimposed kinetic lines, red and black, showing very good reproducibility in clinical trials.

11C, as we also heard discussed this morning, is restricted only to medical centers that have radiochemistry on site. So, to achieve our aim of wider availability of a diagnostic and to reach more medical centers across the

U.S., we went further and improved upon an 18F ligand. Our 18F ligand, which we call AZD4694, similar to the 11C ligand, has very good preclinical properties such as reversible binding and high contrast. It detects amyloid with high specificity and low background, and we believe that this high contrast is very important for eventual early diagnosis.

Similar to the 11C in non-human primate brain, we see good brain uptake and rapid washout. So, again, those short imaging times for patients. The preclinical data will shortly be validated in the clinic.

This is the kind of tool that we would like to share with the community and that we believe will be important in terms of early diagnosis of Alzheimer's disease.

So, to recap on our level of commitment, we have spent this week together with the community, with the Alzheimer's Association Roundtable and the ADNI initiative to address the questions of diagnosis in Alzheimer's disease. We have already heard several times today that amyloid is the criterion at postmortem but we believe that amyloid imaging in living patients is crucial for early

identification of the right patients and early and appropriate treatment intervention, and AstraZeneca is committed to bringing new medicines to Alzheimer's patients and making early diagnosis a reality.

With that, I would like to thank you for your attention and take any questions.

DR. GOLDSTEIN: Thank you. Any questions from the committee? Yes?

MR. BRIDGWATER: What is the half-life of your 18F ligand?

DR. BUDD: The 18F ligand as a class has approximately a two-hour half-life.

DR. GOLDSTEIN: Thank you. Yes, sir?

DR. HERSCOVITCH: Could you comment on the chemical structure or class of these two radiopharmaceuticals?

DR. BUDD: As a non-chemist, I could not. Maybe we can take that later.

DR. GOLDSTEIN: Dr. Temple?

DR. TEMPLE: The potential uses you identified were to choose the right patients to put into trials and then to use it to choose patients once you had a way of forestalling progression. You didn't discuss any of the things that have

been discussed this morning about pinning the diagnosis down, distinguishing Alzheimer's from other dementias, and things like that. Do you have any comments on that aspect of it?

DR. BUDD: I think certainly to be choosing the right patients to include in clinical trials is a component of that, and I think what we heard this morning is the foundation of pinning down the first step.

DR. GOLDSTEIN: Very good, thank you. Our last speaker?

DR. WEINER: I have slides, if my slides could be put up, please? Well, if this were baseball number three would be a good spot, but like the Avis ads, I will try even harder and harder.

My name is Mike Weiner. I am a professor of radiology at the University of California, San Francisco, and I am principal investigator of the NIA-funded Alzheimer's Disease Neuroimaging Initiative. As you can see, I consult for all of the companies that made presentations this morning. I am a site PI for an Avid study and I have a relationship with Avid for an SBIR. I am talking to Bayer/Schering about being a site PI for their

studies, and I consult for a wide number of pharmaceutical companies, and ADNI receives funding from 15 other pharmaceutical companies that are developing drugs for Alzheimer's disease.

So, the FDA should approve agents which detect amyloid in the brain. The FDA should approve these amyloid-PET imaging agents for detection of amyloid in the brain to aid in the diagnosis of Alzheimer's disease and dementia. The primary use of these agents, I believe initially will be to assist in ruling out the diagnosis of Alzheimer's disease.

When the FDA considers approval of these agents for detecting amyloid in the brain I think that the following criteria should be used: Obviously, safety; evidence for specific binding to amyloid in vitro; evidence of binding to plaques in humans and animals in vivo and in vitro; a lack of signal in animals without amyloid; a lack of signal in young, healthy human controls who do not have amyloid; and a high signal in humans with a diagnosis of Alzheimer's disease where we know that there is a very, very high rate of amyloid pathology in their brain.

I think that doing sensitivity/specificity studies

in humans where you are comparing Alzheimer's and FTD and Lewy body to elderly controls are not that useful because we know already, from pathology studies and the 11C-PIB studies, that something in the range of 20-40 percent of healthy, normal, elderly controls in the same age range as people with Alzheimer's disease have high amyloid levels in their brain. The clinical significance of that is to be determined in future studies, but that makes it very difficult to evaluate a sensitivity/specificity study where you are using age-matched controls to your Alzheimer's group.

A good standard of truth is autopsy, and autopsy studies would be extremely useful in this study. I personally don't think that they should be required for FDA approval. I think that the autopsy studies should be done in the post-approval stage. I think that requesting autopsy studies will unnecessarily prolong approval of these very important agents that we are very anxious to get out in use now.

So, why should the FDA expedite approval of these ligands in the way that I am proposing? Firstly, just to give you some background, currently Alzheimer's disease is

perceived by most physicians and the public as a disorder associated with dementia for which there is no effective therapy. In fact, we know that Alzheimer's pathology exists in the brain for many years prior to any cognitive decline, prior to any symptoms and long prior to the development of dementia.

We also know that there are more than 20, probably now more than 30 disease-modifying treatments in clinical trials in human, in phase 1, phase 2 and phase 3. So, we are in a totally new era now with disease-modifying treatment development.

Now, we all know in medicine that in general early treatment of any disease is good. I should say that there are concerns now that in the clinical trials that we are doing with disease-modifying agents in patients with Alzheimer's disease who are demented we are essentially treating brain failure. It is perhaps akin to taking a patient who has had two MIs and who is in an ICU with heart failure and treating that person with statins to remove the cholesterol from their arteries that has caused the heart attack. In other words, it is possible that the treatment trials that we are now doing with disease-modifying agents

are difficult to show efficacy in because so much damage has been done, and we need to identify the disease early and treat people at an earlier stage. This is a very big issue in our field.

Increasingly experimental data will support the view that biomarker measurements, including amyloid imaging, are useful in detecting Alzheimer's pathology and predicting risk, especially at an early stage. Development of effective therapy is going to accelerate the awareness of need for early detection and treatment. And, during the next several years it will be important to shift the perceptions within the public and medical community concerning AD.

Therefore, it is generally agreed in our field that there is an increasing need to, first, develop methods and criteria for diagnosis of Alzheimer's disease prior to the development of dementia; second, to shift the public and medical awareness that AD pathology takes years before symptoms and impairments develop; and, three, to develop methods which predict risk in people who are not demented. And, 18F amyloid imaging is clearly a very important component of this process. It may very well be the most

important component of this process. We don't know.

So, how will the compounds be used once ultimately they are approved? In my view, their initial use will be to rule out Alzheimer's pathology in subjects whose condition could be due to Alzheimer's disease or could be due to other causes.

These subjects would have major concerns about the possibility of having Alzheimer's disease. For example, people who have strong family history who have symptoms, they could be reassured that they could be told that they do not have amyloid pathology in their brain, and especially in those kinds of people who are interested in making future plans which would require a high level of cognition. That is a very practical use of these agents, and there are many other uses.

Another way that they will be used is in clinical trials. We now have two phase 3 trials of disease-modifying drugs. These trials are both using 18F amyloid imaging agents in their trials, and they will be used in many ways as predictors of future decline as potential outcomes to detect reduction of brain amyloid load. That is kind of a hope. And, FDA approval of these agents, the sooner the

better, will hugely facilitate their use in treatment trials because it increases their use, it increases their availability, makes them less expensive, and so forth.

So, other ways that compounds will be used is that ultimately they may be used in the diagnosis of Alzheimer's disease at an earlier stage than dementia. This is the so-called Dubois criteria approach. They could be useful for prediction of risk for cognitive decline and dementia due to Alzheimer's disease in mildly impaired subjects or even in normal subjects. Having a high brain amyloid load in a 65 year-old subject might indicate that this person is at much higher risk to develop cognitive decline with dementia over the next 10-15 years, and that is the kind of thing you would want to use in a prevention trial.

So, although this is not an immediate use, what I am describing on this slide, the FDA approval of such agents will hugely facilitate their use in research and facilitate the above.

Now, I personally don't think that FDA should require an extensive autopsy study for validation of these agents. I think it is something that could be done or should be done in the post-approval but I don't think it

should be required for approval. I think it will unnecessarily prolong approval of the agents, and I think it deprives the community of rapid access to these important agents.

Now, some may think that the amyloid hypothesis is relevant to this discussion. The amyloid hypothesis, for the few people in this room who may not know what this is, it supposes that amyloid accumulation is a causal factor in Alzheimer's disease. This hypothesis has not been proven. We have a lot of work to do to establish it, but we know that Alzheimer's disease does not develop in the absence of amyloid accumulation. You have to have amyloid in the brain in order to have pathological Alzheimer's disease. Therefore, the diagnostic importance of amyloid imaging is not in any way linked to the validity of the amyloid hypothesis.

Now, once these agents are approved and available, without a doubt they are going to be misused because all medical tests are misused. Some physicians are, unfortunately, going to use these to make a diagnosis of Alzheimer's disease, and that is too bad but that is going to happen. Some are going to make false claims and promote

their misuse for commercial gain and we should do everything we can to stop that. That is an unfortunate consequence of the way our system works. This is going on with all kinds of diagnostic tests, and I don't think that this problem should prevent rapid approval of the agents. And, I don't think that any of the validations that are done, that are proposed by any of the companies, are going to do anything to prevent these misuses.

So, in conclusion, I think that the FDA should quickly approve the 18F amyloid agents. The criteria should be binding...

Clarifying Questions to Presenters

DR. GOLDSTEIN: Thank you. Any questions from the panel? Dr. Rizzo?

DR. RIZZO: How do you make the convincing argument that not approving right away deprives people of clinical benefit when there is no clinical benefit yet that has been shown?

DR. WEINER: Well, I think there is a clinical benefit. I think that the first question is, is it important to make an accurate diagnosis of Alzheimer's disease? The fact is that lots of time and energy is spent

by clinicians trying to work up patients and diagnose Alzheimer's disease. So, nobody would argue that it is important to make the diagnosis.

The next question is, is detection of amyloid in the brain a useful tool in performing that diagnostic evaluation? And, if you ask a lot of clinicians they are going to say, yes, this would be a useful tool. In places where 11C-PIB studies are available, they are finding this sometimes a useful tool. So, it helps certainly to rule out the presence of Alzheimer's disease. You saw some examples of that earlier. So, I think it is something that would be clinically used immediately, and that is why I think approval should be done quickly.

DR. GOLDSTEIN: Dr. Holmes?

DR. HOLMES: Yes, having said that, what would be an acceptable false-negative rate in your opinion? That is if the important thing is to rule out with a negative study, what would be acceptable to you? One percent? Two percent?

DR. WEINER: I have to think through that, go through the literature and calculate that. If I was working out a company's formal stat plan I could give you that number, but I haven't thought of that.

DR. GOLDSTEIN: Dr. Temple?

DR. TEMPLE: I understand that you thought the important early use is to rule out Alzheimer's, and other people have said that also. But some of the uses you were talking about later, like early intervention, are actually about learning whether they do have it.

So, my question is in these early studies, even if they are mostly directed at no amyloid disease, wouldn't you want to include a reasonably broad range of patients in them so that you could get some idea of the sensitivity and specificity? I mean, you characterized using that information as misuse, but if properly informed and analyzed it might not be misuse; it might be just informed use but imperfect because it is not a 100 percent signal. So that is my question.

Some of the proposals here were to study people with pretty well documented Alzheimer's disease and completely normal people. An alternative is to study people with a wide range of dementias so you do get some idea of what the test does in the presence of a wide variety of dementia and you could say something maybe about sensitivity and specificity. It didn't sound to me like it would be all

that much harder to do that.

DR. WEINER: I have no argument with that, and I have no argument with the more data that people get and the more different groups they study, the better. I was simply trying to address where the bar should be for approval.

DR. TEMPLE: I understand.

DR. WEINER: And the minimal, simplest thing to do for approval is simply to show that people with Alzheimer's disease have a high signal and people who we know have no pathology have low signal. If you establish that, to me and I think to most clinicians, that is very, very useful and we can go forward from there.

DR. GOLDSTEIN: Any more questions? Dr. Lu?

DR. LU: Yes, Michael, you mentioned that people see the PET and it is useful because it changes their clinical position. Is there any study or evidence to document this?

DR. WEINER: No, because right now there are a number of amyloid imaging agents that are being used. They are all being used in research settings. At UCLA there has been a lot of work done with FT DMP. Whether it is amyloid specific or not could be argued. There is a huge experience

now with 11C-PIB that you have heard a lot about. But they are all in research settings. They are all done under informed consent. I am sure that all the informed consent documents for all those studies say this will be of no value to you, and people have to be very careful about using that information for clinical purposes.

On the other hand, we also know that the reality is that as these groups are doing research studies, and such research studies are going on in the Bay area, for example, where patients with frontotemporal dementia are having 11C-PIB scans. These are collaborations between Bruce Miller and Bill Jacobs, so a completely research NIH-funded study. But they can't help but notice these results, and if you have a patient who has FTD symptoms and they show a really bright PIB signal, well, that is causing people to rethink things. And, if a patient has a diagnosis of Alzheimer's disease and they have a really absent signal, once again, it causes them to rethink things.

You can see Dr. Klunk and Mark Minton, who are in these research settings, nodding their heads. So, this is all kind of anecdotal. The reality is that those of us in the field know this is going on and can see how this can be

used. Nobody is saying that you would want to use these agents on every single patient who walks into the clinic. Intelligent clinicians would use these in a highly selective way initially to rule out the disease in situations where the diagnosis is quite uncertain. That is the big initial use.

Then, as there is more and more experience with these agents, and more papers are written, and there is more autopsy follow-up, then the field will fill in and we will figure out all kinds of other ways that they would be used in the future. And, the quicker we get moving on that, the better, which is why I am advocating very rapid approval.

DR. GOLDSTEIN: Other clarifying questions from the panel? Dr. Lu?

DR. LU: Maybe I just go too far because your ADNI has been more than a year and PET was at baseline of your scan. I don't know if you are ready now to share ideas, you know, about prognostic-related information.

DR. WEINER: Dr. Bucholtz is here and he remembers well when we conceptualized the Alzheimer's Disease Neuroimaging Initiative the FT DMP studies had just gotten started. The 11C-PIB studies were in their infancy. We

talked about whether it was feasible to include some of these agents in ADNI at the time, and the idea of scaling these up in a multi-site trial was unclear.

But then, within a year of our funding it became clear that 11C-PIB was a valuable tool and that there were enough centers in the United States where we could do a pilot study. Therefore, we received funding from the Alzheimer's Association and additional funding from GE to do a pilot study of 11C-PIB in about 100-111 patients. And, they have been done at baseline and, in general, the Alzheimer's patients are positive and the controls are negative and the MCIs are showing a range in between, and we haven't started looking at how the scans predict longitudinal change.

But I can say this, that we are currently in very active discussions with all of our 15 pharmaceutical industry partners to fund a renewal of ADNI that would begin in 2010. There is unanimous enthusiasm that we must be doing 18F amyloid imaging on all 800 or 1,000 patients that would be enrolled in the ADNI renewal. 18F amyloid imaging is so important in this field that we would want a baseline scan and some longitudinal scans on every subject that we

enroll at all of our 57 or 60 sites in the U.S. and Canada.

So, we all want to see these agents become useful in the field and get away from just pure research settings and get out there so that we and the pharmaceutical industry can use them in their trials. That is the level of enthusiasm for the need of these drugs.

DR. GOLDSTEIN: Dr. Katz?

DR. KATZ: Yes, there has been a fair amount of discussion so far, or at least the topic of autopsies has been discussed by a number of people. You recommend that the agency not require the autopsies before approval. We heard that at Dr. Klunk's center a couple of patients over several years have come to autopsy. If I understood it correctly, the proposal from Avid suggests that they are going to get autopsies on all their patients within, I think, 1-12 months of enrollment, or whatever it was.

So, I am wondering do we have difference of opinion about how easy it is to get autopsy in these patients, or is it widely understood that it is very difficult? If so, how does the Avid protocol fit into that? I don't know if you want to talk about that now or in the discussion period but it seems to be a real issue as to

whether we should or should not require it. Everybody agrees it would be good to have the autopsy correlation but there seems to be a difference of opinion about how easy that is to get. So, I am just wondering what people think about that.

DR. WEINER: Obviously, I think the Avid people can better respond to that than I, but for me, I think, first of all from a purely scientific point of view it would be extremely useful to have autopsy validation of any imaging agent. I know that Avid has high enthusiasm that this can be done quickly and, you know, perhaps they are right.

My own view is that, from a regulatory point of view, I don't personally see that as necessary and I see that as something that might slow things down. So, I think that the agency ought to allow more rapid approval without autopsy confirmation based on the kind of approach that I described. Then you could require autopsy validation studies in the post-approval phase.

DR. GOLDSTEIN: I think Dr. Temple had one more point and then we will move on.

DR. TEMPLE: Well, I can tell from your first slide that you know everybody in the field so you are the perfect

person to answer my question, which is would it be of interest if several of these diagnostic tests were used in the same population so that you could see how they compare?

That would probably be of interest both for the initial goal you have, which is ruling out, but also for assessing sensitivity and specificity in more complicated cases. I mean, I know it is hard for companies to cooperate on such things but I just wondered what your view of being able to do it was if you could.

DR. WEINER: I think the more data, the better. Certainly, at some stage of product development various academic or other institutions start doing comparison studies between treatments and between diagnostic agents, and I think that is all something to come.

Speaking for our approach in the Alzheimer's Disease Neuroimaging Initiative, our pharmaceutical industry partners have suggested to us the best way for us to handle the issue of having multiple vendors with multiple diagnostic agents. Assuming our project does get funded and we have 57 sites, we would be willing to talk to any and all of those vendors that have such agents, and we would probably be using multiple agents in the Alzheimer's Disease

Initiative. I doubt that we would be scanning the same subject with two products. That is beyond the scope of ours but at least there would be multiple agents being used in the same very large clinical trial which would provide useful information.

DR. TEMPLE: So, do you think it would be too burdensome to patients to do two scans? I mean, it is not like two therapeutic treatments; it is just a scan.

DR. WEINER: I think, aside from dosimetry issues, it is feasible. That is a feasible thing to do. I personally would not require that for approval but I think it is something that would be interesting.

DR. TEMPLE: Yes, I wasn't so much thinking of a requirement but, you know, this is the era of comparisons. So.

DR. GOLDSTEIN: Dr. Mattrey?

DR. MATTREY: Yes, I am just going to take advantage of the fact that you are up there, Mike, because you are not going to be part of the discussion maybe later, or maybe you will. But I am struggling with the concept of making a claim that you can image amyloid without knowing your imaging amyloid, based on clinical data that is, at

best, 80 percent, according to the analysis that was presented this morning. And I realize that sensitivity ranges from 40-95 percent, as I heard. So, how can you justify saying you have an amyloid imaging agent without knowing what it is actually imaging?

DR. WEINER: Well, I was involved in the very early development of MRI, as you know, and we approved a lot of MRI based on-Bwe never did autopsy validation on use of MRI to detect anything, as far as I know.

That is one answer. I mean, I think we know that Alzheimer's patients have amyloid, and we know from the 11C-PIB studies that the vast majority of patients with diagnosed Alzheimer's disease are positive. They have positive amyloid scans. And, the experience that the other vendors are having is the same.

So, to me, there is a certain degree of face validity here that these agents are detecting amyloid and if you see a lot of positive signal in people with Alzheimer's and you see a lot of negative signal in people who are controls, to me, that is good enough to make a useful clinical tool. Other people might want us to go through a couple of years of autopsy validation, which is going to be

positive in all these studies, so then two years from now we will be in the same place and, to me, that just slows the whole thing down. I don't think it is necessary. Maybe I didn't answer your question.

Panel Disease/Committee Questions

DR. GOLDSTEIN: Very good. I guess that is one of the topics for conversation. If the committee has no other questions of the speakers, then we will conclude now the open public hearing portion. This portion of the meeting being over, we will no longer be taking any comments from the audience. The committee is now going to turn its attention to address the task at hand. We have three questions specifically that we need to deal with and we will, hopefully, be carefully considering all that we have heard.

As I said, the public attendees can no longer participate in this portion of the meeting. Also, just as a general rule for the people in the audience, sometimes comments that are made you agree with, sometimes you don't. Sit on your hands. Don't clap, don't cheer. This is a scientific discussion and, hopefully, not an emotional one.

We have three questions that we need to deal with.

We have heard a lot. Again, I think it has been a wonderful discussion and wonderful background but I think we need to sort of step back a little bit and crystalize what the issues are. In that way, we can sort of deal with them in a logical way.

The first question I think is can these tracers identify amyloid plaque in the brain? That is the first fundamental question that we are being asked, and that is one of the things that was being talked a lot about.

If we can, then what is the standard of truth for determining whether you can or cannot reliably image amyloid in the brain? That is part (a).

Part (b) is assume that you can reliably, with a given sensitivity and specificity and positive/negative predictive value, image amyloid in the brain, then what is the clinical usefulness of that? I think clinical usefulness really depends upon who the beholder is and how they are going to use it clinically.

So, we have one thing where we have folks in tertiary care who are Alzheimer's disease memory disorders experts and then we have the rest of the world, family physicians and internists. From my reading through this,

the idea would be that this would in some way help family physicians and internists make a diagnosis of Alzheimer's disease if they can image amyloid. So, we have to step back and look at it from those two standpoints.

The other thing we have heard a lot about is, well, is this a useful research tool, and apparently it is potentially quite a useful research tool in one way or another. In a sense, you can say that we do a clinical trial, you image it, you don't image it, you treat or don't treat. That is an empiric. If you show that a treatment works, if you can image this, whatever it is imaging, well, that is just fine and dandy. The science is obviously important but, again, it is a somewhat different issue.

So, those are the basic issues, just to frame it. Can it image or not? If it can image, then is it clinically useful? Then, if it is clinically useful, to whom, under what circumstances?

We have had also three different presentations from three different sponsors taking somewhat different approaches. We had one approach where the standard of truth is histopathology. We had another one where the standard of truth is clinical diagnosis. Then we had another one where

it is sort of a bit of a mix, I guess.

Also, we have issues relating to what the appropriate patient population would be when you are going to that next step. Should this be completely normal people compared to people with definite Alzheimer's disease or should this be a mix? Should it also be patients with mild cognitive impairment? Or, should it be a range of people with other dementing illnesses where a clinician in the real world might be sitting there with Mr. Jones who is having trouble with his memory? Can this help me make a diagnosis? Then, what does that mean in terms of prognosis and, again, for clinical trials?

So, that is just trying to synthesize a little bit about all that we have heard and trying to structure it a little bit. Now, we have three questions that I would first like to review again quickly.

The first one was to what extent, if any, would an indication for the use of an in vivo diagnostic radiopharmaceutical agent for the detection of cerebral amyloid provide useful clinical information?

In a sense, I think this question is almost the second one, not the first one. So, let's go to the second

one. If an in vivo diagnostic radiopharmaceutical is clinically useful in the detection of cerebral amyloid, what should be the standard of truth in phase 3 clinical trials? That is almost an easier one. We have heard a lot about it but compared to the first one I think it is a relatively straighter forward discussion.

Then the last question is please comment on the strengths and weaknesses of these phase 3 study outlines.

So, these three questions are really overlapping with one another. If the committee agrees, what I would like to do first is step back to that first question because that is really what a big focus of this discussion has been. What should the standard of truth be? Should it be the pathology? Should it be a clinical diagnosis in some way or some combination thereof?

So, focusing on that, here is the question, can you reliably image amyloid? We will figure that out and then we will move on to the next question. Presuming that that can be done, then what would be the clinical usefulness? So, let's begin the discussion with that.

But before we do that, sorry, I had almost forgotten we had three people that had questions that I cut

off in the morning session. I would just like to give them an opportunity to either ask them or make some comments first. I believe Dr. Jung was one of those people.

DR. JUNG: No, I believe it has been answered.

DR. GOLDSTEIN: You pass? Dr. Rizzo was another. No questions? Dr. Temple was another.

DR. TEMPLE: No.

DR. GOLDSTEIN: No? How about that, my strategy worked yet again. Dr. Mattrey?

DR. MATTREY: This was not from the morning but just to help me from the sponsors. It seems to me that what we see on the images is a balance between the on and off rate of your agent onto the amyloid. So, a sensitivity issue is important because if amyloid is present in 20-30 percent of people and maybe AD has much more in the brain than non-AD cases, then could that sensitivity creep in as a false-positive or a false-negative rate? My guess is it would creep in as a false positive if you are overly sensitive. I would just like to hear what their agent is like in terms of that possibility.

DR. GOLDSTEIN: To whom are you directing that question?

DR. MATTREY: To all three sponsors. I think the GE presenters said that their agent is in the nanomolar range. I don't know whether the off rate is the same, but the on rate, you said, is about the same and it is in the nanomolar or maybe even more sensitive than the PIB agent.

DR. KLUNK: I find myself a little confused by the discussion, not by the way you framed your question but when you are talking about sensitivity, and I think we have to be careful to distinguish whether we are talking about the traditional sensitivity that Dr. Temple, I think, was referring to several times about sensitivity for diagnosing Alzheimer's disease as a clinical entity versus specificity for having a negative result in the cognitively normal individual.

That is one thing, and that is not what GE is claiming. We are talking about the detection of the presence of amyloid in the brain. In our experience in Pittsburgh, and this has been borne out around the world, that happens in about 25 percent depending on the community populations, ADRC, like the ADNI, population 45 percent.

So, there are a lot of cognitively normal people who have amyloid in the brain and sometimes we act like this

is some big discovery of 11C-PIB but the pathologists have told us this for 30 years. In fact, they have told us that 20-40 percent of cognitively normal people have amyloid in their brain so we knew that this would happen.

I think as you are asking the question it is really sensitivity for amyloid in the brain. So, the detection of amyloid in the brain of a cognitively normal person, to me, is a correct outcome. That is not a false positive.

DR. MATTREY: I am sorry, I was not talking at all about the clinical side. I was talking about given amyloid, what is the sensitivity of the agents to detecting amyloid? All I was saying is that if an agent is very sensitive, then you are going to detect amyloid that is not associated with AD because, if I understood it correctly, AD is several orders of magnitude greater.

DR. KLUNK: No, it is about twofold greater than the background we see in people that we have good evidence for that have no amyloid at all. It is not several orders of magnitude at all.

And, as we discuss this I think we are mixing clinical and pathological issues. So, let me just go and

say what I think. There is some threshold below which 11C-PIB, GE-067, any of the other agents we have talked about today will not detect amyloid. I think you will find cases eventually at autopsy where we can identify amyloid with an antibody that we couldn't identify in vivo. We already know in mice we have a tremendously hard time identifying that kind of amyloid even though there is tons of it there.

So, as I think Dr. Lu mentioned, there may be types of amyloid in humans, perhaps these familial rare kinds, perhaps other kinds where we get a negative scan and there is amyloid there. So, I expect that there will be false negatives. False positives I think will be extremely rare. I kind of showed some by visual reads what may be false positives. I showed where a group of readers picked out some scans that they thought were positive when all the quantitative measures suggested that they weren't.

I think one of the problems in all of these ligands, maybe less in the AstraZeneca ligand as I think they are making a case for, is the white matter. So, that is nonspecific binding. The reasons we don't know is that many of these agents hang up in white matter more than they do in grey matter that doesn't have amyloid. So, you could

get a false positive if somebody wasn't careful or you had certain pharmacokinetic algorithms that somehow got that white matter signal mixed up with the grey matter signal and said this is a positive case and it wasn't.

But I think more likely than not there is some level of amyloid below which all of these ligands will be negative. Then the real clinical question is, is that an important amount of amyloid or is that a trivial amount of amyloid, and we just don't have any data that I know of to address that. I hope I have answered at least part of your question.

DR. MATTREY: You did. Thank you.

DR. TEMPLE: If I understood Dr. Weiner and at least one of the proposals, it was that you would do the test and if it was negative, if it did not show amyloid, you could reliably conclude that you did not have Alzheimer's disease. It didn't say what you should conclude if it is positive. That is a different question.

So, one of the things, it seems to me, the committee needs to grapple with is how do they like that as a possible indication. That is not the same as doing the test and then using a lot of information where you have to

evaluate the sensitivity and specificity for actually defining what a person did have. This is just, if I understand the proposal and tell me if I am wrong, this is just to say Alzheimer's disease Athey don't got@ because there is no amyloid there.

But we already know that there are people who don't have Alzheimer's disease who do have amyloid. That is a different question, and you are going to have to do elaborate sensitivity and specificity considerations there and you probably want a broad swath of people in the trial.

But the contention here was if I can be absolutely sure that if I don't see amyloid they don't have it, that is one useful thing. I think that is what Dr. Weiner said but he can't say anything now. But that is one. And, it seems at some point, to me, that the committee needs to deal with that question as a single question.

DR. GOLDSTEIN: Right, and again I think, you know, we are mixing things. I would like to, if we can, either try to first hit in on the question, which is what is the standard of truth for determining that there is amyloid there or not, and at what threshold. Then, if that is true,

once we have had that discussion we can go on to what do you do with this information? Is it clinically useful?

DR. RIEVES: I am probably restating the obvious, but I want to be sure that we are all on the same level in terms of our thinking. It again gets at the prior question. The companies came to us in the Division, asking us a question that is commonly asked in in vitro diagnostics. The common example I have is the CFTR gene mutation. Okay? The FDA is presented with in vitro diagnostic questions like that.

Well, performance characteristics for the in vitro diagnostics, the performance characteristics, are whether or not it can detect that mutation. The performance characteristics are not whether or not it can diagnose cystic fibrosis. There are two distinct differences here. What is on the table right now is not clinical usefulness. None of these companies have proposed seeking a claim, at least an initial claim, related to clinical usefulness. It is solely a claim related to what one might expect of an in vitro diagnostic, CFTR, PSA, alpha-1 anti-trypsin, the list goes on and on. The only difference is that it is an in vivo diagnostic here.

Getting back to what Mr. Bridgwater mentioned this morning, in essence it is a tool. It is a tool. That is what they have posed to us and that is what we really need to know in the Division. Is it reasonable to develop these products as tools? They are not diagnostic so they are not going to make a diagnosis of Alzheimer's. They haven't proposed that. That is not a consideration. That is not on the table. That is the obvious thing we all want to know but that is not what the companies are moving forward with. It is the in vitro diagnostic analogy of testing in vivo.

So, I just want to make clear that the performance characteristics as they proposed to us, such that we stay focused, will be based on the presence or absence of amyloid. It is not Alzheimer's disease; it is amyloid.

DR. TEMPLE: Aren't they saying that it would be useful to show that there wasn't amyloid?

DR. RIEVES: Well, it is very analogous to the same sort of thinking, for example, with CFTR gene mutation. It is one component. The CF foundation has a list of criteria and CFTR mutation is one component of that. I think the thinking from the corporate standpoint is that, yes, this would be that one component potentially.

DR. GOLDSTEIN: Dr. Zeissman?

DR. ZEISSMAN: Thank you. This discussion and these presentations seem to me to highlight the pros and the cons of the FDA approval process. For example, I think a big question is would 11C-PIB be approved by the FDA. No one is sponsoring it and so that is not really being discussed, but I think that is a pivotal question here.

I think the approach, therefore, to doing studies has been very different. You see that multiple studies have been done with 11C-PIB but they are relatively small studies and just look at a little piece of the pie. What these companies are being forced to do is to think in a larger scale and say what would the FDA be willing to approve. Therefore, they thought through these protocols.

I think that these protocols have a lot to say for them. I mean, I think all of them ought to be done with modifications. The problem with the FDA process is that what the companies tend to do is to do the least they have to do in order to get FDA approval and then nothing else gets done afterwards.

I am all in favor of rapid approval of new radiopharmaceuticals, particularly rapid approval of these

radiopharmaceuticals. But I am also in favor of good science and I think that that is one thing the FDA approval process does force to a certain extent, good science. And, I think 11C-PIB has some good science but at least the presentation I saw today didn't convince me that my perspective on the FDA and whether they would approve something like that is not very optimistic.

To me, autopsy studies are mandatory. As difficult as they definitely are to do, it seems to me we need to have that pathological confirmation. I think this approach with the consensus approach makes some sense. That is, if you can have a consensus group out in the community by way of an imaging agent, that would be useful.

But I think that the protocol, thinking in terms of imaging as positive or negative, is not the way imaging is. Images are not interpreted as positive or negative in most cases. They are in some way couched as probable or unlikely. You know, I think they need to look at it in somewhat the same way the clinicians are looking at a diagnosis of Alzheimer's. That is, it is possible, it is probable, and they need to get their accuracy based on those different interpretations. You can look at a binary pattern

of interpreting images but I don't think that that is useful by itself.

Again, I am in favor in spite of that. As has been mentioned already and I had in mind as well, I think that some of these companies ought to get together and support a comparative trial. Do these agents show the same thing? Do they have the same distribution? Do they have the same amount of uptake? Are they equivalent or not? If they are, that would be valuable because then all these different approaches could be looked at as a whole and we would be much further ahead in our knowledge of the value of these agents and their scientific accuracy.

I know that is difficult in the business world, but I think it would in the end help them all and it certainly would help the scientific and medical community. Thanks.

DR. GOLDSTEIN: Dr. Royal?

DR. ROYAL: So, I agree that the focus is, you know, detection of amyloid plaques and it sounds to me like there is agreement that if it were feasible people would agree that histopathologic correlation would be the best thing.

What there seems to be disagreement about is whether or not histopathologic correlation is feasible or not, and I certainly would like to hear from the three sponsors the reasons why they decided it was or was not feasible.

In particular, I was a little bit confused during the Avid presentation because the subjects, it sounded like, were going to be recruited from Alzheimer's disease centers. But when I had read the protocol it sounded like they were going to be patients who had a limited life expectancy who were going to hospice centers.

So, clarification on that point and further enlightenment about why it would or would not be feasible. I completely agree that we should not needlessly prevent these drugs from becoming useful as quickly as possible.

DR. GOLDSTEIN: Response?

DR. SKOVRONSKY: Dr. Royal raises a number of good questions and a number of the panelists have raised questions about feasibility.

First of all, don't get me wrong, this is not an easy study to do. We actually think this is quite challenging but we do think it is feasible and I clearly

differentiate feasible from easy. And, we think we can do it relatively quickly.

Let me elucidate on our approach a little bit more. So, one population that we look at is the Alzheimer's disease centers and in these Alzheimer's centers there are longitudinal studies already under way and we can plug into those. So, if you take an average center that has a list of patients who have enrolled in one of these studies, they have thousands of patients typically and a typical patient who might be in this situation will have a life expectancy in the range of 5-10 years.

That means 10-20 percent of them will come to autopsy every year. So, if we go to a center and we image 100 patients randomly selected from their list we will get 10-20 percent, 10-20 subjects on whom we have autopsy confirmation in one year. We will have imaged 80-90 other patients. We won't be able to use that data because we don't have the reference standard, but we will have 10-20 autopsies from that center. We do this at a few centers around the country and we hit our target number.

Now, the second approach to supplement this if we can't get the patients fast enough would be to enrich. We

can go to those centers who have those lists and cull the lists and look for the patients that, in their clinician's judgment, are most likely to pass in the next 6 months or the next 12 months and enrich the population. Instead of just imaging randomly selected patients from that list, image the patients who might be the most likely to pass. Then we might get to 20-40 percent that come to autopsy in one year. Therefore, we waste less imaging, or are more efficient is perhaps a nicer way to say it.

The other population we can go to is the hospice. If you go to a typical hospice, they typically see thousands of patients in a year, so 1,000 or 1,500 subjects in one year, and almost all of those patients pass within a year. So, certainly we are not going to be able to image everyone in a hospice. Many of these patients will not be good candidates for imaging but there will be some in there whom we can image and with those patients we would have a very high autopsy accrual rate.

So, we can combine those two populations. We have spent a lot of time thinking about it, a lot of time addressing the feasibility. We think we can do it, not in hundreds of patients but certainly in smaller numbers.

DR. BROOKS: Could I comment on behalf of GE? I think there are two major problems with this approach. One is an ethical one. I don't know how it works in the U.S. because I am based in Europe, but we would have big problems taking end stage Alzheimer patients, who really are not sure what is happening around them, and putting them in the scanner and imaging them in this way.

The second one is just a technical problem. The fact is when patients are at that stage it is almost impossible to get technically useful scans because they find it very difficult to cooperate. They don't actually know what is going on half of the time. So, to try and do this study is technically very, very difficult even if you could find the patients.

So, as far as I am concernedB-sorry, were you saying something?

DR. SKOVRONSKY: I just wanted to clarify because it is confusing. I should have spoken more clearly. These are not end stage Alzheimer's patients.

DR. BROOKS: Well, how in that case are you going to get your autopsy so fast?

DR. SKOVRONSKY: Many people die of other diseases,

other than Alzheimer's patients. There are many patients who have Alzheimer's who also have comorbidities that they may die from.

DR. BROOKS: Well, I can see that you would get a certain number through that, but to really guarantee that you are going to get your target numbers it sounds like you are going to have to do end stage cases.

DR. GOLDSTEIN: I am sorry, I am going to have to cut this. This is a debate between you two.

DR. BROOKS: For that reason we are proposing a separate standard of truth. We would obviously follow our patients to autopsy.

DR. GOLDSTEIN: Thank you. Dr. Anderson?

DR. ANDERSON: Well, I want to come out in contrast to what was said. I don't think autopsy should be required. I am not sure it is that feasible. I know, for example, that there has been a study of McMaster who has tried to recruit terminal cancer patients just to look at their brains postmortem it has taken a number of years to accumulate a large cohort of brains that were neuropsychologically studied in hospice-enrolled individuals. I have also been part of an Alzheimer center

and I don't think it is easy and I am not sure it is feasible in the time frame to get it.

But I would like to say that I don't think the standard of truth has to be autopsy confirmation for an amyloid indication. I think it probably would have to be for a disease indication or a diagnostic indication given the ambiguity of clinical diagnosis of Alzheimer's, but not sort of for a biochemical indication.

At least I have a temptation when I sit here to sometimes apply a different standard to what I say than when I actually sit in the privacy of our clinic, talking to another person. I use SPEC scans to, you know, help arbitrate difficult diagnoses and use spinal taps to measure beta-amyloid because with some of these patients it is really hard to try to figure out what is going on and you are trying to grasp at any little piece of information that will help you.

So, I also think your emphasis, Dr. Temple, on sort of signifying this as sole diagnostic criteria for ruling out Alzheimer's disease isn't really the way I would envision it being used and, whether that is or isn't an FDA obligation, I wouldn't think that would be a wise course.

So, I don't see these questions as being quite so separated.

If you could get a PIB scan the way you can get an MRI scan I think people would be doing them not all the time but often, and they would find it useful and helpful. I would think a standard of comparison to PIB or something that had met sort of what the 11C-PIB has done, to my mind, would be sufficient for making a claim. Given the in vitro and ex vivo and limited in vivo and pathological confirmation, it would be sufficient for me to feel I had a clinically useful tool that was helping me determine amyloid in the brain that I would use in clinical encounters in the ways that have been elucidated by Dr. Weiner and presenters and Dr. Johnson, and so forth.

DR. GOLDSTEIN: Again, as we are having this discussion, please keep in mind that what I would like to address first is what is the standard of truth. Again, we are mixing diagnosis and how it would be used and, you know, what would be clinical utility. We are going to deal with these because these are clearly important overlapping issues. But the first question is what is the standard of truth for determining that you are imaging amyloid in the brain. That is why I wanted question two first.

DR. ANDERSON: So, let me be clear. The standard that has sort of been observed in practice by the 11C Pittsburgh-B compound defines, in my mind, an adequate standard of truth which would be met by other compounds showing similar imaging to that compound, as has been proposed.

DR. GOLDSTEIN: Thank you. Mr. Bridgwater?

MR. BRIDGWATER: Thank you. With respect to Dr. Anderson's comments, with exception of 11C-Pittsburgh compound B, I have had those tests. To Dr. Temple's perspective, I think the collective value of that information was instrumental in the diagnostic process.

I am not a scientist, I am here as an advisor, but I heard about ten questions ago asking Bayer, Avid and GE to express their position. Dr. Klunk for GE stood up and expressed his position and then we proceeded. So, I don't know if Avid and Bayer would have a follow-up position that they would like to make but, as a committee, I think they should have the right to if they choose.

DR. GOLDSTEIN: What question did you want them to address?

MR. BRIDGWATER: The one we previously asked them.

DR. GOLDSTEIN: Which is? Sorry, I just want to make sure they are answering the right one.

MR. BRIDGWATER: I have dementia; I can't remember.

DR. GOLDSTEIN: Okay, if the question was what do they believe the standard of truth is, that is fine. Just for the record, say your name again.

DR. REININGER: My name is Cornelia Reininger, from Bayer HealthCare. I would like to elucidate our standard of truth proposal briefly once again because I think it might have been a bit misunderstood.

We are proposing an adjudication committee, a consensus panel diagnosis of experts. So, this is not to be equated with an on-site dementia expert diagnosis. And, the sensitivity and the specificity of a diagnosis of this type has been verified to have a sensitivity and specificity of over 90 percent compared to postmortem. Oscar Lopez and co-workers published this data in Neurology, in 2000.

This approach has also been used as part of registration programs for other neurodegenerative diseases, and we did adopt this approach because we plan to do a global clinical trial with a large number of subjects. We do share the FDA's concern on the feasibility of doing

autopsy studies or including autopsy in a large collective of this type.

However, to conclude, I would like to say that we do respect the advisory committee's concerns around tissue samples and, of course, will take back to upper management these suggestions and consider tissue samples in the development of the phase 3 clinical program.

DR. GOLDSTEIN: Dr. Green?

DR. GREEN: I really believe that the standard of truth without any assumptions about clinical applicability has to be autopsy. If it is inconceivable that a short study be done we will readdress this in a year if we don't do it now on that issue.

However, once you leave that and you talk about anything with clinical feasibility, it changes everything. Then I think autopsy material has to be out the door because you can't look at people who are otherwise medically ill. I am not even sure an expert panel can diagnose Alzheimer's very well in a group of people who are otherwise medically ill. Then we have to look at a comparator of a PIB and clinical consensus.

DR. GOLDSTEIN: Dr. Temple?

DR. TEMPLE: I think I have forgotten my question. No, I know what it is. The truth standard in a diagnostic test helps you get a precise measure of the sensitivity and specificity. So, if you had a postmortem and you saw it is normal you would be able to say, okayB-well, these are normal people actually, so you will be able to say, okay, the test was negative. I am satisfied sensitivity, specificity, or whatever you are talking about, is 100 percent. If you had to go with a clinical diagnosis there would be some uncertainty about what the person had and your sensitivity and specificity measures would be less perfect. You wouldn't know precisely what they were.

And, one of the things I think you need to talk about is how worried are you about that slight decline in the perfection of your sensitivity and specificity measures. I think that is what the autopsy question is really about. You know, if you were very careful and picked just the right people to make the diagnosis could you get close enough?

DR. GOLDSTEIN: Did you have a question that you wanted to direct to them?

MR. BRIDGWATER: No, that was a follow-up to the

question I asked that you were allowing them to answer and they were interrupted.

DR. GOLDSTEIN: Okay. Dr. Temple, did you have anything you wanted to direct to them?

DR. TEMPLE: No, no. There has been discussion. There have been different views presented by the committee about whether you need autopsy or not and I was trying to identify what difference that makes. You won't be all wrong in the value of a test but your estimate of sensitivity or specificity, whatever this actually is, will be less precise if you are not 100 percent sure of the diagnosis, the way you would be with a postmortem, and one of the questions is are you willing to give up that precision a little bit or not, and how much does it matter?

DR. GOLDSTEIN: If the committee has a specific question that they wanted to direct, I would be happy to do that but otherwise we will just continue.

MR. BRIDGWATER: Pardon me, we asked them about 12 questions ago and they haven't had a chance to respond yet.

DR. GOLDSTEIN: I am sorry, what was the question?

MR. BRIDGWATER: It was a question and Dr. Klunk answered it first, then we just gave Bayer an opportunity

and we haven't given Avid an opportunity.

DR. GOLDSTEIN: I thought we had, but if we haven't I apologize.

DR. SKOVRONSKY: Thank you. We will keep it super brief, and I think the question, again, still revolves around the reference standard. Our position has been clear that the only reference standard that we think will adequately address the concern about how do you know the limit of detection, how do you know what you are really imaging is the autopsy study.

What we asked from the agency and from the committee is leeway that this not be a huge multi-year, hundreds and hundreds of patients autopsy study, but that we work together, and we work together on a reasonable statistical plan to be able to accomplish this in a small number of patients in a small amount of time.

DR. GOLDSTEIN: Thank you. Dr. Lu?

DR. LU: So, if we look for the endpoint that we really talk about, you know, the standard of truth is related to what you can measure. So, for autopsy you really get a clear dose-response relationship, the truth in the pathology and the measurement. It is particularly important

for MCI, which is wandering in between the range.

So, if I think about the clinical diagnosis, it is like a rank test so you basically lump all the positives at one point and the negatives at a point, and the huge spread in the middle you don't look at.

Also, I am really uncomfortable with the clinical diagnosis because, as we mentioned earlier, one of the benefits was to rule out the negative, you know, negative predictive value. By just using clinical consensus reading there is no way you can, you know, vary the negative predictive value. Also, when you use that you have a panel of nuclear radiologists doing the consensus reading and I am not sure how much variation among the interpretation there is. So, you still end up with a panel of experts that gives you the diagnosis. I haven't heard about the variation of interpretation by the nuclear radiologists so they may vary and we go back to the same question.

Now, the question about using the PIB as reference is interesting because if you use that as the endpoint you really get concordance of the two. But that still will not answer the real question unless PIB is, you know, in the same standard. So, I just wonder why we are talking about

autopsy for 400 patients. I mean, the reason that you want that is to have some kind of relationship. I mean, the other issue is about safety in other studies. You don't have to go through everyone for autopsy.

So, I think if you nest single autopsy studies in the big study it is still feasible. NIH funds a lot of aging cohorts where people sign up for autopsy and some of those are very old populations, like the Coach Conte study where they also wanted to rule out MCI and AD and all these histories. Those people are really in the late wave of their life and they already signed for the programs. So, it is a matter to take advantage of those cohorts and provide the test.

DR. GOLDSTEIN: Dr. Zeissman?

DR. ZEISSMAN: Yes, in response to your comment, there certainly is variation in image interpretation like there is variation in every other aspect of medicine. That is why I was encouraging the one protocol that suggested that positive or negative was not really the proper way to go because that is not the way images are read and it isn't the real world.

I also would like to reemphasize that I really

think the FDA ought to think about approaching this a little bit differently than they have in the past, and I really think they ought to, in some way, encourage these companies to work together from the standpoint of are their agents reasonably equivalent. If they are, it will be much easier to more rapidly acquire the information we need to know how useful these agents are. It will be easier to acquire the autopsy studies if several companies are trying to get autopsies rather than one. If we can use the data from all these different approaches I think we will learn much more about the radiopharmaceuticals in a much shorter period of time.

I think the FDA could probably figure out a way to encourage that type of interaction to, in some way, support a study that would compare these radiopharmaceuticals. The dosimetry shouldn't be a problem in comparing. I mean, every person doesn't have to get every agent but you need to compare these different agents, at least two in individual patients. But I think that that ought to be done early on. Then all these other studies would more naturally flow and you could make sense of them.

DR. GOLDSTEIN: Dr. Royal?

DR. ROYAL: I first wanted to just echo the comment of Dr. Lu that if histopathology studies were required, it wouldn't be expected that they would be on hundreds of patients but that they would be on a subset of the population that is being studied. I, frankly, don't know whether or not it is feasible or not feasible, but it is interesting that at least there is some enthusiasm from one company to do this. Again, it would be very important data.

One of the things that worries me is having a different standard of truth for each company. It does seem like there should be a uniform standard of truth for these different agents because I don't know how we would make sense out of the data. And, what is being proposed by each of the three different companies is really very different and that is really troubling.

DR. GOLDSTEIN: That is why we are here. Dr. Mattrey?

DR. MATTREY: So, I think Dr. Rieves' statement defined the problem. The indication is that this approach of imaging with 18F amyloid labels will detect amyloid in the brain. And, I think you can only answer that by letting the pathology tell you how much amyloid there is in the

brain.

The problem I have with the clinical approach is that you are now asking the pathologist to not tell you how much amyloid is in the brain but, rather, to tell you if there is AD in the brain which, we heard this morning, is only 80 percent sensitive. So, what ends up happening is you propagate the error so if there is an error in the selection process because if it is AD and there is an error in the pathology it is not actually 20 percent error, it is the square root of the sum of the square. So, in fact, the final outcome would be actually worse than 80 percent sensitive.

So, that is the problem I have when you are developing an agent with a claim that I can detect amyloid and select patients that should have amyloid but might not have AD and may have some other problem. As we heard, there are patients with amyloid that don't have AD. And, that is the difficulty. I mean, I realize I am not even a neuroradiologist, but I can appreciate the problem at the battlefield. But if I am a pure scientific evaluator, then the statement that I can see amyloid, I would like to see that you can image amyloid.

I agree, I don't think you need a huge number. I mean, when you do correlation studies in vitro you don't do thousands of samples. You need enough to bridge the range from zero to 100 percent. So, I kind of go along with the autopsy as a truth standard because then I know. If they tell me they can image amyloid I know they can image amyloid and I think doing 30, 40 cases that have a range of amyloid and you show me a correlation of 0.85 or 0.9, I think then we can feel convinced.

The Pittsburgh molecule has not been confirmed pathologically, as we heard, rigorously. So, proving using PIB as a truth standard still doesn't answer the question that I can image amyloid. It likely is true but scientifically we heard that that data is not there.

DR. GOLDSTEIN: Dr. Anderson?

DR. ANDERSON: So, I am not arguing against autopsy being adequate as a truth standard. I am just arguing that it is a necessary truth standard for these sorts of compounds in this sort of state of time and clinical knowledge.

If you show me something that binds amyloid in the test tube and doesn't bind other brain constituents, if you

show me it binds amyloid in animals, you know, in vivo and in vitro, you go to the pathologists, you take slides of human brain tissue that have known quantities of amyloid, and you show me that the compound labels them auto radiographically in postmortem material and not in others that don't have it, then you show me a human population that is known not to have amyloid deposition, such as young normals, and they don't have staining with this image in vivo, and then you show me a population with clinically suspected Alzheimer's disease that you know is enriched for amyloid, and you show that these compounds label most of these patients very highly and very distinctly, I am arguing that that is sufficient.

Now, if you go along and you show me additional autopsy cases, as has been done for an agent that is not under consideration but is chemically similar to the ones we are considering, and you show me from section to section a high correlation between specific chemically identified A-beta quantities and the presence of binding, I am arguing that that is a standard of truth enough and, you know, there are consequences to exacting a standard of scientific rigor that precludes the use of clinically valuable information.

It shouldn't be a decision simply made in the abstract as to what is the absolute greatest standard of truthfulness that we could obtain. We used MRI scan to diagnose MS long before we started doing pathological examinations of patients with multiple sclerosis because we felt it was true enough to be able to make those clinical-radiological relationships.

DR. GOLDSTEIN: Dr. Twyman?

DR. TWYMAN: I would like to say that it would be very good to get histopathological confirmation of the human condition with the product. I have a crazy idea here that, you know, the label is actually for detection of amyloid. It doesn't necessarily need to be done in Alzheimer's patients.

I just want to hear from Dr. Klunk perhaps on the hydrocephalus study which apparently has had ten more human samples obtained versus the single autopsy Alzheimer's case, and whether or not a trial in biopsy of patients with hydrocephalus imaging in those patients and analyzing that data, much like the case that has been reported here, would be a sufficient standard to demonstrate the reliability of detecting the presence of amyloid, or perhaps confirming the

absence of amyloid.

DR. GOLDSTEIN: I guess we have the specific question that was directed to you. Can you respond?

DR. KLUNK: Well, we just are in the process of rewriting our program project and considered adding a project such as that for biopsy studies in Pittsburgh. Then we began to look into the feasibility of doing it.

We talked to neurosurgeons. Here, in the U.S. the procedure is different in the way that you don't get a core biopsy sample so it would have to be rewritten as a research study that, in addition to putting this needle in, I want to take a little piece of your brain out. In addition, there is usually an extensive LP kind of trial tap before a shunt is put in. So, very few shunts are actually placed.

The other concern I have is not so much when you find amyloid in the biopsy, but what about when you don't? You have sampled such a minute section of the brain, you could end up with a positive scan that is a true positive and call it a false positive because you happened to have not sampled an area of the brain.

So, you know, I strongly considered putting that into our research study as further validation, but when you

look at the practicalities of that, they are really equal to what you face in an autopsy study.

DR. TWYMAN: Yes, but there are a lot of patients undergoing deep brain stimulation and perhaps you can obtain probably a cortical biopsy as you do those procedures. I mean, there are other alternatives to get brain tissue for histopathological confirmation.

DR. KLUNK: We talked to our Parkinson's colleagues about doing that and those talks are actually ongoing. But there are ethical issues. You know, it could be done over a long period of time. The question is, is that something that must be built into this kind of protocol.

DR. GOLDSTEIN: Thank you. Dr. Katz and then Dr. Temple.

DR. KATZ: Yes, this is a follow-up question to Dr. Anderson. I think you gave a very clear exposition of what for you would constitute the elements of standard of truth. My question is do you think PIB has met that standard? If you do, would an equivalent standard of truth be equivalence to PIB?

DR. ANDERSON: For me personally, yes, I feel that PIB has met that standard, and if other issues of safety and

so forth were established, then I would have no problem recommending or saying that I personally feel that PIB has met that standard of truth.

DR. GOLDSTEIN: Dr. Temple?

DR. TEMPLE: I have nothing.

DR. GOLDSTEIN: Dr. Lu?

DR. LU: I was just wondering if the two, GE and Bayer, can give us an estimate of how much delay there would be if they required autopsy. Also, Dr. Feng, you mentioned about self-evidence. What is the definition of self-evidence for the clinical utility that you mentioned this morning?

DR. FENG: We are talking about imaging self-evidence. For example, for a femur fracture we use x-ray. You see it right away. Basically, everybody can tell so you don't need a rule like 100 femur fracture patients to systematically study sensitivity and that kind of issue. But some is not self-evident. Obviously, Alzheimer's disease is more complex than femur fracture so here this is not self-evident so we need a systematic study.

DR. GOLDSTEIN: Thank you. I think Dr. Lu had directed a question to the sponsors.

DR. BROOKS: It is a difficult question to answer because the current study we have planned is not really designed to go to autopsy. I would estimate, based on our experience for instance collecting autopsy material to validate a dopamine transporter marker, that it would take a number of years to collect adequate data because of the problem that you have to work with end stage patients to get a quick result. So, I would say that we will collect that data but it makes it impractical to do the trial in less than, let's say, five years or more.

DR. GOLDSTEIN: Thank you.

DR. REININGER: Connie Reininger, from Bayer HealthCare. I we concur with that opinion that it would take time, dependent upon how many samples are required. However, we will consider that in our future development plans.

If we would do something to that effect, it would be extremely difficult to do that in the multi-center global environment, and that would have to be due to the complexity of the issues around gaining postmortem data, consent, ethical, brain bank availability, etc. It would probably be a separate trial and not involve our global phase 3 that is

currently planned.

DR. GOLDSTEIN: Thank you. Dr. Herscovitch?

DR. KLUNK: Could I add one thing to Dr. Brooks' statement that we haven't considered?

DR. GOLDSTEIN: Sure.

DR. KLUNK: That is the issue that in the broad range of autopsy studies that would include cognitively normal controls. You know, I agree that for purely research validation of this technology you have to include postmortem histology, and I think we have shown we are committed to do that with PIB. It is taking a long time. It is six years since the first PIB scan was done. Two are in the literature and out of 250 cases we have four available to us, three ADs.

You know, finding those cognitively normalB-they are healthy people; they are not going to be dying. Those who aren't healthy, how can you adequately define their cognitive normality? You know, it is a big problem.

So, I understand the scientific need to be rigorous about this, and I hope we can do that through 11C-PIB and then the work that has been done there transfer and facilitate the development of this whole field.

You know, I think an issue-BI am going to be very unpopular now and I might have to change my seat but we, in Pittsburgh, as academics, have felt that it is very important to make this technology available to everybody around the world, whether they end up as an academic competitor to us or not. This same issue of availability has come up with its standard of truth in this setting. So, I think that is an issue that my colleagues are going to have to address. I can't say anything about the commercial realm. Our license agreement doesn't allow that.

I personally feel strongly that if you are going to call this a standard of truth for one company, it has to be an available standard of truth for all companies under some reasonable arrangement.

DR. GOLDSTEIN: Thank you. Dr. Herscovitch?

DR. HERSCOVITCH: So, we have basically three potential definitions of the standard of truth. I think obviously having histopathological confirmation to what you are trying to demonstrate is a standard of truth. The concerns about feasibility, I am not too sure how strongly we should be discussing them. I would propose that this is really Avid's issue or any company that is proposing to do

that. They are going to be putting a lot behind such a trial and if they are claiming to be able to do that, well, they will have to design a study and, in fact, come up with the goods.

One question I have is with regard to going to hospices. Some people have said, well, you can't really do a good evaluation of the cognitive status, normal or whatever, but is that really the appropriate question? Because if one is just looking for people who are soon to die, who may have a spectrum of amyloid deposition, even if you have a good clinical history, yes, this person had a clinical diagnosis of Alzheimer's on the basis of two or three local neurologists and GPs; this person, while he was fine he was president of Lehman Brothers and he just died, then I am not too sure about the ability to do a good cognitive assessment. Is that critical as long as you know that that will, hopefully, provide a wide sample whereby you do both an AD scan and an autopsy? So, that may not be that important a critique.

I think a power analysis might have made us all feel better, and I understand the company is planning to do that and obviously they have to do that before their study.

On the other hand, on the other sort of end of the clinical diagnosis, I have to agree with many of the colleagues on the panel. I am very concerned about only a clinical diagnosis being used. We have heard figures which vary from 80-95 percent of the consensus panel but, at best, it will be only as good as that but there will always be that uncertainty.

I am also concerned-Bperhaps I didn't understand the plan, but if it is being used as a standard of truth, should not patients who have the spectrum of early dementing diseases, in whom this will likely be used to exclude the presence of amyloid, be included in the trial and not just have a trial of consensually diagnosed subjects with Alzheimer's disease. I have a concern about that.

Also, I am not too sure what studying normal patients will show if there won't ever be a confirmation of the presence of amyloid. It has been said that 20, 30 percent of subjects in their 70s and 80s have amyloid, and I think that will be in some ways a false specificity figure because there really is no answer.

The one that I have perhaps the most difficulty with is the one in the middle where they will be using both

the clinical diagnosis and PIB. Initially I thought that seemed quite reasonable, but then I began to wonder is there a logical conundrum in using PIB in terms of sort of the regulations, not perhaps how I might approach a patient in the clinic, which is much as my colleague would with a positive PIB scan, but given the data on the table today about PIB, would it be registered?

Would it be approved to exclude the presence of amyloid? We assume it is safe. We assume the dosimetry is not a problem. We assume manufacturing will be fine. But just on the basis of the studies to date, are they sufficient? And, if they are, then perhaps could not a similar pathway, or why aren't we considering similar pathways to the type of information that is available for PIB being used for these other agents?

Specifically, how much does the FDA consider all these other things which have been shown about PIB, the in vitro studies, the tissue studies against a variety of dementing illnesses, studies of KI, the tracer kinetic modeling, and so forth, they have lent a tremendous amount of support to the utility and meaning of PIB. Could they, should they not be used for the registration of some of

these other agents?

Otherwise, there is perhaps circular reasoning. We will say let's approve the GE agent because it is like PIB but then not let anybody else use similar steps that were taken for PIB to approve their agent. So, as far as I am concerned, my jury is still out with regard to the study that uses PIB but I think I am jawing with regard to the other two.

DR. GOLDSTEIN: Dr. Jones?

DR. JONES: I am a little concerned that we are still on question number two. I think we are getting hung up on the standard of truth because we have assumed, and the different companies have told us, that it is very difficult to get these cases that go to autopsy.

And, I have not seen I guess a power calculation from either the statisticians or the companies as to exactly how many patients we think we are going to need that are negative and positive so that we can really estimate. Because I just can't tell whether we need 100, 20, 40 and whether that is really unrealistic because I think we are really just getting bogged down and I can't decide on the answer to this question unless I have that number in mind.

I am wondering if either the companies or the statisticians in our midst can give us some idea about that.

DR. GOLDSTEIN: Let Dr. Lu, our statistician--

DR. LU: I didn't do any analysis because it depends on assumptions and, you know, I didn't do that. But I guess they gave a sample size there. They did not explain how they got to it but they gave a number there I thought.

DR. GOLDSTEIN: I believe you said that you had done or are in the process of doing that sample size calculation. The point is very well taken. If you don't know how many people you need, how do you know how feasible this is or isn't.

DR. PONTECORVO: I can answer that if you would like.

DR. GOLDSTEIN: Sure.

DR. PONTECORVO: This is Mike Pontecorvo, from Avid, and I am not a statistician so we have asked the statistician for a calculation and I made some assumptions.

So, if you have 26 amyloid negative scans and 90 percent of those are concordant with pathology, the confidence limits around that would be 70 percent the for lower level of confidence interval, which is generally a

reasonable amount of confidence and probably greater than the confidence limits you would draw for clinical diagnosis, given what we know of clinical diagnosis today.

So, a small number is reasonable. That would give you 80 percent power. You know, it is a tough bar. We are asking to have 90 percent concordance. But it is possible and your confidence limit would be 70 percent with that power.

DR. GOLDSTEIN: Thank you. Dr. Mattrey?

DR. MATTREY: Maybe I can offer a solution or maybe a halfway point. I would like to ask the FDA colleagues, since the claim is agent X diagnoses amyloid, why can't a single individual, assuming we have done the kinetic modeling and taken away the effect of blood flow, contribute many data points along that correlation curve because the brain does not accumulate amyloid to the same degree? In other words, each patient could potentially contribute a data point from zero to max based on what part of the brain is sampled. And, if the data on the imaging study correlates with the data on the pathology, then each patient could contribute many data points, which would really not require 20 or 40. It might take 10 brains and you have

gotten your correlation. So, you have 25 on half a brain, not actually one brain.

Since the claim is amyloid, not Alzheimer's disease, not dementia, not normal, not abnormal, why not just collect pieces of tissue from the same brain, assuming blood flow is controlled for because that could influence the data?

DR. GOLDSTEIN: Yes?

DR. KATZ: Maybe I am not clear. You are talking about different time points of the PET scan versus the pathology?

DR. GOLDSTEIN: No. I don't want to interpret but I think he was talking about spatial resolution so you have a given brain being imaged. One part is positive, another part is negative. If you have pathology to co-register with that, then you can say that the amyloid is present here and it lit up here.

DR. KATZ: But I think that was at least Avid's plan, I assume, to look regionally to see that it matches up. You could just put the histology, the brain tissue over the PET scan and show that where it lights up it lights up histologically, and where it doesn't on the PET scan it

doesn't histologically. I assume there will be many, many data points per patient in that sense, if you think of it in that way. I assume that is what they are planning.

DR. MATTREY: So, it would be easy to collect 400 data points out of 10 brains.

DR. GOLDSTEIN: Dr. Rieves?

DR. RIEVES: I was just going to say we will have to talk to our statisticians about that because they are not independent data points. They are coming from the same patient.

DR. MATTREY: They are independent if you take away blood flow because what happens is while the distribution is dependent on blood flow and dependent on the ability of the agent to stick to the brain, that is an amyloid-dependent condition. So, maybe my nuclear medicine colleagues can help me sort that out.

DR. GOLDSTEIN: I would like to try to bring this portion of our conversation to a close. Dr. Herscovitch and then Dr. Lu, and then I think we will try to summarize and try to get a general sense of people's opinions. We have spent a long time talking about a very complicated issue.

DR. HERSCOVITCH: I agree with Dr. Mattrey. That

is something that would have to be done and almost certainly Avid would be doing regional correlation, region by region, of the histopathology with the intensity of the signal.

But we have to realize that when you do a PET scan there are certain things which can make it go wrong which will affect all data points, and we have to realize there are two sets of data that are being collected, the histopathology, which we really haven't discussed much but we assume that is the absolute truth, and the PET scan. There are real-world issues of patient cooperation. I don't think blood flow is an issue here but hyperventilation, cooperation, miscalibration, and so forth, which, if they are not done perfectly, would affect all the data from one patient, even though I think it would be harder to affect all the data from multiple histological samples.

So, I think what you are saying should be done, and almost certainly will be done, to provide confirmatory proof but you really, I think, need multiple data points from multiple different patients.

DR. GOLDSTEIN: Dr. Lu?

DR. LU: Yes, I think you will not gain an equal number of points that you measure because you still have to

adjust the patient effect, but it is certainly increasing the power.

DR. GOLDSTEIN: Well, I think it has certainly been an interesting debate and discussion. I am trying to get a sense of what the committee feels overall because I think that would be helpful to the sponsors and to the FDA as well. I think we have debated this and spoken about it a lot.

So, we don't have a formal vote but I think it is fine for people to just go through and just offer what their opinion is. We may have heard some already but let's just do that. I think that the FDA and the sponsors might find that helpful.

Let's deal with this first question. Really, the second part of this question is what should be the standard of truth for the claim that you are detecting amyloid in the brain? Is that okay with the FDA. Is that what you wanted us go get at with that first point?

DR. RIEVES: Yes, that sounds good. Maybe we could quickly sort of do a roll call.

DR. GOLDSTEIN: That is what I was planning on doing. So, why don't we just go around the table and people

can just very succinctly summarize their opinion about this particular point, what should be the standard of truth for a claim to detect amyloid in the brain.

DR. TWYMAN: Again, I think histopathological correlation is far the best. I am not quite sure what the sample size is necessary for that, but I don't expect it is going to be 100 subjects. So, it is a remarkable result with the single autopsy case with the PIB compound, so I would imagine just a few samples to standardize that this is a performance characteristic of the binding in the human condition with the actual product itself. So, I would like to see the product tested and a histopathological sample in humans.

DR. GOLDSTEIN: Dr. Holmes?

DR. HOLMES: Yes, I definitely think this is an important question. You want to get this one right and I think the only way we are going to get it right is to look at histopathology because if you make a mistake here it is going go compound everything you do from that point on. We are going to get to the other questions about how you are going to use this data, but I clearly think you have to have histopathology.

Fortunately, we are not NIH and we don't have to fund this study. So, if the company can do it, that is great. That is wonderful. If they can do it, I would like to see them do it. That is important.

Looking at PIB, comparing one compound against PIB doesn't make any sense at all to me. Since that is not an approved compound for what we are asking here, it doesn't make any sense to compare it with that.

I think for the clinical having the committee is okay but, again, you are going to create an error there that is just going to be compounded throughout the rest of however this is going to be used.

DR. GOLDSTEIN: Dr. Jung?

DR. JUNG: I think tissue diagnosis is the gold standard and should be used.

DR. GOLDSTEIN: Dr. Rizzo?

DR. RIZZO: I think there is no truth. I think that all there are is relationships between clinical and biological and among different biological measures. I think that to diagnose amyloid in the brain from the PIB compound you need to have brain tissue and also potentially CSF evidence of beta-amyloid.

DR. GOLDSTEIN: Dr. Green?

DR. GREEN: Yes, the only way to close the door on this and prove our point is with histopathology.

DR. GOLDSTEIN: Ms. Bridgwater?

MS. BRIDGWATER: I believe we have only one vote so I will defer to my husband and allow him to speak.

DR. GOLDSTEIN: Mr. Bridgwater?

MR. BRIDGWATER: I would say histopathology and I would recommend that it be in a post-approval time frame.

DR. GOLDSTEIN: Dr. Zeissman?

DR. ZEISSMAN: Histopathology.

DR. GOLDSTEIN: Dr. Royal?

DR. ROYAL: Histopathology. I think histopathology is very important. I also think getting these drugs approved expeditiously is important. I don't have any personal experience trying to recruit people to donate their brains. But one of the things that is different about Alzheimer's disease than other diseases is that everyone knows someone who has had Alzheimer's disease, and I think the altruism of people in a hospice situation might make recruiting easier.

I don't like the idea of comparing one tracer to

another tracer because I just think it is just comparing two imperfect tests to each other and I wouldn't know how to make any sense out of that.

The last thing is that I think I would like to see a full spectrum of patients enrolled. To have the very normal and the very ill just doesn't seem interesting and it is really not where the agent is going to be applied.

DR. GOLDSTEIN: Ms. Bridgwater, you wanted to say something? I am told you wanted to speak. I am sorry, I thought you had said you deferred.

DR. NGO: I just wanted to clarify that Mrs. Bridgwater also has a vote, if we were to vote. So, it is actually two votes for Mr. And Mrs. Bridgwater.

MS. BRIDGWATER: Thank you for that clarification. This is going to sound a little strange but everyone presented a phase 3 study and I think that at the end of that phase 3 they will either prove or disprove what their standard of truth is.

DR. GOLDSTEIN: Dr. Anderson?

DR. ANDERSON: I am certainly quite content if someone wants to do a histopathological study but I feel that that is insufficiently stringent and I would personally

be willing to accept a lower standard, and the standard I feel PIB has met at the moment and, must because PIB isn't approved. It doesn't seem to me nonsensical to make a comparison against something if you feel that it has met a standard. Its value as a truth standard isn't FDA defined. It is scientifically defined.

DR. GOLDSTEIN: Dr. Jones?

DR. JONES: I think we need histopathologic proof. I would like to think that industry and perhaps the NIH could collaborate to make it happen a little quicker than we think and, hopefully, it will be feasible when we get some more information as to the exact number that is needed.

DR. GOLDSTEIN: Dr. Herscovitch?

DR. HERSCOVITCH: Histopathology I think clearly would do the trick. I don't think the clinical consensus diagnosis approach is at all satisfactory even if they were to include, as they are not proposing but even if they were to include the full spectrum of early dementing diseases, not just Alzheimer's versus normal.

I am conflicted with the PIB. Initially I was very positive about it but there is still the conundrum that if it would not meet FDA standards and it has not gone

through the same things we are asking everybody to do, how can we then say it is the standard of truth for something else? So, that makes me concerned about using PIB, but definitely it adds a lot more to just a clinical consensus approach.

DR. GOLDSTEIN: Dr. Mattrey?

DR. MATTREY: Histopathology, but I think they need to work with the FDA to satisfy them that they can use multiple regions as independent variables.

DR. GOLDSTEIN: Dr. Lu?

DR. LU: Histopathology, and I think if the PIB can be also verified in the same way then actually it can be used as reference for those who didn't do the autopsy.

DR. GOLDSTEIN: Dr. Rudnicki?

DR. RUDNICKI: Histopathology. I don't support the use of PIB, and if we were going to use patients I would want all types of dementias included.

DR. GOLDSTEIN: Thank you. My opinion also is that if the standard of truth is can we image amyloid in the brain, then I don't see a way around showing that you can image amyloid in the brain. We heard a lot about what the sample size is going to be, how feasible it may be, and I

think that is a discussion that can go on.

But I think the FDA and the sponsors at least have a sense now of what a group of people who don't do Alzheimer's disease research think from what we have heard.

We were scheduled to take a break at 3:15. What I think I would like to do is take a 10-minute break now. The reason I did this first was I think this is actually the real critical issue. The rest is interesting discussion but this was the primary issue that we needed to deal with which is why I wanted to do this up front and get this one done. So, let's take 10 minutes and we will come back at 3:25. Again, committee, no discussions about anything relative to what we talked about.

[Brief recess]

DR. GOLDSTEIN: Let's reconvene. I don't know where my co-partner is so I don't know how to change the slides on this thing. Oh, she is coming.

Let's assume now that we can image amyloid in the brain and we have shown that we can do that. Then, the first question, which is now the second question, is to what extent, if any, would an indication for use of an in vivo diagnostic radiopharmaceutical agent for detection of

cerebral amyloid provide useful clinical information?

Now we are going beyond that. Let's assume that, yes, we can do this and we can do this reliably with reasonable sensitivity and specificity and we know amyloid is there or we don't think amyloid is there, how helpful is that information clinically?

Again, I would like to just sort of frame this for discussion purposes. When we say useful clinically, the question then is useful clinically to whom for what? We have had a lot of presentation about that. One would be potentially to rule out the diagnosis of Alzheimer's disease. One might be in terms of detecting people who might respond to a therapy or not in a clinical trial, at least initially in a clinical trial setting. Another might be in patients who have minimal cognitive impairment to try to predict how they are going to do over time, to give them and their families information that might potentially be helpful diagnostically.

What I would also like to do, as we are just beginning this conversation, and I would like Dr. Lu to comment about this also, as we think about, in a diagnostic sense, the usefulness of a clinical test like how do you

define that, is that you take your pretest odds before you do the test; you do the test and depending upon what the positive likelihood ratio is in the prevalence disease, you then get a post test odds. So, the definition of clinical usefulness is how the post test odds changes from the pretest odds after you do the test.

So, a lot of that is totally dependent upon the prevalence of whatever it is you are looking for in the population. A wise person once told me though that there is nothing more dangerous than an amateur statistician, of which I rank myself number one. So, Dr. Lu, if you could just frame it statistically then we can talk about that in the context of clinical usefulness.

DR. LU: Well, even for statisticians it is still dangerous to talk about this. But anyway, for a diagnostic test, when we talk about the property of a diagnostic test we also condition it on the sensitivity and specificity. The reason for that is that in general we believe that sensitivity and specificity are relatively stable and not dependent on the prevalence of the disease so it is basically the property of the diagnostic test itself.

When you put it in the clinical application,

because the cohorts are different, as you mentioned, so positive predictive value and active predictive value become very important in the sense that when you call it positive what is the likelihood that actually it is positive, and when you call it negative what is the likelihood that it is actually negative.

Now, in the relative sense, because disease prevalence changes, you are right, basically you look for the post test positive likelihood ratio versus for the negative case and what is the negative likelihood ratio here. So, usually it is the original odds ratio multiplied by the odds ratio defined by sensitivity and specificity. So, it goes back to the property of sensitivity and specificity. So, I hope that answers the question.

DR. GOLDSTEIN: But it is also critically dependent on prevalence of the disease that you are trying to rule out.

DR. LU: Yes, so the likelihood ratio will be the odds ratio of the disease itself. Then the tests really add on as multiply[?] there.

DR. GOLDSTEIN: Well, with that background, let's start. I believe Dr. Katz and Dr. Temple were shaking in

their seats there.

DR. KATZ: I think, you know, the positive predictive value and the sensitivity and specificity are very important depending upon what question you are asking. If the sole question is would it be acceptable to approve this to rule out Alzheimer's disease if it is negative, I am not sure those considerations even apply. If it is negative, if you believe you can image amyloid reliably and not image it reliably and the scan is negative, you don't have Alzheimer's disease. You can actually prove that mathematically or logically.

So, I think the sophisticated discussions about positive predictive value or negative predictive value depend upon what question you are trying to answer.

DR. GOLDSTEIN: Absolutely. So, let's frame it this way, you have a patient coming to you that has a thinking problem, and you are trying to figure out whether that thinking problem is Alzheimer's disease or not. We have patients being seen at various time points with concomitant illnesses, concomitant medications, and a whole variety of other things. That is why even in that situation the prevalence of the disease that you are thinking about

may be important. Now, if you are right, if the test is 100 percent sensitive for saying that there is no disease, the negative likelihood ratio is 100 percent. There is nothing to talk about. You did the test and it Aain't@ that. It is the other side where there is an issue.

DR. KATZ: Right.

DR. GOLDSTEIN: Let's go on now. Dr. Temple?

DR. TEMPLE: Well, that is exactly right but the discussion has to focus on which of the two approaches is acceptable. In the one Russ described and you just enumerated you don't have to worry too much about who you put in the study or a whole lot of things because you are only trying to say that there is no amyloid there. You are not trying to say anything about what it means if there is amyloid there.

My own bias is that, maybe not initially but sooner or later, you want to find out those data. You want to study a broad population and find out what the positive and negative predictive values of a Ayes@ would be in contrast to only finding out what a Ano@ means.

But question one is ambiguous that way because detection of cerebral amyloid could mean, okay, if I don't

see any they are clean. It could also mean if I do see some, what does that mean? So, either of those fit that question and it is crucial that any discussion, I think, advise us on whether you think the limited initial use, that is to rule out, is sufficient or whether they need a more broad assessment.

DR. GOLDSTEIN: Right, and I guess we are saying then, at least from a diagnostic standpoint, it may be clinically useful to say that it is not there and, therefore, it is not AD. On the other hand, what is the clinical usefulness if it is positive. So, it could be clinically useful in either situation, it just is that the parameters around it are different.

DR. TEMPLE: Right, but one of the proposals before us is that they do only the first. That is all that Avid wants to do, only the first of those two. That is their study. Shake your heads if that is not true but I believe that is true.

DR. KATZ: Well, that is what they want to do initially.

DR. GOLDSTEIN: No. You know, we went through the first issue, can you detect amyloid or not. Now we are

assuming that you can detect amyloid. Is that clinically useful information or not?

DR. TEMPLE: Well, tell me if this is wrong. They are planning to compare normals, which obviously are going to be clean, and people with well-documented, autopsy proven Alzheimer's disease. That is who they are going to study. No?

DR. MATTREY: That is the phase 1.

DR. TEMPLE: Well, phase 1/phase 2, but that is what they want to be approved for.

DR. KATZ: The initial study is designed, as we understood it, to rule out Alzheimer's disease. I think it is very explicit. The initial attempt was to say that a negative scan means that you don't have Alzheimer's disease. Presumably, that would be the study and that would be the claim that would accompany the initial approval. That is our understanding, anyway.

DR. TEMPLE: I think.

DR. GOLDSTEIN: I think what I would like to do is try to crystalize this a little bit, not necessarily what their specific proposal is because I guess you guys and them can negotiate that. But we are starting out, again, with

the premise from what we just said that you can reliably detect amyloid in the brain.

So, let's say you can do that. To get to this first question, is that information clinically useful? And, one clinical utility potentially is that if it is negative it means you don't have Alzheimer's. Now, how you are going to do that, that is a whole other issue but that is one potential clinical utility. Another potential clinical utility is let's say it is positive, what does that mean? Dr. Royal?

DR. ROYAL: Every time I hear the words sensitivity and specificity I am sort of cringing over here. The reason is that when you have a complex diagnostic test you can create a whole family of sensitivities and specificities depending on what threshold you use. So, if you are interested, for example, in ruling out the possibility of amyloid deposits you could pick a point down on the ROC curve that would increase your chances of being able to rule out amyloid. Likewise, if you were to pick another point you could increase your sensitivity and decrease your specificity. So, we shouldn't think that there is a single sensitivity and specificity for any of these complicated

tests.

The reason that it may be helpful to rule out Alzheimer's disease is because the presence of amyloid plaques is a requirement histopathologically in order to make the diagnosis of Alzheimer's disease. And, if you show that this diagnostic test correlates well with the presence or absence of amyloid plaques it makes sense that you could then say it is unlikely that this patient has Alzheimer's disease.

On the other hand, if amyloid plaques are found in other dementias, in addition to Alzheimer's disease, which I believe I heard this morning, just because the amyloid plaques there doesn't necessarily mean that the patient has Alzheimer's disease. So, I think it is asking too much to say that it is going to rule in the diagnosis of Alzheimer's disease.

DR. GOLDSTEIN: Mr. Bridgwater?

MR. BRIDGWATER: Yes, thank you. Yes, I think it would be very beneficial, and I think that, as Dr. Weiner indicated earlier today, there is an amyloid hypothesis that is yet to be proved or disproved and I think that this information, based on the decision reached between the FDA

and the pharmaceutical companies, in question two would create the output that would be able to validate or invalidate, as the case might be, the hypothesis.

DR. GOLDSTEIN: Thank you. Dr. Herscovitch?

DR. HERSCOVITCH: I just want to clarify what the question is, asking the clinical utility of what? Initially I did think that the goal was to show that you could demonstrate the absence of amyloid. If that is what the studies are designed to do, that is what they will do. But my concern isB-we all hear, obviously, about off-label use of drugs, but how about off-label thinking about a drug? Physicians aren't going to think, well, the scan does not show the absence of amyloid. They are going to say amyloid is there regardless of what the study really showed and whether the test could show that amyloid is present; it was really designed to show that it wasn't present.

So, when we talk about the clinical utility we have to think about how physicians will use it and, in the worse case, could there be harm for that, what I will call off-label thinking and drawing of a conclusion which the study was not designed to show, if, in fact, that is what the study was not designed to show.

DR. GOLDSTEIN: Dr. Mattrey?

DR. MATTREY: My question was covered.

DR. GOLDSTEIN: Dr. Temple?

DR. TEMPLE: A possible conclusion, and I am obviously not telling you what to do, is that even if you don't believe the test can be properly used to say yes, indeed, that is Alzheimer's, you can try to characterizeB- sorry to do this to sensitivity and specificity of the test at any given value so that people will know what they are getting into if they misuse it in that way. That might be knowledge that is informative even if you don't actually think the test can be used in a yes/no manner in a way similar to saying no, there is no amyloid. I mean, that sounds like something everybody can believe in, from what I am hearing.

But you could still give the probability, if you had a broad population, that there is Alzheimer's. Even if that wouldn't allow you to use it as a diagnostic test, it would give you some ballpark as to what a positive finding means even if it is not definitive and even if you didn't say in the labeling you should use it that way. But it strikes me that it would be informative.

DR. GOLDSTEIN: So, one thing that we have talked about so far is diagnostic use, that is, can you rule out AD, and if it is positive, you know, does that increase the likelihood of AD? We talked a lot about all of these other diseases that may also have it. Or, as heard also, being completely normal 20-30 percent of people may have amyloid.

So, that is one particular potential use for this clinically. The other two usefulnesses clinically that I framed this in first is in terms of prognosis potentially in patients that have some minimal cognitive impairment and there is amyloid there or amyloid not there. Do people feel that that information would have some clinical usefulness? Dr. Green?

DR. GREEN: That is an entirely separate question and we are very far from being able to answer that. I mean, it is a total leap of faith to assume that the burden of amyloid correlates with the disease progression, disease extent, and certainly the effective disease modifiers. I hope I am wrong.

DR. GOLDSTEIN: Dr. Rudnicki?

DR. RUDNICKI: I agree with Dr. Green. I think that is one of our challenges. A lot of things that were

mentioned today about how this might be used are based upon theories that we will find drugs that will make a difference, and we are not there yet. So, knowing the answers to those becomes very tough. Hence, I think it makes sense to look at that, sure. But I don't know that that is a reason to approve a drug when we are not there. You know, technology has leaped ahead of our pharmacology and it creates one of those conundrums we were talking about.

DR. GOLDSTEIN: Dr. Rieves?

DR. RIEVES: Maybe to sort of share some of the dilemma we have, most of the imaging agents, I daresay, do not have demonstrated clinical utility. There are many examples. In fact, we had an advisory committee earlier this year dealing with the safety of some of our ultrasound contrast agents. Agents are approved to visualize endocardial border for example. Okay? I could just as easily be coming to this committee asking, well, is there any clinical usefulness to an ejection fraction? There are products approved for that. There are products approved for methacholine inhalation to detect hyperactive airways. There is no clinical utility demonstrated for those

products.

But, on the other hand, it is accepted and, again, this is a judgment question. So, we bring this question to the committee largely to get a sense of someone with a relatively unbiased perspective, to just get that sense of judgment as to the clinical usefulness. In the world of molecular imaging we anticipate seeing products that will detect apoptosis. We could be coming to this committee and saying we have a molecular marker for apoptosis. Is that clinically useful? We have a marker for ischemia. And, these type of products are in the pipeline.

But as it is right now, we are coming with amyloid largely to try to get a sense, in clinical experience and understanding, as to whether people think that this provides some clinically useful information. The threshold is one of some clinically useful information. The ideal situation would be to demonstrate actually what that clinical usefulness is, and that is what we would like to say. Candidly, I can't recall any diagnostic product where that has been shown.

DR. GOLDSTEIN: Right. Dr. Katz?

DR. KATZ: Just a clarification about how these

products are labeled since I don't deal with these products. So, is it fair to say that you could determine that there was clinical utility but you would not have to specifically describe in labeling what that utility was?

DR. RIEVES: You are right. Ideally, that is what we would really like to see. There are so many examples of imaging agents where that has actually not been the case. We are talking here today really about what may be just the lowest bar. So, this gets into a lot of considerations of safety, of course, and risk/benefit considerations. But, on the whole, we are talking about a relatively low threshold for action.

DR. GOLDSTEIN: Dr. Lu?

DR. LU: Yes, I am just trying to make sense about clinical usefulness that you mention here. And, one thing in a diagnostic test is when you have a test that is clinically useful it will be changing the decision process of the physician. So, in one of the Bayer studies they have clinical diagnosis of AD status and they have a consensus diagnosis, as well as PET imaging. I am just wondering if you send those PETs back to the site clinician and see if they will make a diagnosis more like the consensus panel or

expertise that shows that maybe there is clinical utility and it will change their mind.

Now, this may not necessarily go to the negative side. It could go to the positive side too. So, when they view the imaging they think, oh, you know, this patient may be more likely to be AD. Then, the panel may, you know, at that time serve as the gold standard.

DR. RIEVES: Right, and actually I think some of our sponsors have done that in other trials, but that is a very good clinical study caveat, if you will.

DR. GOLDSTEIN: Dr. Twyman?

DR. TWYMAN: Yes, I believe the greatest utility right now is to actually rule out the diagnosis of Alzheimer's disease. But a positive study actually would be supportive in that most evaluation in the Alzheimer's, or at least evaluation of a demented patient, is to rule out the diagnosis of other dementing processes. So, a positive amyloid scan, although it would not be definitively towards the diagnosis, I think would be supportive. And, that would be one piece of information that would be positive supporting evidence for the possibility of Alzheimer's disease. It may not move the patient from a probable

diagnosis of Alzheimer's disease to definitive, but it could be in the Du Bois criteria perhaps a more possible diagnosis.

In this regard, as Dr. Weiner pointed out, there is a large number of companies looking at Alzheimer's disease for therapeutic intervention, particularly disease modification. Most of these interventions are targeting amyloid. It would be very helpful, because of this environment where we are very much struggling to get enough patients in to study these therapeutics, to have something to help further motivate the possibility of entering these clinical studies.

So, a positive amyloid study could potentially be helpful from the standpoint of being a supportive piece of data, rather than an entire battery of negative tests.

DR. GOLDSTEIN: Dr. Anderson?

DR. ANDERSON: If I had a test for the detection of cerebral amyloid I would find it useful in my clinical encounter. I guess if the CSF detection of amyloid was approvedB-I don't know if it is FDA approved or how the tests are approved, but people do use CSF for its clinical utility in evaluating amyloid. So, that would seem to

suggest that if it is useful in the CSF it ought to be even more useful if you could get it in the brain.

DR. GOLDSTEIN: Dr. Green?

DR. GREEN: I think that how supportive it is for the diagnosis will vary dramatically based on the age of the patient, and so has to be corrected for that given the background noise.

DR. GOLDSTEIN: Dr. Zeissman?

DR. ZEISSMAN: I think the potential for clinical usefulness is self-evident. That is, all these companies wouldn't be here if there wasn't potential for clinical usefulness. I don't think it is pertinent though. I think the pertinent question for approval ought to be does it correlate with pathological findings.

DR. GOLDSTEIN: Dr. Temple?

DR. TEMPLE: I just wanted to follow-up with Dr. Twyman, and it also goes with a subsequent comment. To find out how useful a positive test is you need a fairly representative sample of people in the trials, which is somewhat different from just proving the value of the negative one. So, I wondered if you had thoughts about how to do that.

DR. TWYMAN: I am sorry, Dr. Temple, sample size?

DR. TEMPLE: No, just what you said, you need a bunch of old people who aren't so sick. You won't learn about how predictive it is unless you have people with other dementias, and all kinds of stuff.

DR. TWYMAN: Right.

DR. TEMPLE: So, it is a more demanding kind of study.

DR. TWYMAN: Right, and I am very much with you with regard to obtaining of data, particularly in a prevalence setting. You know, how often is the test positive or negative in the normal condition in age-matched controls, an Alzheimer's population of probable diagnosis of Alzheimer's disease, and also an in between population such as MCI. I think that is very important information that would be useful to the clinician although, as you point out, not predictive.

As far as I understand, at least one or two of the companies have actually committed to that post-approval study in looking at the progression of patients with positive scans versus negative scans.

DR. GOLDSTEIN: Dr. Rizzo?

DR. RIZZO: I just wanted to be clear on whether we are talking about potentially clinically useful or clinically useful. When we say it is clinically useful do we mean that it is ready to deploy in the field to discriminate between frontotemporal dementia in Alzheimer's disease, MCI in Alzheimer's disease, no disease in Alzheimer's disease, or are we simply saying that this has a lot of promise and it is ready to go for clinical trials in all of these different potential studies?

So, there is a big difference because we don't have the data to answer some of the questions that would be raised by the potential studies that I just mentioned. But there is plenty of evidence that it is potentially useful. So, are you asking the question is it potentially useful for clinical application or is it clinically useful and tell the clinicians use it, go with God?

DR. TEMPLE: No, I thought I heard a fair consensus here that it is useful if it is negative right now. How valuable that is could be debated but you really know this person doesn't have AD.

A positive test is more uncertain because there are lots of reasons for having amyloid. So, characterizing

that with diagnostic tests, that is another sensitivity and specificity test, and sensitivity and specificity don't always have to be 100 percent and zero percent with a diagnostic test. Sometimes it is 40 percent. But it still could be a useful test.

What I have been sort of slightly lobby for is that it is of interest to characterize it, and what I have heard is that the companies are planning to look at that, at least eventually.

DR. RIZZO: So, part of clinical utility is even if the absence of findings on the scan may be diagnostic of normal as opposed to Alzheimer's disease. Is that really better than what there is already?

I have been paying attention today and I am not sure that I have heard the clinical trials that show that. Maybe I have missed it but have they been done? I don't know.

DR. KATZ: No, I don't think that with these agents they have been done. We have heard evidence that in a cohort of patients who were diagnosed with Alzheimer's disease, at least in one series 17 percent didn't have Alzheimer's disease ultimately. So, the utility of a

negative test is that. It will allow you to say these people don't have Alzheimer's disease. They may have some other dementing illness or something else and, presumably, if you learn they don't have Alzheimer's you will continue to see what they do have.

But that is the utility. But that hasn't been shown with these agents. That has just been shown in a cohort of patients so presumably are patients who were falsely diagnosed with Alzheimer's disease, which a negative amyloid scan presumably, assuming we can document that the scan is reliable, would document that those people don't have Alzheimer's disease. There is utility in that finding. Again, the specific agents haven't been studied to look at that. And, I don't think we are talking about approving any of these agents in the absence of data on them. But if they get that data, that would be one way to establish a particular restricted type of clinical utility.

DR. GOLDSTEIN: I guess it also gets to the part of the diagnosis of Alzheimer's disease. Right? You have to have the correct clinical situation. You have ruled out other causes. Then, pathologically you need to have the pathologic changes, of which one of the sine qua non is

amyloid. So, by that definition, if there is no amyloid and this correlates very tightly with the presence of amyloid, if it is not there then, by definition, it is not Alzheimer's disease; it has to be something else. Dr. Mattrey?

DR. MATTREY: I think if we assume we can accurately quantify the amount of amyloid in the brain during the response to question two, then how can that data be used? I think what clearly falls out is that if it is negative it is not Alzheimer's disease. But if it is positive now for the first time you can say a person has or does not have amyloid in their brain while they are alive, which opens up an opportunity for time-dependent analysis, interventions, etc.

So, regardless of the clinical utility, the scientific utility would be huge because now you would be able to correlate amyloid with Alzheimer's and nothing else or vice versa. But for the first time you will have an index in a live person that tells you they have amyloid which has so far been correlated with Alzheimer's disease in 75 percent of the time. So, even without that clear-cut what can I do with this patient, I think that data would be

clearly worthwhile.

DR. GOLDSTEIN: Dr. Lu?

DR. LU: I just want to try to make clear that we want to hear talk about whether it is for diagnosis or really using it as a clinical trial endpoint of a prognostic marker. You know, I am not really a neurologist but hearing all the talk about diagnosis of AD is particularly important to rule out the AD. So, I think the clinical value is clear for the practice side to rule out AD.

But I think there is a huge gap in terms of being prognostic markers or surrogate markers for the clinical trials and I think there is a long way to go and I hope we are not talking about proof that we have found those markers. So.

DR. GOLDSTEIN: Dr. Rizzo?

DR. RIZZO: I didn't have anything else to say, except I would say to Dr. Mattrey that we have the CSF markers so the PET markers are not the only markers of disease. The CSF markers of beta-amyloid are already available and are marker of disease.

DR. MATTREY: And how good are they? Positive? Negative?

DR. RIZZO: I would ask the experts.

DR. RIZZO: Are they approved by the FDA?

DR. RIEVES: I can't say so but there are some people in this room who know. That gets into the in vitro diagnostics and a lot of that assessment gets into performance characteristics. So, on the assay itself I can't comment.

DR. GOLDSTEIN: Dr. Zeissman?

DR. ZEISSMAN: CSF findings don't have to be approved by the FDA. It is a biochemical finding that is a laboratory test. What we are talking about is giving a radiopharmaceutical to a patient that does have to be FDA approved. It seems like the FDA regulations just say that it has to be a marker of pathology, a specific pathology and, therefore, that is what is pertinent here. You know, these other questions will be answered later if this can be proven first and then approved as a biochemical marker of amyloid.

DR. GOLDSTEIN: Dr. Rieves?

DR. RIEVES: To clarify our intent with this question, we did not want these companies which, as you can tell, are going to invest considerable effort, patient

resources, that sort of thing, in getting these studies started probably relatively soonB-we didn't want to be coming to you, and you can tell the clinical development program here is focused on performance characteristics for the detection of amyloid, not Alzheimer's diagnosis, we did not want them to complete these programs and to come to you trying to make a risk/benefit assessment where there actually has not been any clinical benefit shown.

And, that is what they are telling us right now. They have no intention for this initial approval of assessing clinical benefit. It is solely performance characteristics to make a pathology diagnosis, if you will, which, candidly, is somewhat a precedent for imaging products.

Our challenge comes in, in making the risk/benefit assessment there because with that relatively low threshold for simply making a pathology diagnosis you would expect pretty incredible safety. So, in the overall development program that is something that we are going to have to assume, that these products are very safe in trying to design the clinical development program right now because the companies are not planning to actually assess clinical

usefulness, as they have outlined it now.

It would be great to do that but our intent here was to just get a sense of the committee's understanding and insight. If amyloid detection was clearly off the table, that would be useful to know. I get a sense that the general consensus is probably that it has some clinical usefulness. It may not be defined yet but it appears, and correct me if I am misunderstanding.

DR. GOLDSTEIN: Dr. Royal?

DR. ROYAL: I guess I am a little bit confused about this discussion about whether or not knowing amyloid is in the brain or not is clinically useful. Since we call it probably Alzheimer's disease until we get histologic confirmation, it seems that the presence of Alzheimer's disease is an important component of that histologic confirmation. And, if you can get that information noninvasively, it would seem like that would be clinically useful.

DR. GOLDSTEIN: Dr. Herscovitch?

DR. HERSCOVITCH: Although I work in imaging now I admit to being a card-carrying neurologist, and even in diseases for which there is no or minimal treatment

neurologists try very hard to get the right diagnosis. It is not an ego thing. It helps in counseling patients, in prognosis, in understanding and explaining what may happen to a patient down the road who doesn't behave the way you think he or she should.

So, I think given the prevalence of Alzheimer's disease among the dementing illnesses and the potential ability of one or more of these agents to show that there is no amyloid, therefor, no Alzheimer's there is clinical utility. One can speculate down the road if there is a therapy for Alzheimer's that was more dangerous than Aricept. That would be valuable, and so forth. That is speculative. But I think there is definite clinical utility.

One other thing, I am not too sure how our discussion fits into the overall discussion of biomarkers, surrogate markers for designing therapies but definitely if one had a therapeutic agent, even if it wasn't based on being on amyloid-busting drug but other drugs based on receptor manipulation, and so forth, if one had a clinical trial I think the power of your clinical trial would be substantially enhanced if on day one you could eliminate all

the patients who had no amyloid in their brain. That would substantially increase the power of the study.

Now, how that would fit into the regulatory framework, I will leave it up to the FDA folks. But just from designing a clinical trial, I think this would be extremely useful, to have an agent demonstrated to show no amyloid.

DR. GOLDSTEIN: Again to try to crystalize this, my view of the intent of this question was that, let's say we do this and we can show that there is amyloid in the brain, would this have any clinical usefulness now. In other words, would people use it because it is giving them useful information. So, I think the consensus, firstly, was that a negative test now would have clinical usefulness. Let's make sure everybody agrees with what I was hearing.

DR. ROYAL: Well, you don't know until you have some performance characteristics for the test. So, assuming that it is good enough you would say yes, but we don't know yet whether they are good enough.

DR. GOLDSTEIN: That is part (a). That was the first question. Then, the second point is, is a positive test useful clinical information? I think we had a big

discussion that it may or may not be. There is a whole bunch of other issues to consider.

The third part of it is that I think it is the sense of people that this is potentially an incredibly powerful tool to further research, potentially for patient selection, potentially for monitoring disease, potentially for prognosis. That is going to require a lot more research. Okay? Please correct me if I am wrong. I just want to make sure I got everybody's sense in summarizing correctly for the FDA and for the sponsors.

Let's go on to question three. See, my plan, one, two, three is actually working. Please comment on the strengths and weaknesses of the phase 3 study outlines supplied by the companies.

I am happy that this is number three because we have sort of done this one already. It depends, you know, on what it is we are trying to do. We have already addressed this I think for the indication of imaging amyloid in the brain. So, it really revolves around some of these other issues, one of which was supporting and not supporting the diagnosis of Alzheimer's disease.

Dr. Rieves, if you can tell us what you would like

us to do with this that you think would be helpful because I think we have actually answered this question already.

DR. TEMPLE: I think all three of us who are sitting here are nodding that we think--

DR. KATZ: Not nodding off.

DR. TEMPLE: No, that would be nodding on.

DR. GOLDSTEIN: We have coffee here.

DR. TEMPLE: Well, we could ask what the sensitivity and specificity of our nodding might be. No, I think we all think you did discuss that.

DR. GOLDSTEIN: Very good. Let me do one other thing before we stop. The sponsors are here and one of the whole reasons for this exercise was to help provide you and the FDA with what a bunch of independent people thought about all of this. Is there anything else that we can do to further explain, or any other questions that we can answer in a relatively short period of time? I want to make sure we have done our job here today. Yes?

DR. BLACK: One question, and Dr. Klunk kind of alluded to it and Dr. Herscovitch, you know, would 11C-PIB be available? I think the point was, you know, if it were used for 18F-PIB, is it available for other things?

DR. GOLDSTEIN: I am sorry, could you identify yourself for the record?

DR. BLACK: I am sorry, Don Black, head of R&D for GE Healthcare, medical diagnostics. The question is, is it available, and it is available. There is a study that is being planned now at Penn that compares Avid to 11C-PIB. It is available globally. In other words, if the committee or if the Division at some point decided that 11C-PIB was adequate, it is certainly something that other companies ought to be able to use for that comparison.

DR. GOLDSTEIN: Very good. Let me give the members of the committee one last shot at making any comments. Dr. Anderson?

DR. ANDERSON: So, I have a question. If any of the products discussed were to establish the histopathological demonstration that has been suggested by the committee as necessary, would it be sufficient for a follow-on product to simply demonstrate concordance with the product that had previously established histopathological demonstration, or does each and every product have to demonstrate its own autopsy-based study?

DR. GOLDSTEIN: That is a regulatory issue. FDA?

DR. RIEVES: I sure don't want to answer something different from my boss who is here. But in general we have a precedent for that, yes, as a reference product. We just approved a product this past spring that compared its performance characteristics to a reference product.

DR. GOLDSTEIN: Dr. Herscovitch?

DR. HERSCOVITCH: I would like to make a general comment that although this discussion I think has tremendously advanced the potential for having an amyloid imaging agent in the field, I would just like to point out that the FDA has probably had another home run with regard to showing their seriousness about considering the indications for a radiopharmaceutical to be approved on the basis of its functional or biochemical capabilities, because there are several other agents that are being considered, especially in the field of cancer, imaging such physiologic or biochemical entities as tissue hypoxia, cellular proliferation and angiogenesis. And, I think the meeting today and the lead-up to it has really been a tremendously successful model with regard to how these other agents coming down the pipeline will be handled by the FDA and I would just like to congratulate them.

DR. GOLDSTEIN: Thank you. The FDA rarely gets congratulated and you should take your bows. Very well, I think we have had a thorough discussion. I hope we addressed the questions and the issues. I want to thank all of the speakers this morning, all of the sponsors for taking the time to come, all of the people who spoke at the open meeting and, obviously, also all the members of the panel and the FDA. Thank you.

[Whereupon, at 4:10 p.m., the proceedings were adjourned]