Dan Perry: Thanks for joining us for today's meeting. My name is Dan Perry and I'm the president and CEO of the nonprofit Alliance for Aging research and more pertinent to today's meeting I am the chair of the ACT-AD Coalition. For those of you less familiar with our coalition ACT-AD is an acronym. It stands for Accelerate, Cure, and Treatments for Alzheimer's disease, and our coalition is made up of over 50 not for profit organizations that represent patients, their family caregivers, seniors' organizations, women's health groups. Some are in the audience and I thank you for being part of our coalition, and the modis operandi that we have developed over the last five years with this coalition that allows patient organizations to play an effective role in moving the process to which we will ultimately see the next generation of effective and safe treatments for Alzheimer's disease is precisely the meeting where you are right now.

These Alzheimer's allies meetings, as we call them. This is now the fourth of these and we are deeply indebted to Dr. Katz, his colleagues, staff, officers of the Food and Drug administration, and of the neurological products branch for meeting with us on an annual basis with patient organizations, representatives of companies, academic leaders, clinical trial experts, when we really can roll up our sleeves and dig into one particular subject in great depth and clarity. We choose the subjects almost a year in advance with Dr. Katz's assistants, and the one that we are going to discuss today is actually a continuation of the allies' meeting of 2010 held just about a year ago.

And that was what is it about phase two clinical trials in this disease. They are getting larger, they are taking longer, and most concerningly, they are not providing the signals that are carrying on to a successful approval in phase three. So last year we drilled into this issue. I think it was one of our most productive sessions. The same subject of trial design in phase two – how to get it right – was taken up again just this past summer at the Alzheimer's Associations Clinical Research round table, and so we thought, "Well, what more can be said about this subject?" And it occurred to us that we really need to have the companies that are making these decisions in phase two and carrying them into phase three meet with us and open up about what decisions they are making, why they're making them, what biomarkers they may or may not be using, and then let some of our clinical trial experts, our academic leaders respond to that. Let's bring the agency in and let's have a real discussion about this.

So we will have some brave presenters from five companies this morning. Dr. Katz has graciously agreed to stay with us into the afternoon, so this should be, I think, a potential turning point in our discussion about the best

way to get the trial design right for Alzheimer's disease. So I wanna thank all of the presenters in advance as well as our friends from the Food and Drug Administration – thank all of you. But we also are cohosting this meeting with two fine organizations that we work with day in and day out and those are the cure Alzheimer's fund and the coalition known as LEAD, which stands for Leaders Engaged in Alzheimer's Disease, and I'd like to ask my friend Tim Armour who is the president and CEO of the Cure Alzheimer's Fund to join me up here and to help us get started and then following that I'll ask George Vradenburg to do the same on behalf of LEAD. Tim.

Tim Armour: Thanks Dan. Thank you very much. George, good morning. Good morning all. Thank you for being with us. It's always an honor and delight and inspiring to be in a room with people so committed, dedicated, and talented in ending this terrible disease. So we look forward to listening and learning this morning. Cure Alzheimer's Fund is supporting basic research into the origins of Alzheimer's, and as such over the last 6 years we've funded about 20 – about 50 different projects in 20 different institutions across the country, and with that focus we honestly haven't been very mindful of the issues that are gonna be discussed here today, but now we are. We are because some of the research that we have funded has reached the stage where drug development is within sight for us.

Secondly, we all know how resource constrained we are and every dollar has to count at every point in the process, and given the expense that Dan referred to and that we all know way too well about phase two trials, it's important for all of us to get this right. And thirdly, the more we know about this disease the more we know that it starts decades earlier than symptoms are manifest. So if that's the case how do you develop a drug and test it where the effects – the behavioral effects – aren't seen until decades later. So these are huge challenges. The kinds of questions that you have on the program that are being posed to the panelist we think are the right ones, and I very much look forward to listening and learning about the expertise in this room and how we're gonna tackle them. They're huge challenges but we have the right people here to deal with them, so thank you once again for being with us. *[Applause]*

Dan Perry: Thank you, and Tim, thank you for the fine work that Cure Alzheimer's Fund does to support fundamental research in this disease. Cure Alzheimer's Fund along with the Alliance Rage and Research and ACT-AD are all part of a – what are we – 50 plus groups now in the LEAD coalition including government agencies as well as patient groups and many others. So George is the co-chair of that and pleased to have you co-hosting today, George.

George Vradenburg: Dan, thank you so much for doing these allies meetings. I was here the last – I've been at two out of three so far, and this is now third out of fourth, and they are all – they get into the weeds in a very critical fashion. They get down to the nub of what we're trying to do and that's accelerate a cure and that's very powerful. Just a word about my organization, Us Against Alzheimer's. Us Against Alzheimer's is a C4. Us Against Alzheimer's network a C3, but we formed these organizations about a year ago in the strong belief with a mission that we could get to us some means of controlling or managing the disabling symptoms of this disease by 20/20. Also, believing very strongly in the power of goal setting to motivate one to think differently about how one goes at the processes of drug discovery of the 12 year, $1 billion therapeutic pipe line. On average now that's just too long, too slow, and too costly to get drugs to patients who need them. So we founded Us Against Alzheimer's really with a different attitude and a different operating model.

The different attitude was urgency in patients in degree of naivety, asking why is it that we can't move faster, trying to develop a whole series of interventions that might shorten the therapeutic pipe line, reduce the cost and time of getting drugs to market. A different operating model is very much an open network model, very much a belief that the power of the network is at the edge, not at the center, that movement occurs more rapidly with more people involved and information exchanged decision making. So therefore with crowd sourcing on the research side and open architecture patient registries and on other operating principles on which we could move, data standardization, data exchange, seeing critical path here in see ____ that we can move more rapidly than we do today using some of the models – operating models, technology models of the 21st century rather than the 20th century.

Part of that expression about using networks rather than just individual organizations is LEAD. Leaders Engaged in Alzheimer's Disease is, as Dan mentioned, now 50 organizations everywhere from basic research organizations both government and private through care organizations down to family caregivers and the national lines for caregiving and many other caregiving organizations and everything in between, and it has everything from government agencies as technical advisors and for profit corporations and nonprofit and academic institutions and patient advocacy groups and national organizations who are members of this all representing an Alzheimer's serving community which is large and unfortunately growing because of the number of people that have this disease and the cost of the nation of supporting those who have it. But with an effort to try and shorten the therapeutic pipe line through efforts

like today's meeting, in fact trying to reduce the time to get to – time and cost to get to market, then we can try and save millions of lives and trillions of dollars.

So I am delighted at every stage of this game to have Dan Perry. He and I have been working now together for a couple of years and it's one of those people you go into battle with you know you can turn your back and in fact he's got your back and I've got his back because we're in the same fight and we're in the same fight with all of you and we're looking forward to finding ways to get safe and effective drugs to the patients who matters so that we can save lives and save money. So thank you very much. *[Applause]*

Dan Perry: Thank you very much, George, for bringing your eloquence to our beginning this morning and for co-hosting and for all that you do. Just a couple of words about the format: As stated we will have a number of companies come up and describe – kind of show us the inner workings of how decisions are being made with regard to design of their clinical trials. We will have questions at the end of each presentation and then after all of the presentations and the reactor panel from the academic leaders and from Dr. Katz and FDA personnel we'll have everyone back again for even more questions. So the format is designed for a lot of interactivity. This is not a didactic meeting where people come up and speak at you and you just sit there and then go home. That would not bring the value that we want. So we really want to engage you. There's not going to be a lot of formal introductions and a lot of titles. The bios of all the speakers are in your folder, so I refer you to that. So let's jump right into it and Dr. Eric Siemers of Eli Lilly Company will be our first to go. Eric, good morning and welcome.

Eric Siemers: Well, good morning and thanks very much for inviting me. Dan says a lot more eloquently than I would, but when we first had this conversation some time ago about what to do at this meeting, Dan said, "Well, it's all about how you do phase two," and I said, "But Dan, we don't know how to do phase two yet and so I'm not sure what we're gonna talk about." But to that point there's a lot of discussion that I think we wanna have and one of the things that I'll get to is that especially within the next year there will become some data available that I think, I hope, will be very helpful in this regard and so I think – well, I hope we're getting close.

Now, the other point just to expand on something that Dan mentioned is that I really do wanna have time to get to the discussion. A lot of the slides I have are slides that many of you in the audience have seen a number of times before. I apologize for that, but just to get everybody on

the same page I'll go through those, but I'm gonna go through, especially some of these biomarker slides, very quickly. So if there are questions that people have about some of the technical details you can find me at our break afterwards or ask a question, but I am gonna go pretty rapidly through some of the data just to get us on the same page to really get to the discussion part of this.

So let me just jump straight into the phase two study that we did for solanezumab. It's 52 subjects with mild moderate Alzheimer's disease, few healthy subjects, and we'll go into that at the interest of time, but the important thing about this study is that patients were dosed for 12 weeks. And so this is a theme we'll come back to, but one of the branch points that we have to make in terms of decisions about phase two trials is do we run them out 18 months like we would a phase 3 but with smaller sample sizes, or do we do it for a shorter period of time and base our outcomes on biomarkers which admittedly – well, I won't say admittedly – but it might be a riskier way to go. And so very briefly, again, here's the kinds of bio marker data that we saw from our phase two trial. So when you infuse solanezumab which binds to a beta with a very high affinity. You see a very mark rise in plasma A beta. This is bound to solanezumab.

You can't actually measure free A beta in plasma but you can calculate that with some modeling and based on that we found that at actually each of the doses we used there was a fairly dramatic fall in our calculated free A beta in plasma so we think that really goes down to not quite zero but pretty close. And then this is where it actually got a little more interesting for us, I think, is that in spinal fluid at the top of the panel there you see that there's a dose dependent increase in A beta so a small percentage of the antibody crosses the blood brain barrier binds to A beta and so the A beta that you see there going up is bound to be antibody.

We also have an assay that spinal fluid can actually directly measure the unbound A beta. It's not possible to do that in blood, but in spinal fluid you can do that, and so at the bottom left you can see this is A beta 1 to 40 and you see this dose dependent decrease in unbound A beta 1 to 40, but unbound A beta 1 to 42 actually increased. And so it took us a minute to think about that, but the bottom line is is spinal fluid concentrations of A beta 1 to 42 or low in patients with Alzheimer's disease, and this actually – if you actually look at the numbers it comes up into close to the normal range, but the thought here is that we've actually reduced the amount of free A beta enough that the plaques actually do start to come back into solution if you wanna think of it that way 'cause the plaques are A beta 1 to 42 but not A beta 1 to 40. That's why you see that discrepancy.

So that's really one of our goals with a lot of our programs is just to demonstrate central pharmacology and we felt like that was at least one interpretation as that's a demonstration of that. We also showed that the amount of plaque load that patients had correlated with the amount of A beta 1 to 42, but again, not 1 to 42, but A beta 1 to 42 in the plasma. So there's some relationship there between more plaque in the brain at base line, more A beta 1 to 42 in the blood after a treatment, giving us an idea that the sync hypothesis that things are moving from brain out into plasma, actually had some traction.

We did a couple of other things, and this is the work from Ron Demotos' lab where we look at certain forms of A beta that we believe are only present in the plaque. One of these is this pira glue A beta and we saw a dose dependent and time dependent increase in this in the plasma. So again, we're essentially seeing little bits of the plaque come out in plasma after a treatment with solanezumab, and again, just to remind you, solanezumab doesn't bind to the plaque directly. It only binds to the soluable A beta. So the plaque coming into solution actually really has to be then an equilibrium shift.

And so we've also identified – well, we haven't identified it quite yet. Ron Demotos is working hard on this, but we're close to identifying a fragment too, which we believe is another modified form of A beta that only occurs in the plaque and we saw the same sort of thing with this is that there's a dose dependent increase in the plasma and we also saw the same sort of thing in spinal fluid. So we have a number of bits of biochemical data that all point us to the idea that we've changed the equilibria shifted the equilibira enough with solanezumab that even though it doesn't bind the plaque directly, that the plaques are essentially starting to come back into solution.

Now, does that mean you have clinical advocacy? Well, we'll know next year, but it does mean we have central pharmacology, and not just mechanistic pharmacology, but some downstream pharmacology. And that was really our decision making in terms of going forward into phase three. So a number of you have seen this slide before and I did wanna talk just briefly about semagacestat. I know this is really about solanezumab, and I just wanted to make sort of one introductory comment here. The results of this were presented at ICAD and there was a fair amount of discussion in the press even about this, and one of the points in one of the articles was that maybe we were a little too cheerful about this. And I wanted to really make the case that we weren't cheerful about the results of the study.

I mean, there are still people on the team that get kind of choked up when you talk about the fact that people actually got worst, and that's obviously not the intent, but what we do think is you have to learn from these things. And so it would be a huge mistake, in my view, to walk away from this and say, "Well, it didn't work. Next compound," and not try to learn something from it, and that's really the intent here. I just wanna be clear about that, but anyway – and again, we've – you've heard this before and a number of you have seen this slide before, but semagacestat or gama-secretase was actually the first compound to cause a cognitive change one way or another, and we actually used the same strategy of a short phase two study based on biochemical biomarkers to get there.

Now, obviously that wasn't the change in cognition that we wanted and maybe during the discussion we can have some debate about why it went the wrong direction, but the point is it actually did make a change in cognition. So there was central pharmacology for this compound which really hadn't been demonstrated for compounds going into phase three previously. So just briefly to go over the biomarker strategy here, it's similar but not identical. In plasma you see a dose dependent reduction with semagacestat and gama-secretase inhibitor. The real data for us, again, that told us we actually had central pharmacology and on the left hand side of this slide here – this is a single dose study actually in volunteers – so not an 18 month study at all, and so this is using the silk technique that was developed at Washington University in St. Louis with Randy Bateman. And that shows that at the doses we used in phase three over a 12 hour period there was about a 50 percent reduction in the synthesis of A beta.

Now, this is based on spinal fluid measurements. Again, this is central pharmacology. On the right hand side of the slide, this is spinal fluid from our phase two study that Kaj Blennow had an idea, asked us to send him the spinal fluid. I didn't actually think this would work, but it actually worked really well, and it showed that because we'd inhibited the gamma cleavage there was an increase in alpha cleavage and then this dose dependent increase in these alpha fragments. But the point here is this is spinal fluid from our phase two study, same doses we used in phase three, and this is evidence in our view of central pharmacology.

And so what happened I think, as everybody knows, we did initiate two phase three studies, large molding national studies, and then in August of 2010 our data monitoring committee looked at the cognitive data and actually that – looked at the cognitive data as we wrote the charter and planned that analysis, could only have shown worsening in cognition. It wasn't really set up to show any improvement and we would have gone

ahead even if it had been improved. And so certainly when we built that into the study the last thing that we expected was for people to get cognitively worst, but we realize that this was a new mechanism. We didn't know our phase two's were short and we left it in there and that is, in fact, of course what the committee found is that patients became cognitively, not a lot worst, but they did become worst and so we stopped the study.

Now, I'm gonna show you just a little bit of the data from the phase three study, and actually for this group I think it's important to make the point that we at Lilly have developed a relationship with the ADCS and formed a data analysis and publications committee. You can see the members of the committee here. The idea there – we actually formulated the idea when we were hoping that semagasisat would be successful, but either way, the point is that we have this outside objective set of eyes looking at the data, doing a completely independent analysis, and coming to their own conclusions, and I think that we're already getting a sense as this committee is started to chew on the data a little bit that this is gonna be really useful, and so I'm looking forward to the committee going forward.

So I'm not really gonna present anything that wasn't shown at ICAD here, but the committee's working on this. So here's the worsening that we see in the ADAS cog. It's dose dependent. It actually does not go away after we stopped the drug. This is the worsening in the ADCSADL. Again, it's – the dose dependence isn't quite as easy to see here, but it does not go away after we stop the drug and then here's the CDR Sum of Boxes. We didn't collect this after stopping drug, but it shows a nice dose dependent change in slope which is a point that's been discussed over and over again in terms of disease modification. Now, we've just – we've started looking at the biomarkers and this is just from one of the studies. All the data on the previous slide is just from one of the two studies, and you can see this trend in the study for change in FDG-PET.

Now, one of the things – and there may be some discussion about this – is if we are gonna go the biomarker route, which biomarkers tell you in a phase two study that this is a compound you wanna look at for disease modification in phase three. FDG-PET may or may not be the best one because there's pretty good data that would say a symptomatic drug can alter FDG-PET, but at least this is a demonstration that in a large molding national phase three trial and one would assume then in a smaller phase two trial, you can see changes in FDG-PET that might lead you to improve your decision making in terms of saying, "Okay, here's our real downstream measure to say that we have central pharmacology."

And so this slide – I'm not gonna really go into the details of this. This is the data that we presented at ICAD from our first identity study, and so I wanna be a little bit careful about what I say here because we have our committee members, Rachelle Doody and Paul Aisen here in the audience, and I think one of the real values to this committee is that it really is a fresh objective set of eyes. But I will tell you that we at Lilly have started to look through more of our biomarker data and looked at both studies together and even though we didn't see anything in one study by itself, some of these things I think – so I'm not gonna tell you that we're gonna see anything, because I really don't know that that's gonna be the case. But it is an opportunity for me to maybe nudge the committee to maybe start looking at these things a little bit more quickly because if we can find some things in here I think this is gonna be extremely valuable in terms of lining up biomarkers now in a large phase three study, but to say, "Okay. Are there changes that we can see in here that would be applicable to a smaller phase two study?"

Now, the one thing as bad as it is that semagasisat made people worst, the fact that there was a drug effect actually in some ways is helpful, because now we can see what direction certain things go when you have a drug effect. Even though unfortunately it's in the wrong direction, it's actually kind of more helpful than having no drug effect at all. So I would say stay tuned and I'll come back to this point. And again, we don't really need to go over this unless there are questions. There are a lot of potential explanations for why people got worst cognitively. It could be related to APP and A beta cleavage. I think a lot of us feel that it's probably some other substrate of gama-secretase and that remains to be seen.

So let me really get to the final point in the presentation, and that is that as you may have noticed, I didn't show any kind of cognitive data in all these phase two studies, and so why don't we do that? Well, and that's the real crux of the question here for the field is that when you look at ADAS cog scores or scores in other cognitive measures, if you do a long 18 month study but with a small sample size you'll be statistically under powered and then you're gonna run into problems interpreting the data at the end of a long 18 month study. In a short 12 week study, the kind that we did for semagasisat and solanezumab, we have our biomarker data, but you're never going to be able to make sense of cognitive data in a 12 week phase 2 study.

So we really took the risk that we're not gonna pay attention – well, we pay attention to the cognitive data – but that's not what we're gonna base our decision on. We're gonna base our decision on whether we have central pharmacology and whether or not we think we're having an effect

in the brain that's the intended effect. And even for semagasisat I think it's pretty clear we did inhibit gama-secretase. That just turned out not to be the right thing to do, but still, we always come back to this. Is there any way that we can look at cognitive data in phase two and at least get a hint or some idea or some improvement in our probability success in phase three?

So we've gone back and we've looked at our ADAS cog data, and again this is for – this has been presented previously for semagasisat and one thing that we did get out of this is that if you wanted to power a phase two study just to exclude worsening, you could do that with a modest sample side. So you could do that in a 14 week study with 68 people per arm. You can – the reason why you can't really – this is actually data now from semagasisat. The reason why you don't see the separation between the treated groups and placebo groups because the error bars overlap because they're so close together which was of course the real problem. But still, statistically 68 people at arm you could exclude worsening of the magnitude that we saw with semagasisat, so that's okay. I mean, it's good to show that you're not making people worst, but it's not really what we're trying to get at. It's not are people getting better? Is there a positive effect of this going into phase three?

So this shows data from what would be sort of a typical phase three study with a blue line with a worsening in ADAS cog. And then at the 12 week time point you see this is the actual data from our solanezumab phase two study, and so you can see actually that the placebo group falls exactly where you would expect the placebo group to be at 12 weeks, and actually if you look at the treated group, the green triangle, there's an improvement there. So should we look at that we say, "Geez, 12 weeks, phase 2. This is what we're gonna go with." If you line up – and I'm not sure – yeah. I think you can see how that projects. If you line that up with our semagasisat data from the same time point, what you find then is for the 100 milligram group we're actually right on the placebo line, there actually is a little bit of a trend. The 140 group was a little bit worst, but you look at the placebo group and it's improved and in fact it's improved about the same amount of improvement we saw in the treated group for solanezumab.

So what does that mean? That the placebo worked for semagasisat? I mean, I don't think it means that, but I think that the point is is that again, there's enough variability in these cog native measures in small sample sizes in short periods of times, probably what you're looking at here more or less is statistical noise. I mean you can't really exclude that. Now, one of the questions, and this gets into how we can accelerate the process, is

what if you would have run this out to 24 months, and what if you beef up the sample size a little bit in a phase 2 study, and then what if you do some trial simulations based on that? Could you get some cognitive data that actually made some sense? I think that's something that really needs to be explored. So in other words you're not gonna do an 18 month phase 2 study, but maybe a 6 month study would make some sense with maybe a little bit bigger sample size. But again, and this is the point of the discussion, I'm not sure I would use that alone to make a decision to go into phase three. I think I would wanna link that up with, again, evidence of central pharmacology based on biomarkers.

And so, again, this is a slide a number of you have seen before, but this is – or I'd like to leave this on a little bit of a hopeful note, is that we've had a number of compounds that's already been mentioned that have failed, and I think these compounds up until semagasisat there really wasn't compelling evidence, and there some nuances to that, but not really compelling evidence of central pharmacology. Semagasisat did and I hope, I think, that actually as we and the committee actually digests this data that we can actually learn some things out of semagasisat that'll actually help us understand the relationship between some of this biomarker changes in phase two and then what we expect to happen in phase three.

The other point – and a number of us have been dealing with this for a while so it's hard to be patient – but next year we're gonna get a big bowl of data from solanezumab phase three and babnezumab phase three. Now, as we all know, at least one of those has to be successful. Right? We don't know that, but even if they're not, I would hope that we can learn something from the biomarkers that are in those phase three studies. Line that up with the clinical measures and that – those data will up us to understand which biomarkers we can apply to phase two that actually do get – do have some predictive value for success and even what direction things will go in phase three. So it's hard to be patient but having spent some time looking at the semagasisat data, it's gonna be a really exciting time for the field when we have this bowl of data from solanezumab and babnezumab. So with that I'll stop and I'll just ask for any questions. *[Applause]*

Dan Perry: If anyone wants to ask a question just raise their hand and then we'll have a microphone for you.

Audience (Doody): Thank you, Eric. That was thorough and thought provoking. I just wonder as you were talking about the modeling of having done a little bit

longer phase two trial with a little higher sample size, I'm sure you've run those numbers. What was your conclusion? I wasn't clear on that.

Eric Siemers: Yeah. No, actually – I mean, we've talked about doing those modeling, but we haven't really done it to the point to get to a conclusion.

Audience: Okay. Thank you.

Audience (Katz): Hi. I'm just wondering have you given any thought to – not that we have given a lot of thought to it – but combining phase two and phase three? As I sit here there are many ways to look at data as it evolves. There's the adaptive techniques. Again, I know there are gonna be some more discussion about this later, but it occurs to me that it's possible anyway that the development could be truncated and you could find out earlier whether something's not working either, which is of course always useful, but just sort of combining phases as opposed to the standard phase one, phase two. I think that's something to think about.

Eric Siemers: Well, no. Thanks for that. I'd almost like to turn the question around, but you've answered. I guess you've thought about it some too and we've thought about it and as probably most people know some of the trial designs that are being discussed for pre-symptomatic patients whether they're patients with genetic mutations or patients with just evidence of amyloid pathology, that's really being actively discussed I think for those groups, but if you just even talk about mild to moderate Alzheimer's disease, more or less standard drug development, certainly – I mean, I can just give you my opinion from an industry stand point – we would be more than happy to have those discussions.

I mean, we would certainly be happy to do that because I think as you're alluding to – you could do a 12 week or even 6 month study, get the data, continue those patients, and then increase enrollment and then that becomes your phase 3. And that certainly in terms of time lines for drug development I think would be a real benefit. So again, I guess you have to have a room full of statisticians to have part of that discussion too.

Audience (Katz): I think it'd be better not to have them in the room.

Eric Siemers: Or maybe not. Could be, but no, I mean, that's certainly something that we would like to think about.

Dan Perry: Any other questions? Well, if not, thank you again.

Eric Siemers: Okay. Thanks. *[Applause]*

Dan Perry: For someone who says that his company really doesn't know how to do phase two, I think that was an excellent start off – an excellent lead presentation – very thoughtful, very candid, and I appreciate Eric. Our next up is Alan Lipschitz of Bristol Meyers Squib. Dr. Lipschitz, and as he's coming up let me just say that we have not scheduled breaks so as needed, restrooms down the hall to your left and then we'll – we're gonna have a working lunch. So this is gonna be an intensive three quarters of a day. So have at it.

Alan Lipschitz: Thank you. Well, we had a lot of – we've had a lot of experience with phase two now. We've had two phase two trials going, both in pre-dementia and in mild to moderate dementia, and we've learned quite a bit from these too and there's been a lot of cross learning as the two trials have progressed. I hope to be able to share that with you today. I am a full time paid employee of BMS and own stock in BMS, if you had any doubt. The mild to moderate study or O13 study, the – I'm gonna describe these in detail and we'll be comparing them.

This was a randomized, fixed test, five arm study. We randomized 209 patients and the patients on the lower doses 25 and 50 were started on those doses and continued on the higher doses, the 100 and 125. They were started on 50 milligrams for two weeks and then up to the higher doses. The doses were fixed. There was no down titration permitted and we did see a CSF sampling in 56 subjects at baseline and then again at either week 12, half way through, or at the end of the study. Biomarkers was really one of the main objects of this study. We were looking for disease modification effects particularly on the biomarkers.

Now, compare that with our pre-dementia O18 study, and this study is ongoing so there isn't a lot I can say about the study, but we'll be looking at some of the baseline findings which are pretty interesting. And sadly you may be seeing this word for the first time – avagesastat. That's our name where before we were just a number. Well, for our pre-dementia study we took patients who had amnesic MCI, screened them, did lumbar punctures, and those who had the amyloid signature in their CSF – pathologic CSF – they were randomized one to one to avagesastat or placebo and the others, well, we took about 100 of them and followed them anyway – not randomized – but followed them through the same study procedures. And in a sub-study we did AV 45 PET scans on 77 of the subjects – subjects from both groups.

Well, in the OM3 dementia study we randomized 209 to those 5 treatment arms for 24 weeks of treatment and this is about a year and a half from first patient to first visit to last patient, last visit. The pre-dementia study randomized about 25 percent more subjects and the treatment period was a good deal longer. It was a minimum of two years, and the study itself is going on for much longer and much longer – much more than 25 percent longer and this attests to the difficulty of recruitment in this state of Alzheimer's disease, and we'll look closely at that. We've learned a good deal about that.

Primary in points for both studies were safety and tolerability. We don't expect to be able to see an efficacy effect in this size of a study and six months is really not long enough in the dementia study to see an efficacy effect, not with a disease modifying drug. But secondary points were CSF biomarkers in the mild to moderate study as well as we had the cognitive measures in there to learn more about our drug. We were looking at PK variability, at the sid-polymorphisms and correlating exposure with biomarkers and clinical effect at 41 sights.

Well, for the pre-dementia study we needed to go to 72 sights and here the key secondary was pre-dementia. For safety and tolerability we were assessing this by looking at the AE's and the routine labs, also MRI in the pre-dementia study. The key secondary's in the pre-dementia study with progression to dementia and how predictive are the biomarkers that we're looking at. Also, what could we tell from the cognitive and functional scales there about progression.

Looking at the demography in these two studies, the ages are pretty much the same. The percent female about the same, 40 to 50. As usual both groups were over-educated, which is what we usually see in clinical trials in Alzheimer's disease, of course, and the ApoE 4 subjects were there in abundance more so than in the general population as we always find in Alzheimer's trials. The inclusion criteria in the mild to moderate study, we took subjects from 50 to 90 years old, MMSE covered the mild to moderate range. They had to have at least six months of cognitive decline that was progressing and they had to meet the clinical criteria for probable Alzheimer's disease and the DSM4TR criteria for dementia of the Alzheimer's type.

For the pre-dementia study we extended the age range down to 45. MMSE's were allowed from 24 to 30. The subjects all had to have a memory complaint that they presented or that their study partner recognized and they had to have really objective signs of memory impairment on either the Wechsler memory scale, delayed paragraph recall, or the FCSRT. CDR's – they had to have a CDR global score of 0.5 and a CDR memory box score of at least 0.5.

We wanted to exclude any other possible causes for the dementia and for the pre-dementia, so patients were not allowed in who had a history of stroke, the Hachinski scale was there as well to exclude those who had strokes in their past. And the Geriatric Depression scale was in there to exclude those who might have had depression concurrently or producing their symptoms. In the dementia study and in the pre-dementia study we permitted stable doses of compound – marketed compounds – for Alzheimer's disease and everyone who was in either study had to have a reliable study partner who accompanied them to the sessions. Partly for the sake of some of the rating scales of those in the pre-dementia studies, they could not have any DSM dementia diagnosis.

Now, the MRI entry criteria in the dementia study – their MRI's had to be normal or to show atrophy that was consistent with Alzheimer's disease and that was initial entry criteria as well for the pre-dementia study, and then midway through the pre-dementia study a new set of MRI requirements were promulgated for all such studies and they – the subjects there had to have – from that point on – had to have no macro hemorrhages and less than two cerebral micro hemorrhages. This was from about, oh, I think September or so of 2010 until the last subject was recruited in June of 2011.

In the pre-dementia study the amyloid signature that we were requiring in the CSF was an AB 42 level of less than 200 pictograms per ML or a tau to AB 42 ratio of at least 0.39. So we were sure that these were patients who had the amyloid pathology on board. Our phase one data had shown convincingly that our gamma-secretase inhibitor that we were investigating here could alter that amyloid metabolism. These criteria made sure that these were patients who did have abnormal amyloid on board.

Well, what we actually found in the baseline populations, MMSE in the dementia study, the mean was 21.4. In pre-dementia study it

was 27.0, which just goes to show that the MMSE as we know is not very sensitive to pathology. ADAS-cog, CDR, and the ADCS all were about what you'd expect them to be in the dementia study at baseline and are considerably less impaired in the pre-dementia study.

Now, in the pre-dementia study randomization has completed all the 72 sights. One thousand, three hundred and fifty subjects have signed consent and been enrolled. About 20 percent of these subjects were randomized, and that's a fairly sobering number. Yeah. We're also following 104 of the subjects in an observational cohort. Well, how'd we get to 20 percent? They're really two phases of the screening process and the first phase was everything short of lumbar puncture. In that first phase we lost about half the subjects. Sixty percent of them failed that was stage one criteria.

Why did they fail – those stage one criteria? Well, about a third of them did not meet the MCI cognitive criteria. They were not sufficiently impaired. About a quarter of them met the dementia criteria or had clinical severity that was too grave. They were too impaired. This sounds like – it's not *The Little Red Riding Hood* – who is it?

Audience: *Goldilocks.*

Alan Lipschitz: Oh yes. Yes. Thank you. Yeah, the – well, we lost about a quarter of them to abnormal labs or ECG or to exclusionary illnesses and that's not unusual. That's what one generally finds in a study, and then there were feasibility issues here. We lost about a fifth to feasibility issues. The feasibility issues – and let me tell you what those were – the number one feasibility issue was the need to comply with the visits schedule and both for the subject and for the study partner. That was the major reason that people who got to that point declined to proceed further. The second was not having a study partner who would be able to accompany them, and the third was antidepressant use where subjects had been on antidepressants, just started recently and had not been on long enough to be stable on their antidepressants. And the small number of a feasibility issue cases were subjects who read the IC and did not wanna sign the uniform consent form.

Again, that's not unusual, and I think there's a real learning here in how to do more to exclude patients before you get them this far in a study. Well, those who got through the 40 percent, we did

lumbar punctures on them and half had pathological CSF didn't, so overall we had about an 80 percent screen failure rate. This was not entirely unexpected and when I was preparing a study I kept thinking – this presentation – I kept thinking, "Never do anything for the first time," but we had expected around the 30 percent success rate and we thought we'd be able to randomize about 30 percent of the subjects. In randomize control trials and MCI about 40 percent to 75 percent of the consenting subjects are randomized and when you use an objective test like the Wechsler, commonly you can randomize about 50 percent of the subjects. Studies of MCI that is CSF about a half to three quarters have pathologic CSF.

So we had expected that in consideration of these things that 30 percent of the consenting subjects would be randomized. So 20 percent was a bit of a surprise but not totally unexpected, and it was those cognitive and CSF criteria that generated that 80 percent screen failure rate and that really points to a learning here of the challenge and recruiting populations who have pre-dementia. It highlights the need for simplified cognitive tests done early in the screening process so that you can exclude those who are too impaired or insufficiently impaired, better cognitive and clinical markers cerebral amyloidosis. So perhaps you won't have to do lumbar punctures where 50 percent of your subjects then cannot move on to randomization, and it also argues for thorough validation of the cut off scores that you use in determining that your subjects have the amyloid that you're looking for – they – in determining the amyloid signature.

Well, we got some information about these cut offs from our sub-study, from the PET scan study in 77 of the subjects. These 77 were divided between those who were randomized into the study with pathological CSF and the non-pathologic CSF, and as you can tell from these different populations in the study, a lot happened in the course of this trial. It was a long trial and went through a number of changes in the middle of it. Interpreting the findings here is complicated by all these different things that happened and changed in the course of the trial. Looking at the two groups in the PET sub-study, the group that had the pathologic CSF were older, significantly. There were more women in the bunch. They're more ApoE 4 carriers. MMC was really pretty much the same in the two groups, again testifying to the insensitivity, the MMSE, and these measures – the ADES-cog, the CDRSB, these were

really quite worst in the group that had the abnormal CSF as was the free and queued.

Well, we found a very good concordance between the CSF and the amyloid PET, and this is another lesson going forward given that in this country and many countries there's so much reluctance to yield ones precious cerebral spinal fluid, particularly among neurologists and others who are being asked to tell their patients to do this. Many prefer PET scans and here we see that there was a 61 plus 26 percent, 87 percent concordance between the CSF positivity, the CSF amyloid signature and amyloid PET visual readings of amyloid PET. If we look at the discordance cases many of those discording cases were near misses.

Here's the amyloid signature that we were looking for in the CSF and here's those ratios and AB42. Six of those qualitative amyloid reads on PET were negative but had positive CSF, and these are all pretty close to the positivity line, and so you wonder if we move the cut point a bit whether we could improve or get more subjects in who otherwise would not have been able to be randomized. This isn't something that can really be answered from baseline data but from continuing to follow these subjects and when the study is over, which will be in – last patient, last visit is two years from now – we'll know more about this. But this also attests to the important of having cut offs that are well-validated so that you don't lose subjects who otherwise would qualify and have a sufficient amyloid signature to try your drug.

The automated readings on PET correlated pretty well with the CSF amyloid signature, and this was – these are amyloid automated readings that were done in four regions of interest, the posterior-cingulate, the lateral temporal, the frontal, and the parietal lobe, and these do not include – the hippocampus is not in here. These were just the four areas that we looked at for the auto baited reasons and these were four areas where you could get pretty clear delineation using the algorithm that we were looking at.

The correlation of the CSF amyloid positivity and the PET really held up pretty well at all four of these areas of the brain – all four of these areas of interest – for really all three measures of amyloid in the CSF and these were highly significant in all of these four areas and in the mean. If we look at the correlations of the PET automated readings and the CSF biomarkers with the clinical

scales, you find a pretty good correlation holding up there as well with the ADES-cog which was highly correlated with the PET findings and the amyloid signature on CSF. FCSRT showed good correlation. Even the MMSE had some significant correlations there, but the CDRSB, the ADCS, MCIADL did not have significant correlations by large in these areas and did not have significant correlation with the CSF amyloid signature, which really says that it's these cognitive measures that had the good correlation while the ones that were more functionally related didn't show that.

This is a subsample what we'll show. Ultimately we don't know. So this was consistent with prior reports. There was a high agreement between the pathologic CSF, AB42, high tau, and the amyloid PET. Both CSF and the amyloid PET biomarkers identify the amyloid apathy and the pre-dementia population and this is consistent with the Dubois international working group criteria that except really either of these biomarkers as confirmatory in making the diagnosis of Alzheimer's disease and the results suggest that CSF or amyloid PET imaging biomarkers are both acceptable and that these can be interchanged in diagnosing pre-dementia.

Well, looking back at the program, the decisions that were made, one key decision was which phase of the disease to treat and there was of course, an immense amount of the discussion of that and consultations. Each phase had its proponents and advantages. Mild to moderate dementia is a presented area where the measuring tools are well-established and the structure of the study could be pretty well-determined ahead of time and we knew what to expect. While pre-dementia – well, there's a lot of feeling these days that intervening earlier is more useful in the course of a chronic disease like Alzheimer's disease in that perhaps to demonstrate efficacy for gamma-secretase inhibitor. You, in fact, may need to intervene at this phase of the disease or early.

The decision – was also key here was the decision that those subjects who was suggested – selected for treatment in pre-dementia had to carry the amyloid pathology. We needed to investigate a wide range of doses to determine tolerability and the mild to moderate study answered that question very well. Actually, I neglected to add that the mild to moderate study showed us that the high doses of 100 and 125 were not well tolerated enough to carry forward in phase three, and once we learned that, that's when we went to the pre-dementia study and

cut the top dose down from 125 so that all patients were brought down to 50 milligrams.

And also, another key decision in this program was to determine effects on amyloid biomarkers and downstream biomarkers is really the key intent of these studies. The key demonstration that the drug might have efficacy was, yes, safety and tolerability in these studies and effects of amyloid biomarkers and downstream biomarkers. The feeling was really – we had shown that the drug could move amyloid in phase one, and so the feeling was that much more extended longer studies were needed to show the effects of downstream biomarkers. And also we were very interested in exploring the usefulness of PET in confirming the presence of the amyloid signature.

I wanna thank the clinical team who spent long hours and is still spending long hours working on these studies and above all I wanna thank the patients and their study partners who put up with an immense amount of bother and inconvenience in order to be able to participate and help us gain this understanding of how to move forward. *[Applause]* yes, sir?

Audience (Krams): Very impressive work. Thank you. I have a question regarding your opinion about what the focused time is that to think your components to be given such _____ and given you're opinion on that how will you construct the screening tunnel such that patients are chosen so that they can complete _____ before they _____ trial_____. So have you looked at the screening tunnel in terms of how close to completion a _____ does it? Two questions, does the focus _____given and _____ *[inaudible due to speaker too low]*.

Alan Lipschitz: Okay. I heard five questions there, but I'm glad we cut it down to two. The shortest time for what endpoint I guess, for a clinical end point you need to be able to demonstrate that the placebo group deteriorates and what we're seeing, not here, but in an abundance of other trials, is after six months in many of those trials the placebo groups have not deteriorated and they don't start to deteriorate to well after that. So I would expect that you couldn't count on seeing any clinical effect until well after that point. How long after that point? Well, I don't know. And your second question, could you do that one again?

Audience (Krams):   So it speaks to the number that is not produced. You need long-term treatments, but the problem is that some patients may not be on the trial for long enough to be observed after the time that _____ *[inaudible due to speaker too low]* for conversion _____. So now we have trial that a number of sections about and what is the type of _____?

Alan Lipschitz: No. Yes. No. Yeah. What kind of inference – well, all right. Tolerability is of course a major question and what can you conclude about those who dropped out? Well, if you ask them "why" and you hear clearly it's because the drug was not tolerated, you can conclude that the drug is not well tolerated, and we actually learned that about tolerability from – in our work in this program. But I'm really not certain what more you're asking and I'm not certain also if that isn't a better question to ask the panelists that are going to be coming up who have a broader experience. Reisa, yes?

Audience (Sperling):   I was struck that you actually saw a better correlation with tau and tau A beta ratios than you did with A beta 42 between the PET and the CSF, and I wondered whether you thought that that was because of instability in the CSF A beta measurement, because of course the PET tracers are really only looking at _____ A beta and especially an F18 shouldn't be tagging tau. So I just wondered why you thought you saw that.

Alan Lipschitz: Well, well, one suspicion that we've been toying with is that CSF may be more sensitive than PET in that CSF may change before PET does, and whether that relates to our cut offs on other things, I'm not certain. Go ahead. Did you wanna –

Audience (Sperling):   No, just a follow up question. So I believe that might be true as well, but I believe that's unlikely to be the case when there's already tau present. So it might be very early, but if there's lots of tau present, probably, I would think both would be positive. So still looking at them unless the A beta 42 measurement was less stable for some reason.

Alan Lipschitz: Well, I guess you're – if I – I have to think about this, but I'll do a little bit of thinking here and embarrass myself in front of everyone. But – so I think you may be suggesting that the PET _____ may not be capturing all the amyloid activity that the drug is producing, perhaps. I'm not sure if that's what you had in mind. What do you think? What do you think?

Audience (Sperling):   We – one way to find out _____ –

Alan Lipschitz: We have time. We have time I think.

Audience (Sperling):   I'm not sure. That's why I'm asking you, but I would a priority think that there should be a tighter relationship between CSF A beta and PET A beta 'cause they're both A beta measurements, so they're two possibilities. One is that the PET is not ideal there. Maybe, again, it's an F18 agent there early, but I think it actually is a good marker of A beta on autopsy or at least the early studies suggest that fibrilar beta. So I wondered actually whether it's more of a problem with CSF A beta 42 instability measurement and that the tau may be – I wondered whether it was more stable the tau measurements in there for a more reliable, reproducible cross subjects and therefore you saw a tighter correlation, but I guess maybe someday I'll be able to look at the scatter plots. I think it would be really useful, not just the correlations, but the scatter plots for each of those three measures in the CSF and get a sense of the variability and what's driving that.

Alan Lipschitz: Yeah. Yeah. Okay. Yeah. So it could be the CSF A beta 42 measures unstable or it could be that really these are accurate measures and I'm kind of obsessed with the difference between soluble A beta and the plaques. The plaques are all that we see with the PET, while what we're seeing is the salable stuff in the CSF and of course the salable stuff is also released from the plaques and whether the plaques reach equilibrium with a long treatment like this you would think that there would be some, but I wouldn't be surprised if there weren't some differences between the effects of oligomers and soluable A beta that was different on the effects on established plaque as revealed by the PET lignin's and I think that's one thing we'll be looking at very intently over the next couple of years. Yes. Please.

Audience (Doody):   A small question and a bigger point. You allowed people in your study up to age 90, and some people feel adamantly that after age 85 or age 80 they're out, okay, because it's an anti-amyloid agent. Have you seen extra difficulties or adverse events in your older subjects in these studies?

Alan Lipschitz: We haven't looked at it explicitly age wise, and so nothing's really screamed itself out at us. It's something we will look at. Of course that study oh and three is complete, and we can do that cut

	on the data. But I thought that you were suggesting that the older subjects might not be suitable not because of – because of AE's or because of amyloid signature issues?
Audience (Doody):	No. I think the older subjects are suitable and there are a lot of very sad, upset 82-year-olds and 81-year-olds and 83-year-olds and 84-year-olds out there who would like to be in these trials, but most of the trials exclude them. So I think it's good that you didn't and I just wonder if anything had jumped out at you and I await your analysis of whether they have been problematic.
Alan Lipschitz:	Yeah. I'm actually looking forward myself very much to that analysis and I think an issue with enrolling older subjects is that amyloid itself – amyloid accumulation – as we know increases as you get older. So it may become harder to find people who have an amyloid signature that's truly specific for Alzheimer's disease in that older population. Whether ultimately our data will tell us that this amyloid signature that we've picked is as effective in predicting treatment response in the older old is something I'm very interested in looking at.
Audience (Doody):	And then I wanna get to the second point briefly, and that is you kept this observational cohort of people who really didn't meet the criteria, which I think was very valuable. Having looked at the patient characteristics at baseline, as you showed us today, do you have a hypothesis about these people? Are these people not Alzheimer's or are these people with high cognitive reserve whose biomarkers don't manifest, or are these people earlier in the process anything leading your hypothesis at this time?
Alan Lipschitz:	I don't know. I don't know. All I can say is stay tuned.
Audience (Zaven):	My question is really transcends this particular trial of design. It's really designed to provoke thinking amongst the industry people as well as Rusty in a way to address the issue that George phrased, what can we do to shorten the drug development period. You indicated that the primary objective of the study phase two is to determine safety, tolerability, yet quite a bit of the discussion has to do with – measurements has to do with the aim of looking for some signal efficacy and you went through tortious explanation why subjects were ruled out and so it's taken a lot of effort.
	Should we design phase two as differently, that is to combine it with phase one where the objective is really to work out the

toxicity and tolerability. Forget about efficacy, just work that out. So make it larger phase one, phase two combined, would that be cheaper, faster, and do a phase three or phase two that would essentially be to determine the efficacy of the drug where you could really get the sample size large enough where you can definitely answer the question. This way we're neither fish nor fowl.

You really don't have enough subjects to determine how well the drug is working with respect to its final outcome. Anyway, it's just – I'd like to get some thinking and discussion perhaps during the panel whether there are different ways in which we should be organizing these trials along with the regulatory requirements that Rusty could participate.

Alan Lipschitz: Okay. I – that's a great question. I look forward to hearing that discussion. Certainly we needed these trials. I mean, we learned a lot. We went into that dementia study thinking that those high doses were going to be well-tolerated. That was all our evidence from phase one and we learned that they weren't. So we really needed to give the drug to phase two size population to understand how to take it forward. Whether we could more efficiently combine that with our phase one work, I'm looking forward to hearing what people can suggest later today. Yes?

Audience (Vradenburg):   I have a question about patient registries and two real questions 'cause you looked at and commented on the difficulty of recruiting qualified participants in your pre-dementia study and you talked about whether or not modify or change or select your inclusion criteria in a particular way. I'm curious about whether or not if you had a very large scale, sort of motivated base of potential clinical trial participants, 250, 500,000, something like that. (A) would that be useful as a pool into which you can shop, at least initially no matter which conclusion criteria you pick, and sort of the second question is what kinds of questions could be easily answered to sort of prequalify those in the patient registry in a way that would be at least somewhat limiting and constraining and potentially expedite their requirement and to qualify them for a clinical trial.

Alan Lipschitz: You're beautiful. *[Laughs]* No. Thank you.

Alan Lipschitz:	You really could cut the recruitment time and the cost of the trial considerably by working with that kind of a registry. So I think it's a wonderful suggestion. Yes, Dr. Katz?
Audience (Katz):	Yeah, a couple of things. First just to pick up briefly on what Zaven is suggesting about combining Phase I Phase II, and it's sort of consistent with that question I asked earlier about combining Phase II and Phase III. The numbers, we could talk about what those numbers mean and what the phases mean. I think it's time to think seriously about doing things like that. And you know we can talk more about it and it's, again, not that we've had any formal internal discussions about that, but as just under the heading of sort of blue-skying things, I think that's a place where drug development can be expedited. There's a lot of things to think about doing that. So we can talk more about that.
	To pick up on Rachelle's point about excluding 90 year olds. There's a whole lot of reasons why people are excluded for trials. I mean we discussed this under, you know, concomitant meds and stable other medical illnesses. Some of that may come from us but a lot of it I don't think does come from us. I think it's sort of tradition. You know, you can't be on this. You can't have this. First of all, you end up – we know why you do that. Theoretically it increases the chance of showing an effect. You have a more homogenous population. I'm not sure it actually does achieve that end.
	But I think that's another place where we can have improvements. There's no particular reason, I don't think to exclude all sorts of people based on their other illnesses. It depends, of course, what the drug does and they're may be specific people you're worried about. Even then, it's always good to get some experiences in them if they represent some reasonable proportion of the population that's ultimately going to be treated. So I think that's a place where there could be lots of savings in terms of not excluding people who are not currently excluded.
Alan Lipschitz:	It's certainly worth thinking about. I was intrigued with, I think it was Eric's suggestion of perhaps take your Phase II trial and just continue those subjects onto Phase III. And that seems pretty straight forward approach. Whether how Phase I might be continued with Phase II is certainly worth looking at. Do you think that Phase II continued into Phase III would be workable?

Audience (Katz):	Give me a microphone. Well, I think it's certainly something that should be seriously considered. And of course there are, you know, adaptive techniques and this sort of thing. I'm not turning around. My statistician is sitting at the table behind me. But I think that's something that – I think there are other fields which use these techniques routinely. And I think we need to be thinking seriously about doing that. Again, you don't tread lightly. I mean there are pitfalls but I think that's a serious consideration.
Audience:	Briefly, in your Stage I selection criteria, you lost, if I recall correctly, about 20 percent due to compliance issues. I was curious if you could say what those compliance issues might have been and, you know, is there any kind of low hanging fruit there. It kind of builds on the disease registry. Are there – you know if there's low hanging fruit in terms of why people aren't coming to the trial, is there things that can be done to help those people get to the trial or contained?
Alan Lipschitz:	Yeah. Those are patients who wouldn't sign the informed consent. I don't think it was as high as 20 percent, but there was some component of that feasibility pie sections. And I don't know more about that. Maybe other people have – can say more about that because in every study it seems that people chug along and then when it comes time to sign the informed consent, there's a certain number that won't. They see something there that they're understanding about the study for the first time and don't want to continue with it. Whether we can do more to explain the study upfront so that we don't get to that point is certainly worth looking at.
Dan Perry:	Alan, we very much appreciate that glimpse behind the frontlines in the midst of this study. Our next speaker is actually new to ACT-AD and to these gatherings, Dr. David Gelmont of Baxter
David Gelmont:	So good morning to all of you. Thank you for inviting me to be with you today. Unlike the previous speakers, we came to our phase III study in a total different way. Our product, immunoglobulin, has been on the market by now in different forms for about 30 years. So there is a huge body of literature and experience with adverse events profile, not only in prior immune deficiency which were essentially were young people, but now in a variety of other disease where immunoglobulin has been administered.

This immunomodulatory and anti-inflammatory drug in variety of geographies in the world and variety of products approved for other indication including Kawasaki disease, again in children but Chronic ITP, thrombotic thrombocytopenic purpura, Guilain-Barré syndrome, and CIDP, and we just concluded a MMN, multifocal neuropathy. So the drug has been given to elderly patients as well as young patients. So all over from age 2 years of age all the way up to very elderly patients.

I just want to say a few things about the drug because it's not the usual drug that you heard they're on this morning. So this is a real polyclonal kind of drug. One gram of immunoglobulin preparation has about 4 times 10 to the 18 antibodies in there which are capable of recognizing about 10 million epitopes. And that's why it's so effective in humoral immune deficiency and primary and secondary immune deficiency. It's a real pulled plasma which means that the lots are made our of about 60,000 liters. So the repertoire of antibodies is really huge and today it's fairly safe. We have a variety of ways to make sure that the product is of high – very safe by screening the patient and having a variety of inactivation and removal processes to assure its safety.

Now there is a huge literature about anti-inflammatory properties of immunoglobulin preparation and anything from Fc gamma receptor which is an inhibitor inhibition of inflammation here through reduction anti-inflammatory expression, pro-inflammatory cytokines and increase in anti-inflammatory cytokines as well as anti-EAT antibodies and mainly also mediation of antibody production and catabolism.

So the story of IVG or as we call it formally IgIV started about a decade ago when Richard Dovell found that normally when plasma has anti-monomer antibodies and since then there are variety of publication regarding natural antibodies in IgIV. So we know that nature antibodies are there and there is a big repertoire of anti-Abeta cross reacting antibodies. They are maybe conformation specific and they are against a variety of oligomeric assemblies and oxidize Abeta pyroglutamates, et cetera. So there are a variety of antibodies, I believe more than 20 different kind of antibodies against a variety of Abeta conformations here. And the spectrum of antibodies against Abeta that we can find in the plasma is very similar to what we found in the CSF. And we can see that purified anti-Abeta IgG reduce the neurotoxicity in vitro and we also confirmed that in our own lab that this does happen.

That maybe the take-home message is that immunoglobulin specific for oligomeric preparations decline with age and advancing AD. So over as we get older, the amount of IgG specific against the oligomerics is reduced with advancing age and maybe that's one of the reason we see Alzheimer's disease in the elderly. So recent article looking at the initial occurring antibodies against Abeta were purified to use IgIV purified against Abeta and administration to transgenic mice here had significant reduction in plaque numbers, significant reduction against CSF Abeta, increased in the Abeta efflux from the brain, and improved object location of dystrogenic mice. There were binding to dimers, trimers, and oligomers. So the conclusion of that publication was that naturally occurring antibodies against Abeta are part of the repertoire that we see, physiological repertoire inhibiting oligomerization of Abeta and consequently degrading the Abeta.

Another interesting publication was that maybe you don't need to have a specific anti-Abeta antibodies. Maybe there are the gamma heavy chain, the fragment one here is good enough and it seems like it is adhering to fibrils, some of the fibrils in a very monomeric level here and it could be that the immunoglobulin itself has a totally different way for adhering to plaques or Abeta assemblies not in the usual CDR FAB kind of way but in other non-CDR way to assemblies of oligomers and plaques around here.

So another thing that may affect the efflux and afflux of the Abeta from the brain is the transport of the Abeta. And one of the reasonable, one area that was described is the RAGE that transport the Abeta from the periphery across the blood-brain barrier into the brain and the suitable LRP is moving the Abeta from the brain into the plasma where it can be degraded. And the immunoglobulins have anti-RAGE antibody that may be helpful in reducing the influx from the plasma into the brain and reducing the load in the brain of Abeta. It's also, again, I'll also show that interception of Abeta with RAGE by infusing of cerebral RAGE that compete with the RAGE in the blood-brain barrier may be improving learning and memory and synaptic function in your transgenic models of Abeta accumulation. So that's another mechanism.

IgG also enhanced microglium. It did at AB clearance. And this is the study here by Kellner. Essentially looked at 48 subjects with Alzheimer's disease with controlled 48 match cohort and they looked at the three origin in the brain, quite a bit of biopsies. And

it was interesting to see that the majority of the neuritic plaques were decorated by immunoglobulin, not natural immunoglobulin. And Alzheimer's disease patient with prominently IgG labeled neurite plaques had significantly reduced plaque burden compared to people who did not have that. And they had an increasing microglia phagocytosis of their plaque whenever they had they had decorated immunoglobulin.

Margaret et al from Finland also use immunoglobulin to show the effectiveness on the microglia and I think that the conclusion was that immunoglobulin enhanced the Abeta clearance mainly through microglia, not through other mechanisms like astrocytes here. It penetrated the brain of these transgenic mice and were pretty effective in the hippocampus and about a selective Abeta deposit there. And here you can see some picture from that publication. So you have control with high-beta burden in Alzheimer's transgenic mice and you have enhanced microglia cell clearance when they got IvIG.

And if, I'm sorry that you cannot look at the cell. This is a triple immune fluorescent and the A-1, the A-panel here you see the Abeta, the B, you see the immunoglobulin, the C is the microglia and here is merging of the three stains, fluorescent stains together. And it seems that the microglia is where the antibody is and where the deposits of Abeta is. So it could be that the microglia are playing a more important role than we thought in the clearance of Abeta deposits in the brain.

Looking more into the clinical areas. So Hammarstrõm and Garda from the Karolinska published about a year or so ago their experience with primary immune deficiency patients who are age 65 or older. They had about 237 patients who were given chronic treatment with immunoglobulin for primary immune deficiency. Most of them are receiving it around 370 milligram per kilo per month. And I believe that most of them were getting it subcutaneously. And they had no case of Alzheimer's disease. When they looked at what is the probability of that, they would expect to have 13 patients in that group with Alzheimer disease.

Similar publication was by Fillet et al. Here you show what they did is they look at the patients who received IVIg for any cause and versus match cohort 100 to 1 ratio of match cohort who did not get it. And they were able to show that the risk for Alzheimer's disease was decreased in the cohort that received IVIg. So the

conclusion here may be that IgIV treatment may prevent Alzheimer's disease, not treat Alzheimer's disease but that's too early to make such a statement.

So how does immunoglobulin differ from monoclonal antibody? So obviously it's a polyvalent antibodies, neutral both for perforin and self antigen. It's a low affinity antibodies against antigen unlike the monoclonals that are mature antibodies and a very high affinity antibodies. The does level that is used with monoclonals are usually in milligrams per kilo at most and also we use in primary immune deficiency is 0.4 to 0.6 gram per kilo per month. It's a huge difference between the monoclonal and the polyclonal here. And in neurological autoimmune neuropathy, you use even higher doses. You use two to three times the PIDD dose. You use about 1 to 1.3 gram per kilo per month. So those are major differences between the monoclonal and the polyclonal here.

Nevertheless with all this antibodies, animal data showed that there's no increase in micro emergis and unlikely to cause vasogenic edema. And in our phase III that is going on, what we learned from the SAEs, there is no – right now there is no worry of such events. So the rationale for using Gammagard liquid in Alzheimer's disease is, as you see, is multiple. We have obviously peripheral sync theory here. We activate microglia possibly here to degrade Abeta deposits. We prevent oligomerization by the Gammagard immunoglobulin here and increase that elimination of that and prevent the inhibition of profibril formation. So essentially we have about four major mechanism of action which I just summarized. But I won't repeat it.

So far we had the phase I and phase II studies. They were both done by Norm Relkin from Cornell. And I present just few slides from his data and this is the key features of this phase II study which was run as double-blind placebo control, parallel arms. Mainly to look at futility of IVIg in the treatment of Alzheimer's disease. If it looks futile, we won't go beyond that. If it didn't look futile, maybe we'll continue with that. There were 24 subjects, mild to moderate disease. They received six months of placebo control and then 12 months of open label extension. The primary clinical outcome was ADAS-cog CBIC and there were a variety of secondary clinical outcomes. Both phase I and phase II patient continued open label. The phase II is still going on. About half of the patients are still there, probably around five years by now. The phase I, I mean I think they are ending this year and

some for the patients, they're probably close to 10 years on the drug.

So this is the 18-month data here and this is al IVIg doses and the CBIC and this is – they were placebo until months six here. Month six and then they continue open label a variety of doses and there is difference here between the all IVIg CBIC and the placebo. You see similar effect on the ADAS-cog here the difference between again six months placebo open label and that's 18 months data and that is continued duration of the placebo partially explained by the fact that they may not have been on the right dose. There have been a variety of doses and this small – it's also small study.

When you look at one of our doses, the 0.4 gram per kilo every two weeks, then there is it seems to be the best dose here and this is the CBIC for the drug. This is the CBIC for the placebo. And this ADAS-cog, very similar. And you can see there is a variety of other measurements of ADL, NPI, modified amino menthol here and went in the right direction as well in overall over 18 months of observation here.

Some of the patient underwent ventricular MRI, and this is the MRI data. This is data on different dose of 0.2 gram per kilo every two weeks and this is 0.4 gram per kilo every two weeks. That's 18 months' data. This got placebo for the first six months and then the 0.2. This one got 0.4 every two weeks for 18 months, so continuous treatment with IVIg. And it's essentially shows that the ventricular enlargement rate was higher in the original placebo group. And this give you a variety of doses and that difference in the ventricular enlargement rate between the placebo here, all IgIV and different doses of IgIV.

And this will give you some idea what to expect in Alzheimer's disease and this is what you expect, and that's what you received in the placebo. And there is somewhat a decrease in all IgIV and also mainly in the 0.4 gram per kilo every two weeks. All brain atrophy had similar pattern. Again, the 0.4 gram per kilo every two weeks was the lowest one of atrophy. And this is what you expect to have. So again, the Alzheimer is around 2-4 percent reduction here. And this one had the lowest reduction in atrophy. Both measurements essentially correlated with CBIC and ADAS-cog and this is the brain atrophy. Again, some correlation with CBIC and ADAS-cog. So the conclusion of the MRI, measurements indicate a significant reduction in the rate of

ventricular enlargement rate and brain atrophy in 80 patients over 18 months of uninterrupted IVIg treatment. The IVIg effect on brain atrophy correlated well with the clinical outcome at 18 month. The best dose was 0.4 gram per kilo every two weeks and obviously we need that phase III study which is the study.

So this study Gammagard Alzheimer pathogen of the Gibbs study is done with ADCS and with NIH through a grant to Dr. Relkin, and it's sponsored by Baxter Corporation, and Paul Aisen is in the audience here and he will keep me honest. He promised, right? And so the Gibbs study design is based on the phase II study. And when we designed the study, we had data, nine months data. Now we have 18 months and beyond data. So we did some adjustment accordingly to meet what we found in the nine months data. So the two studies suggested – these two studies suggest the phase I and phase II that uninterrupted Gammagard liquid treatment is less declining in neuropsychiatric functioning. The base dose 0.4 gram per kilo every two weeks. That the Gammagard liquid is effective for at least 18 months treatment. And it has a very satisfactory safety profile in 120 subject per arm may be adequate to demonstrate this statistical and clinical event effect.

So the primary efficacy endpoint now is changed from based on 18 months ADAS-cog and ADL in the secondary, a variety of others that most of us are using but will include some caregiver assessments and more like patient-related outcome or caregiver-related outcome such as caregiver burden questionnaire that we have here. We have a safety objective obviously and after nine months treatment and more than, yeah, more than 300 repeated MRI, we found that the drug is safety with regard to micro hemorrhages and to vasogenic edema. The biomarker objective are very similar to all other studies, and they are mentioned over here. And the study design is essentially 400 randomized patient, 42 places will have substudies with CSF AV-45 and FDG PET and all of them getting volumetric MRI. Assignment is one to one to one, two different dose level and one placebo. And this all levels and I'm out.

Audience (Hampel): Thank you, thank you. I just wanted thanks for presenting this interesting data. I'm interested your phase II sample characteristics with the volumetric MRI. So how many subjects did you investigate from this 24N that I'm recalling and how – just let me finish with that – how are they characterized? Do you have ApE,

	age, and education data on that? And are these multicenter investigations or is this a monocenter trial?
Dr. Gelmont:	So this was a single center. phase I and phase II were single center. There were another study done in a small number of patients being modeled by Richard Odell with a different product. So there are 24 patients in the phase II. I believe 21 had MRI. I don't know if all of them had all the stuff, but it was done a long time ago so that the ability to do a more sophisticated MRI was not available at that time when they did the study. Most of the patients are ApoE4 positive. Both groups? The entire study had about 70 percent ApoE4 positive, the same we have in the gap phase III study. Around 70 percent, 68 percent, ApoE4 mild to moderate, I believe were in the gap was about 60/40 mild to moderate. In Relkin it is maybe similar but I cannot recall exactly.
Audience (Hampel):	Since you see this very clear effect in your group, I think it's very important to see if they're really comparable regarding main variables that interfere with, let's say, rate of change with MRI measurements. And I don't have a clear picture of that.
Dr. Gelmont:	Right, so you know the phase II study we usually have at least three important things that we need to do. Safety, number one. Dose ranging, number two. And proof of concept, number three. And it is a very small study with multiple doses, it's very difficult to start cutting and looking into that. And that's one of the issues why we need to have a good phase III study.
Audience (Hampel):	So I am wondering, you presented these MRI data. It was a central part of your presentation. What decisions were made out of this?
Dr. Gelmont:	The decision what to go to phase III was before we had the MRI study. And it was based on ADAS-cog and CBIC at that time. So we said, okay, we have this data. The other neuropsychiatric tools measurements were the right direction. Safety was there. So said, okay, it's reasonable to go now to phase III study to assess that in a more proper way. Yes, Rachelle?
Audience (Doody):	So in the spirit of this meeting where we're talking about strategy, design, you had a drug that had been on the market for 30 years. You had some idea of safety, but two really unusual features. One of them Harald is honing in on is the very small sample size of your phase II trial. And then the second feature is the futility analysis. Futility analysis I believe you defined it as ADAS-cog of

1.75 points and superiority on the CBIC. How did you decide to put in this futility analysis? How did you decide to interpret it? You know this is something that gets talked about a lot in the field.

Dr. Gelmont: So we got into trouble with that in a way because we have a futility analysis in the phase III study but it's way less than that. I think thinking backwards about it, and Paul is with me, we want to put the futility analysis on one side to protect the patient from untoward too much risk. So we want to make sure that the patient, if we find there is any safety problems here, we should stop the study or if there's no response. Getting the drug twice a month is a lot of burden on the patient and the caregiver. So you need to have some kind of futility.

On the other hand, we want to continue the study to the end if possible because if one group of patients doesn't respond, maybe another segment will respond. For example, patients who have ApoE4 negative will respond, ApoE4 positive would respond or gender above 80 would not respond, below would. So there are a variety of ways so we want to do everything till the end. On the other hand we need to – so our futility analysis has been kind of minimized to really a train wreck to make sure that we don't expose the patient to a train wreck on one side but will continue to the study if possible to the end.

Audience (Aisen): I was just going to contribute to that answer. So Rachelle, I think you were asking about futility in the phase II – that the phase II was set up as a futility design. And I think that speaks just to the purpose of this meeting which is to discuss the approaches that different individuals and companies have taken to learning something from phase II that will inform a phase III trial. And this also speaks to Harald's question about how the MRI was viewed in phase II. I think that the IgIV study is kind of remarkable story in this regard. I think David's a little bit on the spot here because phase II was not done by Baxter. It was done by Norm Relkin, and he designed it, and he decided that well he'd been presenting phase I data, open label data as pretty encouraging. And he was very excited and wanted to move forward but got a lot of criticism that there was no control group and what could we learn from phase I.

And so he tried to think about how he could do as a single-site study, a phase II study that would be useful in gaining further adherence and allowing him to move forward into phase III and he actually managed to do this. I think it's quite incredible that he did

since he only had a 24-subject phase II with four arms. That's 6 subjects per arm for six months to provide information that would guide a decision on a phase III disease modification trial. It's kind of an incredible idea.

But to his credit, he did something that we often don't do which is clearly prespecify what the rules were gonna be. And the prespecified rules did not include MRI or FDG or Amyloid. He said, well, I'm not gonna look for statistical significance, an interesting decision. I'm gonna rather make a futility judgment and I'm gonna tell you what the futility requirement is gonna be. It's gonna be that we'll consider this futile if there's not a 1.7 point difference favoring drug on the ADAS regardless of statistical significance and numerical superiority on the CBIC. That's what I'm gonna make my decision on. He hit both of those and made his decision – could therefore call phase II positive.

What's the problem with that is I don't think there was any rational basis to make those guidelines. I think it turned out – it should have been considered a crapshoot that a study with six subjects per arm for six months was going to have this kind of an effect. He said it would because he strongly believed in his own phase I data which showed a dramatic, symptomatic rapid onset improvement in ADAS and CBIC. I was quite amazed that he hit those two endpoints. So to his credit they were prespecified. He chose the ones based on his phase I experience. He had no statistical power, roughly zero, to actually achieve those endpoints and nonetheless he did. And he stuck to what he said and Baxter went along, the ADCS went along, and moved into phase III. I think it would be interesting to discuss this whole idea further but even in retrospect I believe it was a very fortunate outcome given that there was no statistical power in a study this size with this group size for six months to actually achieve those endpoints.

Dan Perry: Dr. Hampel, you have something to add?

Audience (Hampel): Thank you, Paul, for clarifying. I totally agree on your notion. What I cannot support is the presentation of the MRI data. They are not informative and they should not be used. We have publications on Aricept in the *American Journal of Psychiatry* published with larger groups showing significant effects on hippocampal volume and whole brain volume just to show the complexity of MRI measurements and standardization and how to

interpret those measurements even in large groups. So that's just my point.

Dan Perry: There will be an opportunity to have Dr. Gelmont come back along with the other presenters after we've gotten to our final one. The next 30-minute segment we're going to have share two presentations, first by Dr. Carole Ho of Genentech and secondly by Susanne Ostrowitzki, sorry to do that, Ostrowitzki. Let's start with Susanne for the first 15 minutes and please hold your questions until the second presentation.

[End of Audio]

Carole Ho: Thank you. So good morning. For those of you that don't know me, my name is Carole Ho and I work at Genentech within the Roche Group. So I just want to say how excited I am to be here and I want to thank the organizers for inviting us today. Our programs are a little bit earlier in the development cycle and so we're happy to share with you our current thinking up until this point. I would say that as a neurologist by training I'm extremely excited to be working at Roche where there is quite a large commitment to neuroscience drug development and particularly for Alzheimer's disease.

And I wanted to just show this organizational slide because I think given that our organization has changed a little bit since 2009, since the Roche and Genentech merger, I thought it would be good to just give an overview of the two programs and how we're organized within the Roche group. So as part of the Roche's commitment to innovation and diversity in approaches, we actually have two early development research organizations within the Roche Group. So there's the Genentech research early development organization that I work in and Susanna works in the pharma research early development organization.

So these organizations have separate budgets and they're under different management and so it really does support a full diversity of approaches to treating Alzheimer's disease. I would also just note that because of preexisting partnerships with other companies, with AC Immune for the Genentech compound and with Morphosis for the pRED compound, these drug development programs are firewalled within the company.

So with that I'll give an overview of the MABT program that is gRED right now. And to start, because I think this is fairly new to some people in the group, we're currently in phase II and as one of the questions of the panel today is around our selection of patient choice in phase II. I thought it was very important to share some of our basic science work that we did which really, I think, underlies the foundation for our choices of where we went in clinical development.

So to begin when we approach this problem in treating Alzheimer's disease we came a little bit later to the field but really had the benefit of, I think, a lot of learnings that had occurred up until that point. And I think as we approached this we really thought there were two things that were really important when we wanted to design a molecule to treat in the clinic. So the first was we really believed that more is better. So in the sense of the most, the highest dose that you could administer to patients would likely translate to more effect.

I think related to that, the second point is that we believed that because we wanted to achieve the first goal, that limiting vasogenic edema that safety adverse event would be really important in achieving our dose. I would say that from a clinical perspective the impact of vasogenic edema is certainly debatable and that the effect it has on patients; however, what I think is clear is vasogenic edema does limit the dose that you can actually give to patients. And so in with this framework, one of the things that we really try to do is engineer a molecule that had reduced effect or function which really translates the FC binding properties resulting in less microglial activation. We didn't want to have absent effect or function but reduced. And with that we have a unique IgG4 backbone in our antibody. We also observed n our mouse models that we – our preclinical models that there was a reduced incidence of micro hemorrhages which would support this hypothesis.

So our phase I program, I'm just gonna really summarize in the fact that we did not see any vasogenic edema. And our goal in phase I was simply to really test the hypothesis that at high doses of drug, could we limit vasogenic edema. So we dosed as high as 10 milligrams per kilogram IV in our single dose phase I study and 5 mgs/kg weekly for four weeks in our multi-dose study. We enrolled more than half were ApoE4 positive patients and we saw no cases of vasogenic edema. I've also noted that we did a sub-q

bioavailability study in our phase I program to also support sub-Q dosing in our phase II program.

So of course a molecule that's safe but not effective is not going to fly in the clinic. So the second part of our preclinical explorations were really to make sure that this drug had evidence of efficacy preclinically. So regarding the binding profile, we thought that it was important that it bind to known species of Abeta that may be toxic. So to that regard it binds monomers, oligomers, fibers, peptides, Abeta 1-40, 1-42. It also binds plaque. We have also found in vitro that it inhibits aggregation and promotes disaggregation.

Another example of one study that we did to really address this issue of is more better is depicted on the right, and it's a little bit hard to see. But this is in an APP transgenic mouse model where you would not expect to see the assay use any peripheral Abeta. And what we found is as you dose with different doses, you can see up there it's a 1.5 and a 15 mg/kg dose. You see on the Y-axis that the plasma total Abeta level is dramatically increased with higher doses. So there's a clear dose response in terms of the more we put in, the more Abeta we see from the brain in these animals in the periphery that can be detected.

I'll also note that I think there's – we don't – there's a lot that we don't understand about the mechanism of how Abeta is cleared in patients and whether it's a direct model or a peripheral sync type model. What we believe again is that without knowing for sure what that is, we want to make sure our antibody addresses both. Our preclinical experiments have also demonstrated that there is an equilibrium, a steady state between the amount of antibody in the periphery, in the serum, and in the CNS. It's approximately 0.1 percent. So again, the more that we put in, we believe that we're getting more into the CNS.

On the bottom, I just wanted to highlight this experiment that was done. This is using a very novel imaging technique that is a live imaging technique using a cranial window in animals. We did this experiment to address the question of whether plaque that had already been accumulated could this be removed with our antibody, and what we show here in blue you can see these Amyloid plaques and we dosed two doses at week 3 and week 7. And it's a little bit hard to see in the light, but as you can see there's a reduction in the size of this plaque after dose one and further

reduction after dose two. On the bottom row here, there's another example of this plaque with decreasing size over time. This is quantified on the right. And what we were very pleased to see was that there was a reduction in the amount of plaque, preexisting plaque in this model. So I'll not that this has not – efficacy has not been tested in the clinic yet. That's what we're doing now and that's what the goal of our phase II program is.

So then to get to the question that really was asked of this group was how did we decide what patient population to go into. So we turned to available data at the time and ADNI data certainly I think really helps us understand the longitudinal course of Alzheimer's disease by looking at cross-sectional data that is modeled into this longitudinal graph that I think everybody knows very well. And where we really struggled in defining what the best population was to study and where it was most practical to study a population. We ended up choosing the mild to moderate population on the right hand side of this curve for a couple of reasons.

So one is I shared our preclinical data, we really felt that we may have a differentiated approach to doing this and we also demonstrated that we could reduce plaque burden that was preexisting, that we may be able to address the mild to moderate clinical spectrum, we certainly realized limitations of this approach in that it's an unknown question of whether removing Amyloid at this stage in disease is going to be efficient to impact the clinical outcome.

That being said, you know, I think that there's been really quite amazing work in the past couple of years in the community by Reisa, Paul, Pierre Tariot, Eric Reiman, Randy Bateman, John Morris in really addressing preclinical AD. And I think this preclinical or presymptomatic AD is really probably is the next frontier in our approach to treating this devastating disease where prevention would really be the goal. I would also add that I think there's a lot of regulatory support from the FDA and the EMA for a very progressive approach towards this and it's something that we at Genentech are very interested in exploring further.

So that being said, I think again, we chose to go into the mild or moderate patient population to summarize because of the clear, unmet medical need because we felt that we have potentially a differentiated approach and because the pathway from a regulatory perspective and a clinical endpoint perspective was well paved.

Okay, so here's a schema of our phase II design and we are going, again, in the mild to moderate patient population and MMSC range of 18-26, so a little bit on the less severe side compared to other studies. We are enrolling patients 50-80 years old. And with our previous discussion that Dr. Doody had raised, I just wanted to take a minute to explain our thinking around that. You know I think one of the things that really plagues clinical trials in AD is the diagnostic issue, and I think it's something Susanne will talk about next in her approach to – the pRED approach to the program. But really identifying the right patients to bring into the study that not only have Amyloid pathology but have Amyloid pathology that you think you can impact in a relatively short-term clinical trial.

And we reviewed some of the literature of pathological studies in Alzheimer's disease patients and what we found was that with increasing age there was a lot more concomitant pathology in patients that were over the age of 80 or 85. So in other words there as a lot higher burden of ischemic disease. There's one paper that demonstrated only 35 percent of, I think it was, 95 patients in the study had pure AD pathology. So in a way this was a patient selection approach acknowledging that there's clearly an unmet medical need there and if we have a drug that works, we certainly would want to apply it to older patients as well.

So our phase II development program is actually two clinical studies. And I think to address the discussion earlier, you know this really becomes almost like a mini-phase III program. I think our reasons for this were twofold. We really believed that we do want to test cognition in our phase II program before we ungate resources and enroll patients in a study to test this drug that is of potentially larger number of patients and potentially longer duration.

And so in that regard we have two studies. Our first study is a cognition study which is 360 patients we are testing two doses. We have 120 patients in each active dose arm and 60 patients in the two placebo dose arms. The key endpoints are ADAS-cog and the CDR sum of the boxes. We also have a separate biomarker study and we separated out these studies partly for feasibility reasons but this is a 72 patient study that looks at Amyloid imaging, FDG PET, volumetric MRI, and CSF analysis with sample sizes as you can see on the right, 24 patients for each active group and 12 patients in placebo. We really believe that this

number of patients will give us adequate data to really be able to make an informed decision of taking this drug into phase III and exposing additional patients to this agent.

So with that I'll move to the final slide that really just summarizes what our vision is for this drug. We really do hope that this drug will be differentiated and be able to treat the full range of the Alzheimer's disease spectrum; however, we believe that our first step will be to test this in mild to moderate disease but we're certainly very interested and motivated to look at this in earlier stages of development. We are also exploring biomarkers in our phase II study to potentially support disease modification and to guide our design of our phase III study to address these. So I think we're going to do the next presentation and then questions, is that?

Dan Perry: Susanne and then questions.

Carole Ho: Okay, so thank you.

Susanne Ostrowitzki: Good morning. So I'm Susanne and I will take you through the second anti-Amyloid antibody program that the Roche group has in development, and it's quite differentiated. You will see the molecule is very different and also the approach we've taken is different. So this is the molecule's name is Gantenerumab and it currently is in a phase II trial for prodromal Alzheimer's disease. I don't have time to go through the full preclinical profile, but it has recently been published, and it is a fully human IgG1 with – where's the laser? Here it is.

So it's a fully human IgG1 with high affinity for aggregated Abeta to 40 and 42. It has a robust preclinical package and has shown decrease in plaque load in mouse model of disease and also an neutralization fo the toxic effects of oligomers in an in vivo LTP model in rats. What the drug does not do, in comparison for example to what Carole just told you about, it does not elevate peripheral total Abeta concentrations. We have conducted phase I in mild to moderate Alzheimer's disease and in single dose study, the drug was well tolerated and safe. The multiple dose study treated patients for up to six months every month and also included an Amyloid PET substudy. That multiple dose study had two key findings. One was that at the high dose of 200 milligrams IV certain individuals developed ARIA findings. The Amyloid related imaging abnormalities that are now well known that were at the time referred to vasogenic edema and micro hemorrhages.

That actually resulted in early discontinuation of dosing at that dose.

The other key finding is described here and has also recently been published that is we saw in the small substudy a dose dependent effect on Amyloid load. So you're looking at the median percent change from baseline in a variety of brain regions here in the placebo group, in the 60 milligram IV group, and in the 200 milligram group. And it's evident that in the placebo group there was an increase from baseline to the end of treatment. In the 60 milligram group nothing too much happened. And in the 200 milligram there was a clear decrease.

We then had two subjects in the study who were ApeO4 homozygous and developed these ARIA findings. Then we took a closer to look to see whether the ARIA findings and Amyloid removal were somehow related. And images from one of those patients are here. You see on the left top panel the baseline Amyloid load. So red means more Amyloid. And at the end of treatment a lot of this Amyloid has disappeared. A different way of expressing this is a change map with the color coding being inverse if you like. So red means there's more Amyloid removed. So most of the Amyloid is removed in the frontal cortex, in the parietal cortex, but you will note also this small focal local maximal of Amyloid removal in the left caudate and that actually colocalizes exactly with an area of Amyloid related imaging abnormality.

So we interpreted this then as that particularly susceptible individuals or individuals exposed to a very high dose may show this sign of excessive pharmacology, but in the same patient or in other patients at lower doses there was still Amyloid removal as indicated by the PET data yet no MRI findings. So we were very encouraged that we could move into phase II and the next logical step after having shown biological activity in patients here based on the PET was to conduct a phase II study to show clinical efficacy of the drug.

So is this Amyloid removal indeed relevant for patients? This decision to move into phase II was taken at a time when it became very clear that Alzheimer's disease starts way before the development of dementia. There's data here from Chris Rowe for example to suggest that there's a 15 year gap between Amyloid deposition and the occurrence of Alzheimer's dementia. This data

together with the biomarker data coming from studies like ADNI and others that led to this graph here, which is still hypothetical yet very data driven, suggests that a couple of things.

One is that patients can indeed be identified in the early phase of Alzheimer's disease. If the dementia phase is here there's the mild cognitive impairment stage in the clinic into which the prodromal Alzheimer's disease stage falls where there are a number of markers based on which you can identify patients, and it is maybe even possible to identify them in the cognitively normal stage. The other point we learned from this is there are a number of biomarkers that are in the dynamic phase prior to dementia stage. So they can be targeted to show drug effects. So the decision was then taken to conduct phase II in a prodromal Alzheimer's disease population.

And how do we select the patients? This is according to research criteria that have been proposed by Bruno Dubois and that are also reflected in the recently updated diagnostic guidelines. Patients who have a subjective memory complaint or were close person has noticed a memory decline are then tested with specific cognitive tests to identify the memory decline as being of the amnestic type which is the typical presentation for Alzheimer's disease. Then with the help of biomarkers of those patients with amnestic MCI we can enhance the likelihood that indeed the amnestic MCI is due to Alzheimer's disease. And there are several candidates for these biomarkers. One of them is the CFS-Abeta measurement and we have seen data earlier this morning and there's published data of course that another possibility that is very highly correlated with the CSF-Abeta measurement, maybe the Amyloid PET. There are other ways and we heard on the BMS compound, the presentation this morning, there are CSF tau measurement for example that might also be used to enhance the diagnosis or the likelihood that amnestic MCI is of the Alzheimer's type. And these patients are functionally fairly intact and they are not demented.

This then is the overview slide at a high level of the phase II study that's designed to show clinical efficacy. As I said it's in patients with prodromal Alzheimer's disease. We are testing two doses of Gantenerumab and placebo dosed every month for two years, and the total sample size is 360 patients. The study again has an Amyloid PET substudy where we hope to confirm the findings that we had in phase I. The primary endpoint is the change in the CDR sum of the boxes which we have chosen over an endpoint of the

conversion to Alzheimer's disease based on data such as the ADNI data and based on a growing consensus that the conversion endpoint is problematic because Alzheimer's disease a continuum. It's not something that happens overnight. And the PET substudy, obviously the endpoint is again the change in brain Amyloid load.

And then we have a number of secondary endpoints, many of which are geared towards showing effects of disease modification. So these are the usual suspects here. There is their CSF markers of new degeneration and brain volumetry. And then obviously there are other very important secondary clinical endpoints which is cognition measured by the ADAS-cog and function. Overall this design we feel is backed up in the expert field here. It's based on ADNI data and other published work. It was backed by the international task force on designing clinical trials in early AD and aligned with the novel diagnostic criteria for early AD. Thank you very much.

Dan Perry: Dr. Ho, do you want to come back to the microphone? We now will be taking questions from the audience. Thank you.

Audience (Krams): *[Inaudible comment – off microphone].* And what was the smallest amount, shortest amount of time that might be required to see a treatment effect and will that be an operational issue?

Susanne Ostrowitzki: We of course don't really know what the dropout rate is going to be and there aren't all these many studies out there on prodromal Alzheimer's disease where we could benchmark. But I think we have a primary endpoint that's a continuous variable. It's not the conversion to dementia endpoint. So that I think we will have to treat dropouts just like in any clinical trial. You know, we will try to avoid them, but the study will be informative even with data up to the time point where patients might drop out of the study. But in terms of numbers, I think it's a little early to predict this.

Audience (Sperling): Actually this is a question for both of you about the plasma Abeta elevations and maybe as a discussion for biomarkers and how we'll use them in phase II and what is that really reflecting? I'm not an immunologist. My understanding is that it may really reflect the affinity for the monomer and so I wondered across your two different antibodies what you thought about that and how much we should rely on that evidence we're really moving it out of the brain?

Susanne Ostrowitzki: You want to go first?

Carole Ho: Yeah, so I think those are very good points. And I think in terms of a preclinical model, we do believe that it does demonstrate in this case because there isn't peripheral Abeta that it has to come from the brain. So I think that your point is a very good one. So in clinical studies however when you look at peripheral Abeta, it may not be very informative because most of the peripheral – that Abeta could be coming from the periphery and not necessarily from the CNS. So I think what it really helps you with is it tells you you've engaged the target but where you've engaged that target, you don't necessarily know. So I think as I described earlier, you know, our test of efficacy is really going to have to be this large phase II study and the biomarkers such as Amyloid imaging and other biomarkers that we're looking at in the study. But from a preclinical model, the particular transgenic APP animal that was used, that Abeta is actually coming from the brain.

Susanne Ostrowitzki: So I mean I have to agree of course, and we don't know yet what, if any of the Abeta species is gonna be the truly toxic one. I guess Gantenerumab is targeting aggregated Abeta species starting from oligomers. It's not targeting the monomer. And when we discussed this, we thought well the fact that it doesn't complex monomers in the periphery means that's the antibody that's circulating is available to further penetrate the brain and bind aggregated species. So you know it all depends on how it will pan out which species is the culprit.

Audience: Can you be more specific on the entrance criteria for the biomarkers that you plan to use? Are you using cutoffs like BMS is using?

Susanne Ostrowitzki: Yeah, can't really provide the cutoffs but I can say we've chosen the CSF-Abeta as an entry criterion and the FCS-RT on the cognition side.

Dan Perry: Question? If not, we will thank you very much. The last of the company presentations –

Michael Krams: I'd like to thank my colleagues at JI also for presenting on their behalf, not talking about Bapineuzumab today, but about some thinking that we have on how we could all cooperate better. So this talk is an invitation to collaborate. It is also very high-level. The Devil will be in the details, but at least it's food for thought,

and the case study, Randy Bateman has allowed me to disclose, we are actually discussing within the DIAN Consortia. So it is substantial now, not only just a high-level discussion, but I'm giving a study also as another case study that's already running in oncology, and the question that I would like you to go away with is, how could we all work together?

So, Carol, it strikes me that when I visited San Francisco, I never said hello. I think you work very close. Susanna, you mentioned that there are firewalls even with your company, and it is quite extraordinary that a meeting like this is one of the rare opportunities for people who work in a pharma R&D environment to touch base with each other, albeit only on a very high level.

So look at this slide, this is my title slide, and it has all the ingredients in it that will ultimately make the message. Of course, if I organize these same words in a different way, it is much easier to read. Now, look at this slide, which looks at a number of studies that are currently happening or have happened in Alzheimer's, and not many of those interact with each other. And of course wouldn't it be much easier if we connected this information such that we would understand.

So imagine that we think about pharmaceutical research as an opportunity to have an indication as the center of a solar system. It's the Alzheimer's problem. And around it, there's some information about targets that we think are relevant. Around each of these targets there might be moons, like compounds, that might modulate these targets. And imagine that we build a research infrastructure that is able to put the different words together such that there is semantic meaning coming out of it, as opposed to lots of individual, small efforts where the question at the end is, was the trial big enough, and have we observed for long enough.

Now, maybe this is just a dream, but ultimately what we're here for is to serve the future patient horizon, and it is somewhat concerning that when we work on our day-to-day basis, we are very concerned with the individual trial. We may still think about the program that it lives within, but rarely do we think about the entire portfolio of R&D opportunities and really rarely do we think about the R&D opportunity in the entire space of research that's going on. And yet that's what we should be doing. I think if we did that, there might be better efficiency.

So the outline of this discussion is to first give you a case study in oncology that many of you have heard of before, to then apply this principle to Alzheimer's disease talking about a prodromal trial within the DIAN Consortium, but then to also think about how we can even apply the same principle more widely, thinking about neurodegeneration rather than just Alzheimer's versus some other neurodegenerative disease. And eventually, hopefully, there'll be some discussion on how we can make this happen.

I want to thank Don Berry, who's been my inspiration and mentor for this for many years, but also my colleagues at JI where I have been able to implement some of this thinking, and what I will not tell you today is how tiring and hard it is to make it happen. It's very hard work. It requires more thinking time than we usually get when we plan our project timelines. So we're very fortunate that we have this opportunity to implement some of these ideas in a much smaller context in real life. But the Devil is in the detail.

Anyhow, here is the first case study. It's an oncology trial. It's a trial that's trying to establish proof of concept not for one treatment, but for a whole class of treatments in patients who suffer from breast cancer – breast cancer that would be treated for these subjects with neo atrovent chemotherapy. So the idea is that people who have this disease will go into an umbrella clinical trial process, where they will be allocated to one of several treatments, such that the benefit to the individual patient will be maximized, given the current level of information available. And as you will see in a minute, it's the Cat's Meow, as Don Berry often says, because it's not just trying to learn about the compound, but it's also trying to learn about the background of biomarker partial information that can help to make decisions, and we'll talk about this in a minute.

And Dr. Katz, I was very encouraged by your comments. The idea of looking at this framework from an adaptive design angle is a great opportunity, but again, the Devil is in the details. So the idea would be to have the prospectively defined framework, which allows us to accumulate data, and then make decisions during the process of the clinical trial as it accrues patients and observes them, in a way that does not undermine the validity and integrity of the trials.

It's a little bit like a GPS system that's looking at all the information and is trying to make its next move. One very big

concern is, imagine that there is information becoming available that would be available also to the investigator who makes an observation on a subjective endpoint, starting to introducing all sorts of crazy biases. So that's one aspect. Another aspect is the control of type one error. It's a statistical issue, which I will not go into at all.

So here's the outline of the I-SPY 2 Trial. From the time at which a patient gets recruited, to the time when the final observation will happen, I think it's an eight month treatment, there will be many interims looks at which a number of biomarker observations will occur. And the idea is, over time to establish the signature that would best identify people who might benefit from a particular treatment. And it might be that as this trial moves on, the signature becomes clearer and clearer, such that at the end, two things are achieved. Compounds that really work have been promoted, and patients that really work for that particular compound have been associated with that treatment. That's the idea.

So here is how this works. There are many treatment arms in this trial, and only one common standard therapy as a control, and it might be that over time a particular treatment arm graduates and will be brought into a conformity trial. The trial process overall, however, continues, maybe another arm drops for futility. Maybe later on there will be an additional arm introduced into this mix, and think of this as an ever-ongoing process that never ends. Now there might be times when there are no treatments in there. During those times they'll be learning about the biomarker infrastructure. That's the dream.

Now let's apply this to the DIAN cohort, that you're all aware of. So we are now taking this solar system that we thought about, but make it a much smaller problem. So imagine that we're going to focus our attention on just one target, and we look at just this particular sun, and we look at the moons that circle around it. Maybe three compounds, maybe two, maybe five, who knows? A small number of compounds. And we're going to ask ourselves, is there a way within an overarching trial infrastructure to learn efficiently about these compounds if we all integrate them in one clinical research process.

And so this is a figure out of Susanna and Carol's work on one compound that might be able to modulate the underlying biology of Alzheimer's. Here is a compound that we work on with similar

data on PET that indicates that if you give these compounds over time, it appears that amyloid can be reduced in the brain, and let's now take these observations just conceptually. I don't want to talk about the detail on what the decision criteria would be, but just conceptually to ask whether we can establish a proof of concept trial for potentially disease modifying treatments to explore initially just their effect on biomarkers.

And I'm plugging this figure out of the air. Say this was possible in 30 subjects. And say that we will use biomarkers as a necessary condition. We want to see something. If we don't see it, we're going to say no further allocation of patients onto this particular treatment, because we have a strong belief, just as we heard earlier about the story in IGG, there are certain people who have strong beliefs, we take that for granted and then apply that in a research infrastructure.

I'm throwing into the mix as an example another biomarker. Imagine we were to believe that movement on phosphatase might be an indicator for a reduced rate of neuronal loss. Just say that's the case, imagine we can agree on what these thresholds might be. We now apply this into an adaptive design.

So the approach would be that if we have a pre-specified minimal acceptable threshold on these biomarkers, and we can meet these pre-specified thresholds, then we graduate the treatment down into a confirmative trial. If we can't, we stop. It's very tough to have that discussion. In our shop it's taken us more than a year and we're not done. Because the knowledge isn't there yet, and we are suffering from the fact that yes we have access to ADNI, but ADNI, as wonderful as it is, doesn't answer all questions. And there are all these other bit and pieces. But our problem is we see the pieces of the puzzle, we don't see the picture. So we need to think on how we can recreate the whole image rather than to have to always have to deal with one piece of the puzzle.

Now, for the DIAN trial, the idea was to maybe take three treatment arms of different steady drugs, maybe drugs that we already know something about. Maybe there's some information about these drugs so that we're not going in there entirely carte blanche, but we have some idea. And so here's the basic notion.

Imagine that we recruit subjects over time, and quite frankly, these subjects are incredibly valuable. They may not be more than a

thousand worldwide, who knows? So we have to make absolutely sure that we get the best out of every single subject in terms of information value. In functional brain imaging, our experiments rarely were bigger than six subjects per paper, and it was a given that we needed to find out a design such that we could make sense of the data. So I was surprised when I started in clinical research that all of a sudden there were hundreds, sometimes thousands of subjects, and yet we got inconclusive results from time to time.

So the idea would be to take the people who come into this trial, see it's a prodromal Alzheimer's setting, and look at some biomarkers. For argument's sake I'm saying maybe we need to look for nine months before we can make a determination of whether we can continue to invest or not in a particular treatment, whether we have proof of principle, say on a phosphatase or a PET amyloid removal signal.

But imagine that after some time, when we have information on this follow up, for some patients we can base a decision on it, such that subjects who will be recruited later on will benefit from this piece of information.

Now, it is very important that we do not truncate the observation. Usually when we do proof of concept trials, we look at biomarkers and then we're done. What should happen is that we continue the observation all the way to whatever is required to find some clinical end point information also within the same subject within the same clinical trial. Very important. If we dissect these two pieces of information, it's so much harder to make sense of the data in the end.

So now here is the I-SPY 2 design applied to the DIAN cohort, the same slides as before. A drug might drop out, another might go in to confirm, a third one might be added to the mix. The Devil is in the detail – there are lots of technical issues to be sorted. I'll just give you one example.

Imagine that the clinical endpoint would be timed to some event. Say that's the argument. Timed to some deterioration. Say this is the Kaplan-Meier trajectory on untreated subjects over time. We don't know what that curve looks like presently very well for prodromal patients because we haven't got the benefit from very large longitudinal trials. So there's uncertainty on what that curve looks like.

Now imagine you have a silver bullet of a treatment that is so good that events don't occur any more. And imagine that we declare a clinically meaningful effect as described by this arrow as we find it here, and then maybe this arrow can fit in after an early time when only very small numbers of events have occurred. But of course if the treatment isn't quite as good we may need many more events before we can declare success.

So the point I'm making is we don't know enough to have robust assumptions to build good clinical trials, therefore I believe the premise is there to apply adaptive designs in a good way where we pre-specify all our assumptions and pre-specify our decision criteria. And therefore I believe that if we were to extend this proof of concept trial, and also look at, say, a time to event clinical endpoint, we'd have to have a design that is able to adaptively allocate the timing of the interim analyses conditional on the data. So we look at the data, we look at what is the trajectory of the placebo treated Kaplan-Meier curve, and in light of that we determine when is the right time to look. It's very complicated.

Now, Dr. Katz, you mentioned seamless phase two/three designs, and I think for the DIAN Cohort, this is actually a potentially appropriate proposal, because there is such pressure to get it right within a very small group of people. So there aren't enough people around to just fool around and burn many, many trials and many, many subjects.

So imagine that instead of doing a phase two trial where we may have different treatment arms and placebo and then stop and think and then do a phase three trial where the ultimate inference about whether or not there is substantial evidence for benefit comes from the data in the phase three trial, imagine that we had an operationally seamless phase two/three design where all we do is to cut out the time to think, and we just glue together the phase two and three with no time in between. Maybe phase two and three look very similar, but ultimately the data that we base our inference on still only comes from phase three.

The challenging aspect would be to build a design where we have such a seamless approach, but the inference at the end is based on data not only from the phase three data, but also on those patients who received drug during the exploratory proof of concept phase, and morph these together and then make the final inference. It's

complicated, it's something that the current draft FDA guidance does not recommend to be done as a standard because there are all sorts of issues, statistically and otherwise, and yet I think for a DIAN group that is something that should be explored, and the statistical methodology is worked out for it, but the execution of such a trial has a number of challenges, I won't go into it, but they can be dealt with.

Now, another problem, what is the correct time for treatment intervention. We make choices not so much based on what we know is right, but what's feasible. So we all agree that it would be nice to have early intervention in Alzheimer's trials. But I'm a stroke neurologist. What I've seen in the stroke field is that it went down because we did too much of what is feasible and didn't do enough of what was biologically plausible. And so it would be nice if we could ask ourselves what exactly is the right time of correct treatment intervention.

And now another dream, imagine that there was a Framingham study on steroids. So we take a million people in Boston or elsewhere, chosen out of the telephone book, and we're going to observe them for 100 years. And we observe them with the five or six or seven biomarkers that as of today we think we have an interest in, we want to build longitudinal information about these people. So we build a natural history study in a grand scale. We look at these biomarkers across subjects, but we have an intention of morphing this natural history study into a pharmacological intervention trial eventually.

And what we'll do is we'll apply vector physics where we look at the trajectory before the treatment intervention and the trajectory afterwards. And the types of designs that will be possible by doing this will be very much more efficient than the types of designs where we get a snapshot of a look, ignorant of what happened to these patients before, and then we hope to see something that we can interpret. And I very much agree with your comment earlier on, if we don't understand the confounding factors very carefully, how can we make sense of the data?

Now imagine we had all these confounders very well prescribed and could include them in the analysis. Then we would be doing what in functional brain imaging we routinely do, using packages that are built to make sense of sick subjects but with very careful experimental design at the front end.

So the idea is, maybe we don't have to start with mild to moderate or prodromal or a secondary prevention approach or a primary prevention approach. What if we were to say we have a solar system where at the center of it there's an interest in a disease, and around it the moons, this time, are different time points.

Now, it might look outrageous, but let's just think about prodromal and mild and moderate and maybe just mild patients. How different is a very advanced prodromal patient from a very early mild AD patient biologically speaking? So from our phenotypic perspective they belong into different categories, but do they really? And so is it therefore possible that we can apply the I-SPY 2 principle to a research question which has at the center what is the correct time of treatment intervention? And so we're now building designs that think about maybe combining late prodromal with early mild patients and considering them the same group, and we're thinking about how we can go even wider. It's complicated, but at least in principle.

Now let's do the final step and think about the underlying biology. We think of Alzheimer's as if it existed. It's a notion in our head. When we look at brains under the microscope, they often have a combination of amyloid pathology with vascular disease with other things. So the notion in our head is what determines our discussion. There's no such thing as a pure Alzheimer's patient with absolutely no other pathology, I think. And so what if we were to say, well, what is the principle? What is the underlying biology that is the core of the solar system, the Sun?

And I'll give you an example. We're very interested in mitochondrial disease. So mitochondria, at the core of many things. So imagine that we could build around this core of the mitochondrial biology a clinical trial design which starts by asking, is there a disease where mitochondria are involved and we understand everything? Maybe a single point mutation rare disease in children and optic neuropathy levers, something like this. And we can take a handful of subjects and we have a compound that does something around mitochondria and we want to get proof of concept very quickly, very efficiently.

But if that is the case, we'll apply this principle to a Russian doll experiment where first we deal with the easiest, smallest doll and we get quick proof of concept. But then we think about, are there

other diseases where mitochondria are involved? For instance, Chorea Huntington, ELS, Parkinson's, eventually even Alzheimer's. And so rather than asking ourselves very important, very complicated research questions, a whole enchilada of research questions starting with Alzheimer's disease, the most complicated doll at the very end, it might be better to dissect the problem and start this process of creating knowledge in a more biology based way.

Now, the opportunity is there that I'd like to invite us all to think about. How can we improve our understanding of the longitudinal trajectory of Alzheimer's disease? As simple a question as one of the compounds, yours or the one that we're working on, what is the earliest time point at which we can see a phosphatonin movement in CSF? Is it day 1, day 13, day 29, or day 67, or month 9 or month 12? Well, we get a snapshot and never longitudinal data. That's very unfortunate.

Why don't we take compounds that we know has biological activity, and we ask that precise question in a way that we can observe it in a human patient setting. It would be incredibly informative. If we had the ability to say, it is at week three that the phosphatase starts to move, very more efficient designs could be built using the adaptive principle. But we don't have that piece of information. So what we need to create efficiently is longitudinal understanding of the trajectory of many of the different pillars of biology that we don't yet have good understanding of. But then to come up with a way of building sentinel cohorts out of these epidemiological studies to make them into pharmacological intervention trials.

And I'd liked to invite us to think about adaptive concepts as a way of thinking collaboration. And so next time I'm going to say hello to the Genetech colleagues perhaps when I work next door. But how can we make sure that we go from this setting where there's all this incredible work ongoing, and it looks like my introductory slide of the title that we don't understand, to a more integrated approach?

Again, many things to my colleagues at JI who are allowing us to make this type of thinking a reality. It's very hard work, it requires much more time, and definitely in our setting requires thinking maybe even beyond the signs. I can tell you when we tried to do this in oncology for the I-SPY 2 trial, it took five years to deal with

the lawyers. I'm very happy that we ultimately got it done, but I'm very unhappy that we didn't make a Henry Ford T model production out of it. The knowledge in the different companies on what it took to convince lawyer A, B, C, D, E is all gone and evaporated. What we would really need is a top down concerted effort to allow us to work together much more closely.

Thank you very much.

Dan Perry: Thank you very much Dr. Krams. If you'll take a few questions?

Michael Krams: Sure.

Dan Perry: Very much in the spirit of knocking down the barriers.

Audience: I'm with the Coalition Against Major Diseases, and I just want to thank you for your presentation and tell you what you articulate so well at first is actually what we're doing. We have built a consortium of several of the people in this room, where companies are sharing their data, as well as we're getting data from ADNI. The first thing we've done is worked on developing Alzheimer's data standards, because I'm sure, as everybody well knows, everybody uses different terms, so it's impossible, or at least it's very difficult, it's very time-consuming to be able to analyze the data. So we start with everybody using the same terminology no matter where the data comes from, that's the first step. Then we pull together this data so we now have a common database of 15 clinical trials from seven different companies. And then we make this data available to qualified researchers.

Now this data is only placebo data. What we'd like to do, we'd really like to go to the next step and have drug data. And again, this could be de-identified, whatever, but we think we need to learn from successes and failures in terms of moving forward. What we have been able to do with the placebo data – and I say "we" meaning experts from the companies who have looked at this – is being able to separate outpatient groups very distinctly. And again, our focus is on biomarkers, just what you've articulated, looking at the biomarkers, see how they relate to clinical endpoints, and then letting the companies use these biomarkers in terms of their drug development program.

So our group is agnostic to the particular drug. But what we have seen is you can very clearly separate out mild, cognitive, impaired

patients from moderate and from disease severity, so that these biomarkers really will have some utility in terms of improving clinical trial designs. So I hope that we can talk further.

Michael Krams: So Alicia Dibanada in my group is working with you, and what you're doing is great. I'll give you just two pieces. One is, the level of meta information required to make sense of the data… Imagine you have a phosphatase assay in one part of the world that is not quite comparable to the other, but you forget about it and just pool the data and think you know. But you have forgotten about something very important, namely the fingerprint of the assay that qualifies what the information means. We often don't know about this.

The second comment is, yes, that's great. We are now starting to collaborate on data that already exists. The question to us here is, how can we start collaborating when we think about what the design might look like, and go prospectively rather than just retrospectively. And that's very much what we're trying in DIAN, and I think it's a great piece there, and would be great to take DIAN back to the question, can we take a result in the end and get a substantial evidence out of it and make a claim for it?

Audience (Katz):   Yeah, I think there's a lot in what you said. I think even if folks started to think about the first sort of adaptive design that you talked about, which is sort of would allow you to decide whether or not to go in to do sort of a more focused phase three study, would be an improvement. That sort of thing, of course, is never done. I mean even within a drug, looking at dose and trying to get the right dose for patients and which biomarkers are sensitive and that sort of thing. So I think that would be a big plus.

The inferential, seamless phase two/three design is more complicated, the Devil is more in the details there, and there are many issues that have to be discussed. It's not impossible and I don't think our guidance says you can't do it, but I think it says you really ought to think really hard about doing that. So I think that's probably a tractable problem and people are doing it, as you say, in other fields. In other fields way in advance of Alzheimer's. And most fields of neurology don't do that, and we rarely see that.

Again, for the truly inferential seamless design, there is some reluctance in the agency, but I don't think we're inconvincible. I think it's absolutely the case that if the goal really is to cure

Alzheimer's disease or prevent it or do something very big about it as opposed to what has happened today, there has to be collaboration.

And I'd like to extend the concept of collaboration well beyond what you have even proposed, which is great – which is looking at combination therapies, which we never see. And whether that is a question of intellectual property and Macys not talking to Gimbals or whatever it is… [someone comments, inaudible] Yes, I am, I recognize that. So are you. But no, I think that's a real problem because there are many fields where combination therapy clearly has been the answer, and I think that is really something that people need to be considering from very early in development, and it's doable, but it's never done.

Michael Krams: Couldn't agree more, and we don't understand the dance that's danced between amyloid and tau, but we all know at the bottom of our hearts that it's not just the amyloid full stop.

And so one of the questions, Dr. Katz, is, coming from my experience, I've worked in big companies most of my life – I've argued for the iceberg principle and combination therapies from 1990 onwards. The reason I've never been able to do it is my regulatory experts sometimes tell me that there's just no simple way of taking one compound we don't understand anything about, and another compound we don't understand anything about, and developing it.

So I think what we've achieved for the adaptive design world would be a wonderful model to do something similar about combination. If we could have a dialog between regulators, scientists, clinicians on how to tackle this important problem, including regulatory expertise, that would be terrific.

And I want to highlight Brenda Gatos who works at Lily, who has co-chaired with the Pharma Working Group, I think that has been a very nice example of how a big idea that looked crazy 15 years ago is becoming a day to day reality, including inferentially seamless _____.

Dan Perry: That might be the subject for next year's Ally's meeting. George?

Audience (Vradeberg): I'd just as soon not wait for another year. So Dr. Krams, speaking from a patient point of view, you are singing a song that

we would like to hear. That is that the research world sets itself up as a single enterprise that is designed to solved the problem of our patients. So I totally applied your exposing this, putting it on the table, and we would love to work with you on how to continue to press this conversation forward. Because as you say, there's levels of complexity and complexity.

I would also ask you just an enquiry. We now have an annual wellness exam inside the annual Medicare exam. There is a cognitive assessment element to that. Right now it's observational, it's pretty informal, it's pretty not clear at all what it means, but NIH and FDA as I understand it are thinking about five or six recommended cognitive assessment tools. Is there a way to begin to regard the Medicare population and the annual wellness visit with a standardized assessment tool, as the beginning of what you've been talking about as a natural history thing. Maybe coupled with some more sort of patient reported outcomes documents that are scientifically valid, so that we begin to create an entire population that itself from the patient side begins to relate to what you're talking about on the research/enterprise side.

Michael Krams: Thank you for throwing me that ball. For 20 years I've tried to do this longitudinal trial using a PET association learning test together with a measure of executive function which are well standardized and go beyond the particular region where only one language is spoken. There are these tests available. We don't have the longitudinal normative data yet. But the PET association learning test, as a measure of visual spatial memory, is ideally suited to dissociate cognitive decline that might happen in subjects with amyloid related disease where initially there are certain regions in the brain affected and the visual/spatial memory loss is the expression of that phenotypically, from cognitive decline as we see it in all of us from the age of 20 onwards, which can be nicely measured with other tests. So the trick is to have one test that is measuring the decline that we all go through, and the other test that gives us that dissociation for something specific associated with whatever the underlying Alzheimer's biology is that we believe in.

Audience (Gelmont): I have two questions. Regarding the combination therapy, doesn't the FDA require independent contribution of each drug, each compound in combination therapy in order to approve two or three drugs together, that's one thing. The second thing is to Dr. Kramer here. It took five years for the lawyers – it probably took ten years for the directors to come to an agreement on study design. Do you

have any plan how to make it work in less than 15 years, like in a year or so?

Michael Krams: Yes, this afternoon we have a teleconference with my senior management where we're trying to bring together the CEOs of companies at a very high level, and to break the mold that we have. If we go to our individual experts who have to deal with defending the legal framework, given the infrastructure that we live in, bottom up, this cannot be solved. But imagine that the key drivers of people who want to really do something good about moving pharmaceutical R&D to a world where we have better efficiency, agree that we should do what the semiconductor industry does as a standard – pro-competitive collaboration. What Airbus and Boeing do, even though from the outside world they look as competitors, there's a lot of cooperation going on. What the car industry does, but for some reason, pharma R&D isn't quite there yet. So that's what we're doing and there's going to be a workshop next year, and hopefully we'll also involve shareholders from many different angles, including regulators, to try and tackle this top down.

I recall we had this discussion in the DIAN group, and the question was, how do we get around the legal piece? And I was already saying this at a workshop a year ago, and unfortunately it hasn't happened quite as fast as I want, but I think that's the way forward, to break the mold top down.

Audience (Sperling): So I think it was terrific, and I applaud that we're doing it in DIAN and I think it's a great model, but I am concerned because of the limited patient population. And that thousand includes people across the whole spectrum of symptomatic disease. I also applaud the idea of going at the wellness exam, but I'm concerned again by the time there are symptoms that may not be optimal for some therapy already to intervene.

So as a very concrete proposal for how you might do this, there's an unlimited supply of baby boomers who are at risk for Alzheimer's disease, and I think that one place where pre-competitive would be, would be to identify individuals at risk by both basis of genetics, basis of amyloid biomarkers, presence of very, very subtle cognitive impairment. To do this kind of I spy too in pre-clinical, older individuals requires thousands and thousands of individuals, especially if we do combination therapy.

So why not go out and screen 50,000 now who would be ready for these trials as we make them.

Michael Krams: So Reisa, I have the proposal on my table – it's looking for a home.

Audience (Sperling): And money.

Michael Krams: We've discussed this for some time now. The proposal is written, including a lot of detail around it. It's a very big proposal though. It's looking at 500,000 subjects. And what I'd like to do is piggyback on existing studies of elderly subjects, and that started 30 years ago, 20 years ago, to benefit from prior phenotypic observations, ideally if there's some bio bank associated with it would be the best. But yes, I'm all for it. If you have an idea, it would be great.

Audience: Hi, I was just going to add that last December exactly FDA provided industry guidance on use of two unapproved investigational products and a pathway for that development, which is an alternative to the typical factorial design. And that may be an aspect in terms of developing combinations. I think the key there is that they were looking at products that would not be developed separately, that they work in a complimentary way by means of pathway and providing a framework that would allow a reasonable dataset that would not have full development program speech product, but would be mindful of the fact that they would be used in combination, and let that be paramount in how the products would be developed in combination.

Michael Krams: Yeah. I think there's a *New England Journal of Medicine* editorial with Janet Woodcock on it.

Audience: Uh-huh, they published it on it as well.

Dan Perry: We have time for two more questions before we bring everyone back for continuing this. I guess we have three. Zaven, Rachelle and Dr. Hampel.

Audience (Doody): Well, I want to bring another type of research to bear, somewhere between what you're saying and what George was saying. So really this experiment sort of is taking place. Because all over this country you have people who by different criteria are being diagnosed with Alzheimer's disease and prescribed medications.

And they take them for different durations of time, and they take them in different combinations.

So there are long-term observational controlled studies out there that are trying to assess the impact of what's happening now on the natural history of the disease. There's a paper summarizing this, actually, at Alzheimer's and Dementia that's under review. And there are places like Pittsburgh which have been looking at their Alzheimer's Center population and looking at nursing home placement. And Mass General which has been looking at modeling Cohen's d effects sizes. And our center which has been looking at factors that predict progression and what the persistency of treatment does in those mixed effects models.

So you've got this going on now, and I think that there are preliminary data from these type of long-term observational controlled studies that could inform this adaptive design.

Michael Krams: Two comments. First, personally I believe primary prevention is probably what's required, my personal belief, so we need to start at what age? 40, 50, 60, 65 – but not much beyond. Second, for adaptive designs, what we've learned through interactions with the FDA, the key is prospective definition of the decision role. So this came up earlier today at some stage around biomarkers – what is the decision criterion. That's the painful piece. So it's not easily possible to take existing information and try to integrate it in the meta analysis way. So the adaptive design idea is different. It's saying, given what we know, what are our criteria for making decisions, and how do we apply this prospectively.

Audience (Doody): I think what it brings to bear on the discussion is the pragmatics of it. Because when you design this trial, you're going to have issues related to attrition. You're going to have issues related to biomarkers not behaving the same way in different places etcetera. So I think it's an important aspect to examine as you go into these adaptive trials, no matter what point you put them in. And I must say, the interesting thing that's happening is there is adaptation. So people are being treated earlier in MCI stages. And people are being treated with drugs outside of their indications. I think it is informing the design question regardless of whether you're doing prodromal or early symptomatic.

Michael Krams: Yes.

Dan Perry: Dr. Hampel and then Zaven, and then we will get one more shot at all of this morning's speakers.

Audience (Hampel): So I like the idea to map out the entire biology on a systems based approach. You didn't mention that, but I thought you meant that. And also to map out the trajectories of the biomarkers in a large concerted effort. I think it's the only way to go. We shouldn't underestimate, though, that we are dealing with really complex target populations. And even in DIAN, it sounds great to have a Mendelian group of people and you can do what you want, but the truth is, we have 200 plus mutations with very small numbers. So that's the reality, and I don't want us to be too overly enthusiastic about this. Which is very much placing to the sporadic, non-Mendelian field, with a growing number of genetic risk factors and high risk genes we don't even know of. So the entire population might be, like in cancer, a very heterogeneous field. And I think that has to be somehow put into the model that you propose.

Michael Krams: I couldn't agree more, so thank you for making that critical remark. The issue is that even taking all of your thinking into account, we will be faced with difficulties because it's such a difficult problem, but consider the alternative. The alternative is that we're running prodromal trials, making the very naïve assumption that we have a homogeneous population. We have a mixture of people who are 3 minutes to 12, 3 years to 12, maybe even more, and we consider them "the population." And that's the alternative at this point, and that's not right. And so even though it will be far from the perfect solution, it will be a small approximation towards it, and that's the intention.

Audience (Zaven): Mike, I liked your presentation very much. As you know, you and I have spoken about this before, and I hope we continue talking. One of the great limiting steps in what you're proposing is trying to create the infrastructure, the large populations that can be followed longitudinally a la Framingham. Which in regard to that, there has been quite a bit of thinking that has gone through a series of the thing tank meetings under the rubric of Leon Thal Symposium where Paul Aisen and Rachel and others, Eric, have participated in developing the conceptual model for registry, if you want to call it. But the most parsimonious way to describe is a large international database for healthy aging. As you know, there is quite a bit of traction. The idea is gaining quite a bit of traction.

OECD now is becoming very much interested in that concept. Harald Hampel and I recently participated in their planning, where they're approaching it from the point of view of having such a national/international infrastructure for identifying validating biomarkers, but there's no reason why such a population cannot be used for clinic trials a la the model that you prescribed. But that's not going to happen unless countries make national commitments as part of their planning. In this country we have an ongoing effort now under NAPA, and George is a member, perhaps he could take the message to make such an infrastructure building a national priority. If EU does the same thing, I think then all the pieces will come together.

I think there is quite a bit of consensus in the scientific community for the need for such an infrastructure and I think, as I said, there has been quite a bit of thinking and we've published in the journal a number of the recommendations from the community. I think it's doable and I think we should do it.

Michael Krams: So I was in Brussels last week when the Euro still existed, I'm not sure at the end of the day, but at the time the Innovations for Medicine initiative was talking about something very similar, more details to follow. But I would ask you for your help. If you have ideas, I think the patient advocacy groups in particular, if you have ideas, let's assemble them and make something out of it. We have been talking too long, too fluffy. It's time to get down to the detail and do something real. And I want to thank again our colleagues at JI who make this possible in a much smaller realm where we look at seamless phase one/two, seamless phase two/three and all that stuff. But we all know how difficult it is in terms of detail.

I want to close by telling you what Henry McFarland said yesterday when I discussed this in the context of MS, because that's where we also do this. He said, "Three things, Mike. Number one, phenomenal idea. Number two, you clearly believe in Santa Claus. And number three, you should be work…

[End of Audio]

Dan Perry: All of the doctors please come on back up: Dr. Ho, Dr. Lipschitz, Dr. Gelman. Please, have a seat. So you've heard from them. You've gotten a peek behind the curtain of where some of these companies are in their clinical trial designs and decisions they're making. We're not going to ask them to lead off again, so it's up to

the audience. There must be some additional questions. We'll start with Phyllis Greenberger.

Audience (Greenberger):   I'm Phyllis Greenberger, president of the Society for Women's Health Research. And this has been very interesting and provocative. And I'm not a scientist, so there was a lot of it that went over my head. Our focus is on sex differences, and we held a scientific roundtable of about 18 researchers, scientists actually from industry as well as academia and the NIH looking at sex differences in Alzheimer's. Not just because women live longer or they're the caretakers, but in fact that there are sex differences.

And it turns out that the number of sufferers of Alzheimer's are predominantly women. And, as I said, since I'm not a scientist I can't give you sort of a lot of the statistics and research findings that they brought to the table. But there were enough to keep us going for a whole day looking at these differences. And then the day before yesterday we did a briefing on Capital Hill, and I don't know if George was there also. And there was a lot of really interesting information about sex differences and inheritance, et cetera, the effect of hormones and estrogen. And I just wondered, I guess, first of all, are you looking at sex differences?

No one mentioned any breakdown in terms of sex in any of the trials. And obviously it's not enough just to include them but also to see if there are differences and what they are. And so I just wanna bring that up. We will be publishing a paper if any of you are interested. There was actually someone there from Jansen and from Pfizer and from Merck as well as the academic. So I just want to bring that to your attention and hope that if you haven't thought of it, that you will think of it.

Michael Krams: Then we could start with an anecdote. It was late '80s that Upjohn developed an acute stroke neuroprotectant. I forgot the name. But the bottom line is that after the fact they – what was it?

Female: Tirilazad.

Michael Krams: Tirilazad. So it turns out that it has a totally different operating characteristics in men and women. And I learned from these guys at the time and have ever since, of course, looked at the differences. But I think in the outermost context what you mentioned is one of a panel of different things. And when I say panel, it might be thousands.

But maybe it's 20 or 30 important ones. And what we need to establish exactly what is important when is precisely this longitudinal natural history study effort to make sense of it, I think. How one phenotypic piece belongs together with another biomarker piece with another something else? The trick is in thinking the sentence, not each individual word. In short, yes.

Dan Perry: Any others on the panel?

Eric Siemers: I guess maybe the only other thing I'd add to that is I think besides for a biological differences potentially, Alzheimer's has been described as being more of a women's disease 'cause it's a little more common in women, but caregivers are certainly more women. And so I think especially in what we might call health outcomes data where we look at caregiver burden, then those gender differences I would guess would be significant. But that's the sort of thing we can look at.

Audience (Greenberger):   And we had actually. And those are gender differences, and I'm talking about sex differences. We did have actually have two women on the initial panel. And then – from Columbia University, and then actually at the briefing as well. But my concern is that most people think of the affect of Alzheimer's on women as caregivers and don't realize that the numbers of sufferers are predominantly women and that there are sex differences. And there are a lot of other things that came up at that conference.

One of the women there, maybe George can help me on this, really doesn't think that the amyloids and the plaques are – they think it's protective. They don't think it's a biomarker. So there was a lot of interesting things there that sort of contradicted. I'm not saying any of you are wrong. I'm just saying it was interesting to hear people that were doing research that had a totally different take on it. I don't know if George want to add to that or – that's – but it was very interesting.

Audience (Female):   I'd like to get your comment on something that came up in our meeting last week where actually was an industry person suggested that we need to revise the informed consent form for patients so that we can make this data publically available, that we can bill these larger databases. And part of the resistance to letting companies have their data has been the fact that it wasn't included in the informed consent form. So for Alzheimer's again, I think we

need to identify these barriers and work to change them and move on to build a better research database.

David Gelmont: I can answer that. Informed consent is usually driven by the institution. It's not driven by the company. So every institution has a different informed consent. Although there are parts of the informed consent that are common to everyone in the United States. However, between states there are difference in the informed consent and there is significant difference between European informed consent and American informed consent.

The American informed consent is about 40 pages of legal language. The informed consent in Europe is way more try to be fourth grade level and not getting into all the risks, et cetera. But it's a different culture, and we have to be very minded of the culture in Europe, for example, and the culture – the difference between nationalities, so even the different culture between California and New York, it can be much difference and the required may be different.

Audience (Vradenburg): The patients out there obviously are looking for a safe and effective treatment for Alzheimer's. The length of time between a validated target and getting drug approval is estimated, and I've heard wide variations, but 10 to 12 to 14 years and at a cost that is very, very high. So if you were to sort of be asked, and I'm asking you, what are the two or three changes or reforms in the entire process after target validation to FDA approval that would shorten that time from let us say 12 years to like 9 or 10 years?

I would love to hear them. And part it is because of a patient population that appeals to sense of urgency about this disease as the baby boomers are passing 65 at, what, 10,000 a day. And at the same time for companies obviously who are looking at shortened patent life because the length of this process. And the fear, I guess, from the patient population is the companies, either private equity or public companies, are pulling capital out because of the very high financial risks associated with this space. So what are the two or three changes that might be orchestrated in this therapeutic pipeline that would save some time?

Michael Krams: Can I just jump in because this is such a great point? The first one is to make the work between target identification to target validation public. So at Oxford University that's happening. So there are people who produce probe compounds. They put once

they've done it everything on the Web for everybody to see. So rather than 20 competing companies all in isolation, very slowly discovering the wheel one by one over time, eventually figuring out that a particular mechanism is the wrong way to think about it.

You jumpstart the system by having a piece of research happen in a pro competitive early space. So that's the first suggestion. The second suggestion is a invitation for political action. Imagine that there is a requirement, a legal requirement, for a patient when that patient enters a trial to decide whether he or she thinks that the information being provided should also be available to society.

And if yes, that data that I as the patient provide is available to the world. Not in the constraint of a very siloed research effort as it can because now that flies in the face of everything we can be doing. And I agree; it looks like utopia. But Dr. Henske some years ago had a similar suggestion on what it takes to publish a paper about a clinical trial. At the time there was big uproar. Now everybody accepts it. So those were my two points.

Carole Ho: So I think as for those of us on the panel that are clinicians, I mean, I think we share the desire to bring drugs as quickly as we can to patients. I think from a company perspective obviously there is a very large investment and there is risk aversion. And I think part of that risk aversion is the fact that we have other things that influence our design other than just the clinical trials as we look at them as we're designing them but really the endpoints that we're gonna be using to actually get approval.

So I think one thing that would really be helpful is having a more progressive view towards endpoints that may be meaningful that may not have been as well validated as I think some of the endpoints that we are currently using. So for example, and I mentioned this in my part of the talk, we went with the mild to moderate patient population probably because there were validated endpoints that we could use. And for us to say, well, let's use a non-validated endpoint that seems to make sense. There's huge risk in that for us to embark on a large clinical trial, then find out that those endpoints are not valid for registration.

Zaven: I want to follow up on the question that George was asking about what are our different strategies we could use to shorten the periods prior to phase 3 trial period. One idea would be to perhaps create more of a collaborative environment in the precompetitive

phase of therapy development. We already have, in a way, the mechanism for doing that. What would happen if the preclinical phase and the early phase 1 and phase 2 were done in a more collaborative way through something like ADCS?

ADCS is ideally set with – I'm now taking liberties. I don't know if Paul would agree with me or not. But to create a multi – using combination of ADCS and ADNI model where there is collaboration between industry, academia, and government in the precompetitive area where you accelerate the process by which you're identifying a putatively workable compound. And then have after that phase have industry come in and take over the phase 3 trial periods. I think obviously there are a number of intellectual property issues, those kinds of issues.

But those are, I think, are doable, but it would be a very efficient way of putting ideas, therapeutic ideas into place. We're writing a – we're putting together a workgroup as a proposal to go to, again, Napa as part of Napa priority for public/private partnership. I think this should be a way in which we can accelerate things.

Dan Perry: Response from the panel.

David Gelmont: It's very, very difficult. It's more of wishful thinking than being able to create that. There is so many hurdles here, as you heard before, and I don't want to repeat that. We need to look at what we call low hanging fruit. I mean such as for example, as you mentioned before, having the placebo arms available, data available on the registry or data on registry, et cetera. But going to real propriety information and display it all over, it's not going to go well in my management at least.

Eric Siemers: So one thing I might add to that, and I think a lot of these questions really the suggested answer is a lot more collaboration and I would agree with that. And certainly if you look across the whole drug development process, there's a lot of places where industry academia collaboration I think probably could be helpful in a lot of ways. But to bring up the idea of clinical trials running through the ADCS, now that's something I personally always been a big proponent of, but in terms of what are the barriers, first of all, people have already brought up the legal aspects of that.

And we won't have lawyer bash anymore I suppose. But the other point, and I thought maybe Dr. Katz might wanna comment on

	this, is I know that there's a certain amount of angst, at least at Lilly, that there would be regulatory delays let's say that if something went through the ADCS where we don't have the same sort of control, tight control over our regulatory group, and I think they do a great job. But then when there is this leap of faith to say we're gonna let this outside group do this, what kind of potential regulatory delays could that lead to? And is that a real concern or no?
Audience (Katz):	I mean if the ADCS did a trial, I mean it was sorta the sponsor of a large phase 3 type trial, regulatory delays I can't really – I mean you know obviously would have to meet the standards for data capture and quality of data and all of that sort of thing. And I don't see where that would necessarily impose significant regulatory delays. I'm not sure what the concern is. I mean we assume there would be some central monitoring capacity in a multistate, in a multicenter study run by the ADCS or whoever. It's not –
Eric Siemers:	But even in a phase 1, phase 2, that the vial formatting wasn't correct. I mean more of the nuts and bolts kind of aspects.
Audience (Katz):	You know, I don't know. It doesn't strike me. I'm not – I don't think too much about the data sets and what they look like. But I don't see that really as huge problem. I really don't.
David Gelmont:	I'm glad to hear that.
Audience (Sperling):	I just want to come back to a couple issues about these hurdles. So first the informed consent, we should stop talking about this issue of each individual – I think I'm _____ today – each individual IRB I think I said on that ADNI data and publications committee. And that was the broadest language ever seen which went through 52 IRBs and also went through Europe. So I don't think we should use that as an excuse for not making data public anymore.

And secondly not to always applaud ADNI is that ADNI did this great job with biomarkers but didn't go after these novel cognitive and new composites. And in the new utopia, I very much like to see us embed lots of potential, cognitive markers because the issue besides validating the biomarkers and what changes we need to link them to cognition and if there's a temporal lag, we're gonna need big, long studies to do that. |

David Gelmont: I'm sorry that if I meant – that if I misspoke. But I thought I'm answering the questions. We cannot have one informed consent everywhere. And we cannot simplify it because it's different from place to place. And that has been my experience for decades.

Audience (Sperling):   I think we should change it.

Carole Ho: I meant on your point about collaboration and looking at the combination of biomarkers and clinical endpoints. So I thought that some of the discussion that has already happened today has been really valuable in that sense. I think, Eric, your description of the gamma secretase data where there really was a cognitive outcome and is there something that we can learn about that in relationship to other biomarkers. And I think for all of these studies, whether they succeed or fail, these are our opportunities for us to understand that correlation. And if we were to understand that, I think that would greatly accelerate the ability to do trials and understand if there's a meaningful effect much faster.

Dan Perry: We have time for one more. Right here.

Audience: Hi, I just wanna go back to the informed consent issue. And many of you in this room may know this already, but HHS has issued a advanced – well they issued the advanced notice of a rule making regarding the common rule which – and they proposed, asked for comments for new informed consent law/rule. And that, the advanced notice rule making time period has closed, but they will be coming to the notice, just a regular notice. And if anybody has commented like to make on the informed consent, I urge you to do that once their rule making period opens again for comment.

Dan Perry: Thank you very much. I think before we break, let's pay our industry speakers a big round of applause.

    [Applause]

    I think they're candor and they're openness and thoughtfulness in their presentation was really first grade. It's exactly what we were looking for. So I thank all of you very much. And I know the allure of the boxed lunch is calling out to all of you. And let's take ten minutes, get our lunch in, reconvene. And then we're going to have our reactor panel and then more –

[End of Audio]

Dan Perry: I apologize for being such a taskmaster, but because we have fairly limited time to pull together our reactor panel and give you specific time for some interaction, I'm going to ask everyone to take their seats, and let me ask our reactor panel to come up here. Dr. Doody, Dr. Sperling, Dr. Aisen, Dr. Hampel, Dr. Katz, please. Go ahead and bring your lunches, this is all very information. You can chew into the microphone, we won't hold it against you.

Rachelle Doody: We're missing some of our panel. Dr. Hampel? Harald? Could you please release Harald from your discussion so he can come forward?

Okay, let's go ahead and get started, and I'd like to begin by thanking our presenters from this morning. You guys did an outstanding job. It's exactly what we needed. There are a lot of decisions being made in phase 2 clinical trials that don't end up being discussed. They may end up being read by somebody in a publication, they are discussed in advisory board meetings, but then can never be discussed in another setting because they're proprietary. So by you coming forward and putting these things out in the public domain, it really enables a much better discussion for us all.

So equally exciting is our panel, who are here not only to respond to what happened this morning, but also to a specific list of questions. So I didn't ask you, panel, to make a presentation because what we really want to maximize our time for today is having you interact with what's happened this morning. So we've organized a set of questions, but if you have a slide, or two slides, and you might need to or want to use those in one of your responses, please do, and we'll make sure that that slide gets shown. Have you given your slide already, Harald and Reisa? Okay.

So we will begin by at least going along the list of these questions, and I've added a couple of other points that came up this morning in case we can work them in. And the first set of questions really centers around who are we studying? Are we studying everybody in the solar system, which has actually been proposed today, in a way, or are we really suiting our population to our drug, which makes a certain kind of sense? Or have we decided as a field that all interventions must be made early or in a pre-dementia state? Obviously not, based upon what you heard this morning.

So the first couple of questions I'd like to consider together are what are the best strategies for improving the identification of study subjects in the absence of a validated anti-mortem diagnostic test, and is there a rationale for combining patients at different stages of presume AD dementia in clinical trials, and we actually touched upon that this morning. Particularly in a genetic form of the disease where everybody with the mutation has the disease. So does it matter if they have symptoms or not? Does it matter if their symptoms are mild and meet an a priori threshold or criteria for a diagnosis of a certain clinical entity that you might find in the diagnostic and statistical groups? Or does it matter at all? So, panel, what are your thoughts about that? Let me start with Paul.

Paul Aisen: I guess I would start by saying this has been just a tremendously useful discussion on what we're doing now in phase 2 and what the issues are and what we might do to move forward. And as a preamble to trying to answer Rochelle's question about who should we be studying and should we be combining different stages, I just want to, I guess in a positive light, remind everybody that we've done I think a very good job in working together to address some of our common issues. I think more than in any other field, cancer or any other field, we regularly bring together as is happening today academic individuals, companies, regulators, foundations, and we share information and we share ideas.

I think ADNI is a wonderful example that shows that companies are not only willing to work precompetitively together, but actually will fund such efforts substantially, and that's terrific. I think the companies are very eager to share as much as they possibly can. So I think the companies clearly want to work together and come together in these kinds of organizations and meetings and work together in settings like the ADCS and ADNI, and build up our knowledge, which is what we need to do.

So just as ADNI has laid the foundation for understanding those biomarker trajectories that have led to moving from studies in dementia to studies in prodromal AD, I think that work has to continue, and indeed is continuing as we move from Prodromal AD to earlier stages like the pre-clinical AD defined in Reisa's paper recently, and even into primary prevention. We still need more data, better understanding of biomarker and cognitive data at the very earliest stages, and even the.. [Problem with mike]

So as we want to move our populations for study earlier, we need to continue to accrue the data and share it and discuss designs, from pre-clinical data to even primary prevention data, meaning data surrounding the conversion from entirely normal status, no amyloid, no symptoms, to the earliest stage, which is probably amyloid accumulation and the starting of other biomarker abnormalities. And I think it's work that has to be done together and should start now, because it does take time. But the collaborations are in place and we should keep aiming for this.

Now, closer to Rochelle's questions, who should we be studying and can we combine different stages of disease together? Well, sure, I think it's one disease, and I think that's one of the developments of recent years coming out of this collaborations is an understanding that this is one disease, it's AD. Dementia is the end stage. Prodromal AD is the near end stage. Preclinical AD is a relatively early stage, and we have to keep moving earlier, but it's all one disease. Change in everything that we measure is gradual and not stepwise. Study designs based on survival moving from one stage to another make no sense because the disease does not have any discreet stages, and each time we try to do that, not only do we have operational difficulties, but we're throwing away data, because in fact, data change continuously and not discreetly.

Rachelle Doody: That being said, do we have the outcome measures to combine the groups?

Paul Aisen: So selection wise it's not difficult to combine the groups, because it's one disease and I think we can select. As far as the outcome measures go, certainly we do not have standard cognitive and clinical outcome measures that work across all stages. Some measures will work across most stages to show target engagement of an anti-amyloid drug; I don't see any reason why you couldn't combine preclinical prodromal and AD dementia, because they all have a similar amyloid signal and they all could show a readout on an amyloid measure, meaning amyloid PET or CFF, that would not preclude including them all in the same trial.

But when we want to move from biomarkers to clinically oriented and cognitive outcomes, then of course the story is different, where we have symptoms at one stage and milder symptoms at another stage, and even across prodromal and AD the measures should be adjusted to be robust and dynamic to pick up treatment effects. So I think it becomes problematic when we move to cognitive and

clinical outcomes and know we don't have measures that would allow us to combine all stages of disease.

Rachelle Doody: Rusty, you wanted to comment on that?

Dr. Rusty Katz: Yeah, I agree with the part about it all being the same disease. Yeah, to the extent we're convinced that the various stages that we can define are in fact all Alzheimer's disease, then, yeah, you can enroll them in the same trial. But again, it complicates things. There's no rule against it, it complicates things because some people you might only have to follow X amount of months to see an effect on a particular outcome, let's say the people who are further on, and some people you might have to follow much longer to see some sort of an outcome.

The question of whether you would have to assess in all stages a cognitive outcome, or could you get by in the very early stages with just a biomarker outcome, is an open question. You know, of course, we've been reluctant to approve a drug solely on the basis of an effect on a biomarker. But I suppose you could consider having let's say a biomarker for the very early patients, and biomarker plus clinical outcome for the later patients. And if you showed a relationship in the later patients between the biomarker and the clinical outcome, you might be willing to say, well, for the very early patients who aren't going to have anything measurably clinically for ten years, maybe get by with a biomarker. In other words, you sort of internally validate the biomarker. I'll just say validate with a small "v" and not a capital "V", because just for that drug, and many assumptions go into it also.

But you could imagine, that would be a very complicated study to do I would imagine. It's really two or three studies in one. I don't know what the advantage would be. Maybe there would be advantages. So I do think that the stage of the disease will be inextricably linked for the time being with the outcome measure, and that will perhaps have to vary.

I want to also say, if I could, a couple of other things. I think sort of the name of the game in many ways beyond sort of what's the outcome measures, enriching the population, make sure we get the right people. So one of the things we heard was this sort of early adaptive design to sort of match the patient to the response, to the drug, and some people will be responsive and throw arms out early or doses out early if patients aren't responding.

The other thing I would just urge folks to do is very basic, very simple stuff, should happen very early and often doesn't, things like looking at the PK, making sure patients are getting the appropriate plasma levels, looking at sex differences early to see whether or not one sex or the other is over or under-dosed, looking at something as simple as food effect. Because if it's a big food effect and you don't know about it and you're dosing patients with no particular relationship to food intake, those plasma levels could be all over the place. So there are some simple things that could help to enrich the population that are independent, that are not Alzheimer specific. But I think finding patients who have an appropriate response to your Alzheimer's drug specifically early on, typically early on I would suppose there would be a biomarker, that is an enrichment move that I think is very important if it can be done.

And I do have some comments about the outcome, because I think Dr. Ho said that there was a certain amount of uncertainty about outcome measures. I could do that now or we can come back to that if you want.

Rachelle Doody: Let's come back to outcome measures. Reisa, you wanted to comment specifically on the populations?

Reisa Sperling: So that was very exciting and I think it's a terrific idea at least within the spectrum of pre-clinical to think about a group that might only change on biomarkers, and a group that was closer to a cognitive outcome, meaning just about to tip maybe towards MCI where you could use a cognitive outcome.

I guess my only other concern about combining across stages of the disease, if some of the basic science models are correct, like Brad Hyman's where there's an Amyloid dependent and an Amyloid independent phase of the disease. Then it makes me a little concerned about combining these groups, unless you're directly going to ask the question about whether this intervention only works at a certain stage of the pathophysiologic process, and I think that's conjecture right now, but I think it's something as a field we really need to answer. Does it matter if you already have neurodegeneration or not.

Rachelle Doody: But, Reisa, does it matter what the mechanism of action of the drug is?

Reisa Sperling: Yes, absolutely. That as a specific comment in thinking about anti-amyloid therapy, because we have that now. And similarly, actually on the opposite way, if we had a drug that was really going after neurodegeneration, I wouldn't necessarily try that in people who didn't have neurodegeneration. So I think this question of where the intervention, when it has to happen with a specific target mechanism is key.

Rachelle Doody: So, Harald, I know you have a slide you want to show. Does that relate more to the populations issue or the trial design issues?

Harald Hampel: Well, to both. As the last person on the panel that has been asked, it's always difficult to say anything meaningful. I think the whole field is moving from disease categories to dimensions, and I'm just coming back from a DSM meeting and an EMA and OECD meeting on these questions, that the general notion is dimensions, to appreciate the disease in its entire spectrum. And I fully agree with Paul on that.

However, it's a difficult thing to conceptualize. What are we talking about? It's a very complex disease. It's chronically progressive. It's non-linear, and it's dynamic. I hope I got all the key words. So, to conceptualize this and mold it into, let's say, a spectrum that can be treated in trials, it's unclear how to do this. It's not an easy thing to do. So we have to categorize, and I think the biomarker model is the most convenient one to go.

Rachelle Doody: Let me also frame the question here, because it directly relates to your slides. So what are the most promising candidates for and uses of biomarkers?

Harald Hampel: That's not my slide. I didn't prepare a slide, I'm really sorry for that. I just put on in a second, it's an entire presentation, I'm not going to show this. I thought you'd appreciate that. Let me check this. Okay.

I just wanted to make this point clear again. What we are dealing with, that's the original model that the amyloid treatments were conceptualized with, the autosomal dominant mutation carriers. And as I said, we have more than 200 mutations, and we don't know how these individual mutations in the APP or peers 1 genes really react to treatment, what the differences are, we haven't

worked this out. So to combine a group out of all of these might be convenient, but I don't know what we are getting.

The same is true regarding biomarker validation in this model. I mean, we probably see different biomarker trajectories in these individual mutations, so that's the one situation. But I think we should be clear about the second situation that is unfolding the sporadic non-Mendelian Alzheimer type that is the target of treatment here. And I think this slide shows that this is a complex genetic situation. And what we are getting recently with additional information from genome-wide association studies is there are other pathways, like the lipid signaling pathway and inflammation immunology and all kinds of other things, like the mitochondria and much more involved around the amyloid hypotheses.

And I'm ending with this, Rochelle, if you will allow. I really like this slide of the evolving landscape of Alzheimer's disease pathophysiology. I just want to put this out because this is a thought provoking meeting and what you see here is Karl Herrup has somehow brought the amyloid deposition cycle, this is how he calls it. *[Walks away from mike]* _____ cycle which is somehow in proportion then to other _____ and other inflammatory responses which lead to a change in cellular state and could independently lead to new degeneration, and also things like tau phosphorylation and other cellular events, cytokine elevation and so on. And clearly these systems interact. These molecular systems or cellular systems interact.

And this just shows that the appreciation of the pathophysiology is evolving. I think we have different types of patients in this population that we are studying and what I've seen at the CTAD meeting, I think Cliff Jack has shown that around Peterson, that there's a group of patients in the Mayo Clinic longitudinal study of aging, that doesn't show A-beta changes, whether in the CSF or with PET, but they have neurodegeneration changes. And it was about 25 percent of their cohort.

So these people that have neurodegeneration signals, like with FDG-PET or CSF-tau, they don't show any A-beta signal and they might be in your study if you're not selecting a good population. I'm ending with this.

Rachelle Doody: I think that opens the door, before we get back to outcomes, for the biomarker discussion that we need to have. So we saw today from

Alan's presentation that the biomarkers have a moderate correlation with the imaging. And from other studies we know that the biomarkers have a moderate correlation with the clinical picture. But there are all sorts of exceptions. People who have A-beta and tau but they don't have the amyloid imaging. Or they have FDG-PET but they don't have A-beta. So there's a little bit of wiggle room there in the biomarkers. They're not interchangeable within a subject, they're not completely reliable, yet they've helped us a lot.

So given what we know about the biomarkers, how comfortable is the panel with saying we know the biomarker for X with respect to population selection. Or we know the biomarker for progression that we can use as an outcome measure. Do you as a panel, or as individuals on a panel, want to express any uncertainty at all about the biomarkers, or are you fine with them?

Reisa Sperling: So I'm a biomarker person but I'd like to express great uncertainty about them in terms of outcome markers. I think using them as markers to define people who have amyloid, either CSF or amyloid imaging is probably pretty good, actually, at saying who's got amyloid in their brain and does that put them at increased risk for decline at at least the prodromal stage and maybe at pre-clinical, we don't know. But where I'm concerned, and particularly as we talk about adaptive design, is are we sure enough about any of these biomarkers to make no-go decisions in the context of an adaptive design without having any cognitive thing to pin it on? And this is a real problem as we go earlier and earlier in the disease.

I think CSF-tau or phopho-tau is probably the one I feel the most confident in, because I haven't seen people say that should go in the opposite direction. But pretty much everything else I've heard arguments going up or down could be good or bad. And even fibular amyloid imaging, which I think is actually a very good biomarker for target engagement, we don't yet know whether dropping fibular A-beta really will translate into a clinical benefit.

So I think we have to have some link to cognition in making these decisions as outcomes, and again, I like the idea of having some biomarker change and then embedding at a later stage some link to cognition. But if there's a time lag between a change and a biomarker, and a change in cognition, just like the time lag we see in this Cliff Jack's model, this is really problematic? We might see

a change a year or five years before we see the change in cognition, how are we going to do that in an adaptive design real time?

Rachelle Doody: Before we got to the rest of the panel I want to press you on two points. So yes to a biomarker to say who has too much amyloid in the brain, is that also a yes to positive study means Alzheimer's disease?

Reisa Sperling: Positive study means amyloid doses, which is a critical hallmark of Alzheimer's disease. It does not equal Alzheimer's disease, meaning that you know you will progress to the clinical form yet. We need bigger studies. I do think it's evidence that the disease is beginning in the brain.

Rachelle Doody: And if it's normal, is that a no to Alzheimer's disease?

Reisa Sperling: Yes. I won't say absolutely, because I believe there are occasionally negative individuals, but I believe that if you're symptomatic and you don't have any evidence, again not just below some threshold but there's no amyloid on either marker, by definition, I think you don't have Alzheimer's disease using neuropathologic criteria, because I think those autopsy correlations are pretty tight. We need more data before I'm willing to say absolutely, but I'm up in the 95 percent range, which is pretty high.

Rachelle Doody: So the suggestion would be a no on imaging, might be a yes if they had spinal fluid?

Reisa Sperling: Again, at this stage of symptomatic individuals, I don't think that's an issue. I think this mismatch between CSF and amyloid imaging has really only come up in very, very early people, probably five or ten years before symptoms. So again, at the stage of symptomatic disease, I would say a negative amyloid image would make me look for some other cause for their impairment.

Harald Hampel: I'm not exactly sure about this point. Just looking at Cliff's data, just the 25 percent new degeneration positives. We don't know. It's just a descriptive phase of the study at this point. I don't know if we have more information on these subjects if they have additional factors that could categorize them into maybe, let's say, other new degenerative disorders, what they suggest. But it could also be looking at the genetic model that I showed, that there are

indeed Alzheimer's patients with less or no amyloid pathology. I'm just putting this provoking thought out.

Another point, the biomarkers are not pathognomonic, they are not specific for a so-called disease concept. They increase probability that a subject has the disease. So in combining these biomarkers you increase the probability, and this is what ADNI has shown very nicely, that the multivariate analysis comes up to, let's say, a 95 percent accuracy. If you take the CSF and the MRI information together we don't have the combined amyloid information with that. There's some data from Australia, they don't use the CSF and look at the MRI and the amyloid imaging and come to very similar risk probabilities on that magnitude. So it's, let's say, times five to times ten increased risk, and up to, let's say, 80, 90 percent accuracy with combined biomarkers.

Rachelle Doody: Just a quick question, then Reisa's response. So how many biomarkers do we need to have positive for our inclusion criteria in a study?

Dr. Katz: Wouldn't that depend on the stage of the patient? When patients are asymptomatic. It's one thing if you have what is ____ dominant, but for sporadic patients, if you're asymptomatic ____ very, very early, I'm not the expert obviously, but you would assume you'd want more reassurance the earlier you're going.

Rachelle Doody: Or perhaps more probability that that person will have Alzheimer's clinically at some point in time. Harald, do you have an opinion?

Harald Hampel: Well, just recently there are mono center studies with the highest degree of standardization, particularly from Sweden on the CSF, and there is an international study just published on CSF plus imaging biomarkers, and you see a clear incremental value in adding these modalities in a logistic way. Also our ADNI analysis, looking at all 24 indicators shows there's a best indicator in the biomarker which may be the MRI procampo volume, or the CSF A-beta. And the best predictive value is achieved by combining up to four of these measures. But this is an incremental added value, which adds very little but some significant evidence of probability.

So the question is, I think the consequences for the patients in a trial are important. So if you have a compound that is potentially detrimental and you just don't want to have it tested in people that don't have Alzheimer's disease, then I think you should achieve the

highest possible accuracy. I think the costs of these biomarkers, that's another issue, are not really relevant to the trial, their calculations on that.

Rachelle Doody: Paul, do you have any comment before we go back to Reisa?

Paul Aisen: Well, in answer to the question how many biomarkers do we need for an early stage study like a preclinical or primary prevention study, I think the answer is one. I think practically speaking one is doable, feasible. Difficult but feasible. And good enough when we're talking about an amyloid biomarker, either amyloid PET or low CSF A-beta-42. It's not perfect. You can improve your predictive value with additional biomarkers, and as I think was said often but maybe not often enough, everything's in the details for what's the treatment, the duration, outcomes. But I think the answer's one biomarker.

Reisa Sperling: Which one?

Paul Aisen: Today I would say amyloid PET.

Two, the question of, though, outcomes rather than selection, I think the really good news is the more we look, the more we see that there is subtle cognitive change from the beginning. And so that's not a good thing for people, but even at an asymptomatic stage when people are not seeking any help and they're enrolling in a normal cohort, if they have amyloid they are showing amyloid related cognitive decline, and that means that for outcomes we can use a combination. We can use a subtle cognitive signal to demonstrate that we're moving in the right direction, and that will anchor our biomarker outcomes and strongly increase the acceptability, I think, of the movement of the amyloid markers and neurodegeneration markers by the treatment.

So I think that today we're looking at very early trials, preclinical AD trials that look at subtle cognitive change, as well as impact on a panel of biomarkers.

Reisa Sperling: So I very much agree with what Paul just said, so I think that is a positive aspect. But I wanted to go back a little bit, Harald, to what you were saying, and particularly first of all back to that Cliff Jack paper just so we don't confuse that. The 24 percent did not all have neurodegeneration, they had either FDG or hippocampal atrophy, or cognitive problems. So they could be any of those

three. And in fact a large percentage are those who perform below the ten percentile but didn't have neurodegeneration. And the question there is, what do they have? And I think this is a real question for the field, and it really depends on the mechanism of action of the drug.

To me, if you want to define Alzheimer's disease for an anti-amyloid trial, then you need to have an amyloid marker to say. If you have a general neuroprotective drug that'll save neurons from any possible age-related neurodegeneration, great, then we can call Alzheimer's disease the very, very few people who don't have amyloid. But by definition, pathologically you have to have amyloid to get a pathologic diagnosis for AD. And if your drug is targeting that mechanism, then for me, that's where I think this has value. Not so much for clinical use but in defining the population for a trial.

Harald Hampel: That sounds very logical and it's also, let's say, politically correct regarding the traditional development of the field. I was just amazed hearing this descriptive data that we have these 24 percent of people with neurodegeneration markers positive no amyloid. I'm not inclined to speculate too much about that. I really want to know how are these people going to develop over time.

And there is evidence from basic research and genetics that there can be, in fact, let's say a category of however you call it, of people who develop dementia or whatever, in the end, that are driven by neurodegeneration without amyloid. It's a conceptual debate whether this is possible or not or whether this meets criteria or not. I think we have to acknowledge that this is out and not jump to integrate this into traditional thinking. That's just my point.

Rachelle Doody: We focused on the question of the biomarkers in the pre-dementia or very early stage. What about as we get into actual Alzheimer's disease, how comfortable is the panel with biomarkers as outcomes in established Alzheimer's, and which biomarkers?

Dr. Katz: I'll start. I'm obviously not an expert on biomarkers in Alzheimer's disease, but if you're asking the question, how comfortable are the panel members, being one, I'll give you my answer. We're not comfortable with an effect on a biomarker solely as an outcome. This is not a surprise to anybody in the room. But we should just go on record as saying that. I don't

think we have sufficient evidence available to meet the standard in law that says the effect on the biomarker has to be reasonably likely to predict a clinical outcome. I don't think the experience to date, such as it is, supports that. It may, of course, ultimately turn out to be true, but I don't think they can serve as sole primary outcome measures.

Rachelle Doody: So let's deal with them as supportive, and what are the committee members' feelings about which biomarkers available to us now are showing themselves to be supporting as outcome measures, or are there any, or do we lack good enough drugs to know? Where do you stand on this?

Harald Hampel: I agree with the point that these biomarkers as outcome are not validated and are not qualified. That's a big gap I think we have to fill. But they are supportive, and I think there's sufficient evidence that what kind of role these biomarkers play in pathophysiology. So to move these biomarkers in a certain logical direction is in my view clearly supportive – a supportive indicate that target engagement is moving something desirable.

The million dollar question is how does this engagement of the biomarker into the right direction correlate with clinical outcome, and that's I think the big, problematic question of the surrogate marker that we haven't solved, and I think which deserves really in depth discussion how this could be achieved.

Rachelle Doody: I think there's a difference between a biosignal of target engagement and a biomarker of outcome. So if we show that we move a beta or we change some functional aspect of brain glucose metabolism, it's different. So do we feel like the biomarkers that we have are useful as outcome measures? Let me raise structural neuroimaging. It's the one we seem to have the best handle on. It's the one that people seem to be putting in their studies.

Paul Aisen: Well, I think we should be putting as many biomarkers as we can into our studies because we learn about the biomarkers and we learn about the disease and we learn about the treatments. But structural imagine is a good example of a biomarker that has not yet been useful as an indicator of eventual cognitive and clinical benefit. We see discordant results. And while I think volumetric MRI, which is easy to include because we often have to use it as MRI for safety anyway, should be looked at, it's certainly not at a

point where we can rely on it as an income measure to predict eventual cognitive clinical benefit.

Each of the biomarkers is different in what we learn, and we need to continue to study them as extensively as we can in as many drug development programs as we can to answer these questions. But all biomarkers are obviously not the same. Some are going to have specific effects with certain treatments, like reducing information, reducing brain volumes, for example. Some are going to reflect cognition, like FTG-PET. Some are going to reflect fibril amyloid to the extent that fibrillar amyloid is in equilibrium with other forms, total amyloid load, and that's likely to be an important pharmacal dynamic indicator. But none of these yet has risen to the point that we can think about it as a key outcome measure in a treatment trial.

Rachelle Doody: How about as supportive of disease modification?

Paul Aisen: Well, I'm not sure that's even an important question. I think that we want treatments that have a favorable effect on symptoms over a long period of time, and many of us, I think, are not too concerned with whether this can be labeled as disease modification. So again, I think the biomarkers are important and help us understand impacts on various aspects of neurobiology. I'm not too concerned about whether it all comes together to support a phrase "disease modification."

Harald Hampel: But if your trial results suggest after a phase three trial that you have a symptomatic, and in the co-primaries you have a symptomatic result, very similar to the cholinesterase inhibitors would be great, but could that substantiate a claim for disease modification without biomarkers, or is it just the same like the cholinesterase inhibitors? I mean, that's vital.

Dr. Katz: Well, obviously there's a lot of interest in obtaining a claim for disease modification or progression, you know, they're all the same to me. I think it's possible that at some point a biomarker or a combination of biomarkers, I wouldn't know which ones at this moment, in conjunction with clinical effects, could be used to support a claim for disease modification if you really think you're looking at the structure of the brain and you've shown there's a clinical benefit. We might get to the point where we understand these things sufficiently to say, yeah, this is a mark of disease modification. How critical that is, I don't know, but obviously

people are interested in it, and if the field were convinced that this sort of panoply of results on clinical and biomarkers established that, we would certainly take that very seriously.

There are other ways to look at disease modification, we think, that don't involve biomarkers at all. We've just been through an example of one of these randomized start designs that was used in Parkinson's disease, but it seems to me it would be applicable to Alzheimer's disease, and was first proposed in the context of Alzheimer's disease. So we think that, if done well, which is very hard to do, comes out the right way, that could be used for disease modification. A claim for disease modification certainly has implications presumably, like people might feel that everybody ought to be on it because it modifies the disease, and how could you withhold that from people?

On the other hand, you could imagine a drug that has a symptomatic effect that's much bigger than a disease modifying effect that persists in time and might be much more valuable. So in and of itself, an effect on the underlying disease progress, without saying something about how big that effect was or how long it lasted, would be nice. But I agree with Paul, it's not the be-all and the end-all.

Rachelle Doody: Reisa, did you have a comment?

Reisa Sperling: I agree, if you would see an effect of any of these potential disease-modifying therapies above and beyond the standard of care that we have now, that lasted for three years, I could care less whether it's disease modifying on a biomarker. I want the patients to stay stable or get better. So I'd be thrilled with that.

I do think if we're trying to understand what our drugs are doing in the brain, and trying to refine our models and try to understand again when to intervene and what we're doing, then the biomarkers hopefully will be helpful to us. So I'm very pro biomarkers. And I think, again, I don't trust any single one right now as being theragnostic, that really tells me we're changing the course of the disease except maybe CSF tau, or CSF P-tau which is problematic to get multiple LPs on everybody. So I think that's unlikely to be a primary outcome in larger trials.

Rachelle Doody: So on the issue of outcomes, we've already addressed that in the sort or pre-definite AD stage, especially if we had a combined

population that included definite AD, that we might be able to have biomarkers in the asymptomatic people, biomarkers in the symptomatic people, and cognitive outcomes in the symptomatic. Rusty, you had a comment earlier that was specifically about outcomes, do you want to start that off?

Dr. Katz: Yeah, thanks. Yeah, I think it was Dr. Ho who raised the question that one of the points of uncertainty in industry is the fact that we don't really know what outcome measures to use. It's a well-worn path to look at mild to moderate, moderate to severe. We know what the clinical outcomes are. But in the earlier phases we don't. Depending upon, of course, how early we're talking about.

I think, as I said, we certainly do want clinical outcomes so far, in the absence of any data that links a biomarker to a clinical outcome, we're going to want clinical outcomes at any stage people are contemplating studying it at the moment. But I understand the point that the earlier you go, the less well understood is the question of what ought to be the clinical outcome, and whether it ought to be some subtle cognitive test, as Paul says, which we have certainly discussed as being possibly acceptable in the context of an effect also in a biomarker very early, or whether it should be something more functional, which can be hard to do in patients who are not particularly functionally impaired. I don't know.

I gather there is some angst on the part of industry and others I suppose about the question of fully validating these cognitive measures or the global measures, whatever clinical measure we're talking about. And you know we're paying more attention to trying to have sponsors adequately, psychometrically validate these newer scales or scales used in earlier patients. And we have a whole apparatus in the agency that does this, but that this is time consuming.

There is an interaction between the review divisions and the group external to the divisions that works to validate these scales. Ultimately my understanding is that it's the review division's decision about whether or not a scale is acceptable in the context of a trial, with input from our colleagues in the other group.

So we have for many, many, many years relied on scales that have not been adequately, fully, pristinely, psychometrically validated, and I expect we'll continue to do that. But it will take some give

and take between a company who's proposing it or an academic consortium that's proposing it and us to try and figure out is it validated enough? I mean, I think we ultimately are going to require if nothing else, some reason to believe that a change on it reflects something that's clinically meaningful to the patient, which to me is the overarching consideration. But whether it has to go through every possible step that the guidance lays out on validation, that's a matter for discussion on a case-by-case basis.

Rachelle Doody: But this raises a related issue, and that is, as we go earlier in populations, we have people who are more and more intact, and it raises the issue of patient reported outcomes. We had a session on this at CTAD, CPATH is working on it with input from the FDA. Is there an acceptance of the idea that we may be counting on patients to tell us how they're doing in these earlier stages?

Dr. Katz: We're willing to consider it as long as we can be convinced that patients are at a stage where they really can reliably report. And that, of course, is the question. You could certainly imagine a stage that is sufficiently early that we might consider. We still would probably, in a case like that, like some cognitive measure. As Paul says, even at early stages there are cognitive changes. So I think that's a possibility. Again, as long as we were confident that the patients could report reliably.

Harald Hampel: I would like to make a comment on that. There's a French population-based study just looking at people that evolve into Alzheimer's disease over many years before clinical symptoms. And what they show is that nine years before the dementia threshold, the people that are less educated have a considerable decline in the MMSE even, and they carry this through time, long, long, let's say, almost asymptomatic prodromal time. Whereas the highly educated, they come at the same time to the dementia but they have a rapid decline at the end and they cannot be self-reported or, let's say, classified by physicians. So in these studies you have all these over-educated people that's just a subgroup. Just look at the entire population. I think that's an issue that should be integrated as well.

Dr. Katz: Well, certainly from a drug develop consideration you have to establish – and if the drug works, presumably you would establish in the study that the outcome measure is sensitive. So more poorly educated people might have a decrement in the MMSE early, whereas very educated may not. But there may be another scale

that very educated people will have that decrement and so on. I could certainly imagine a trial that looks at different outcome measures for different patients, which is pretty much never done, but certainly something we have endorsed at least as a concept, the sort of patient specific outcome measures as an acceptable design element. You rarely see that.

Reisa Sperling: I just wanted to ask, because again, the French study showed changes and some on different measures, and we've been working across the Alzheimer's prevention initiative, DIAN, and A4, to think about how we'd create this new composite. And I was actually surprised, because I would have thought a single measure might be more powerful. But looking at these data so far, it really suggests that composites are more powerful, and including the MMSE.

So my question really is a very practical one about validating these composites separately on a preclinical population could take another ten years, which we don't have. So to what degree can we kind of put these together in different arrays that seem powerful from these natural history studies as a critical piece of that validation just because we don't have time.

Dr. Katz: Well, as I said, I think the question of what's an acceptable outcome measure, if it's novel, there are many people in the agency interested in that question. But as I say, ultimately I think we get to make the call, and with input, obviously, from other folks, but it's a case-by-case basis. So I don't think there's anything I could say here that would be less general than that. It's certainly something that we could consider.

Rachelle Doody: But is a composite of known measures a little bit more acceptable than something totally novel?

Dr. Katz: Well, you would think it would be, but again, when you start combining things that weren't intended to be combined, or you're combining parts of things that weren't intended to be combined, you do have to think about it a little bit.

Rachelle Doody: Any other comments from the panel before we open up to questions from the group and further discussion?

Dr. Kaatz: I think there's been some sort of intermittent theme throughout the morning about really looking at ways to more rapidly develop the

drug, to truncate development time. I think there's certain things you can not do. But the notion of combining, or thinking, at least, about combining phases. Zaven said, how about phase one and phase two? One person's phase two is 25 people a group, or total, somebody else's phase two is 350 people, and you're not looking for statistical significance, or maybe you are looking for statistical, so it's all over the place. We should try to think about what is phase two for.

It's interesting, I remind people that if you look at the regulations which define the different phases – there are other ways to define them – but if you look at the regulations, it defines phase two as the phase of drug development where you do your definitive effectiveness trials. Everybody calls those phase three trials, but the regulations call them phase two trials. So it doesn't matter what you call them, but I only point it out because at least whoever wrote that many years ago sort of anticipated that the definitive trials would be fairly early.

And someone else said, I think it was Dr. Ho who said we believe more is better. That's probably true almost all the time. Maybe not all the time, but that's probably true. So there's a lot of work about phase two and dose finding and this sort of thing, and I think probably the highest dose you can give is probably the best dose if it can be tolerated, so somehow you have to learn that. And we're always asking sponsors to study a higher dose, and a lower dose by the way, but the doses tend to be picked in some magical way, it's always clear.

But the idea of getting into definitive trials earlier, there's lots of things you can do. You can build intensive monitoring into sort of definitive type studies for the first X number of people till you decide that you don't have to monitor to that extent intensively any more, in terms of sort of like phase one/phase two kind of thing. So not everything is acceptable.

But I think the thought of using more adaptive designs to look at doses and which doses aren't going to be valuable and just throwing those out, or adding doses and looking to see whether or not you can figure out which patients are going to be responsive on a particular outcome to a particular drug. So I think the idea of trying to truncate the phases of development, I think it's worth talking about, worth considering more seriously than we probably have.

Harald Hampel: But why is there such a confusion about an oncology model in dosing, that say highest possible dose, that's the oncology philosophy. Or the primary care model that's just saying what's the minimal dose that is effective?

Dr. Katz: Well, again, we go through great gyrations to talk about dose, but I think probably most of the time the highest dose that you can tolerate probably is the best. Now, you might get the same effectiveness out of half the dose too, and you wouldn't necessarily want to push it. But I think these things hopefully can be learned sort of earlier than we're learning them. The minimum effective dose, I think that's a potentially problematic concept. I mean, it's fine, but it certainly doesn't guarantee that you've identified the biggest effect that you can get. Whereas pushing the dose, if you can do that, that probably works most of the time. That's probably going to be your best dose most of the time.

Rachelle Doody: And lends credence to the presence of an effect when you have a dose response.

So the theme of the morning has been in some sense combination, so we're talking about combining populations, we're talking about combining stages, we're also talking about combining sort of previously excluded people with included people, loosening up. As we understand the stages of disease better, including people who don't have just Alzheimer's disease, or just pure Alzheimer's disease. So I think that is a good observation, combination inclusiveness has been a theme.

One quick comment, is anybody from Abbott here, because when we're talking about adaptive design, I believe there's a paper under review of just such a design for ABT-089. Nobody? They were invited but they weren't able to come.

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Audience: …doing well in a trial, then take that patient population and confirm it in another study. I mean, the whole thing, remember, about mild to moderate that we got into this whole issue was actually wrong, the premise. For Aricept, the patients, actually the

more moderate patients in that study did well, and the early patients didn't do well. But when we analyzed the whole mild to moderate, it came out positive and we got the mild to moderate label claim.

So are we doing the same thing again, perhaps, that maybe we're making it too narrow? And if it really slows down the enrollment, should we take that risk? Should we slow down the enrollment if we have to, to get that patient population? Or should we be a little bit less defining, because we really don't know. I'd hate to go down that path and repeat BMS and take forever to get the patients into a study.

Rachelle Doody: And it raises the issue, if there's a drug that works best in the prodromal stage, does that mean it won't work at all in Alzheimer's disease? Probably not. So maybe we are being too strict. I started in the field at the year of the Tacrine study, and I thought we were painting ourselves into a corner. We were painting ourselves into a corner that said we wanted a drug that could only work for mild to moderate patients, and that's because we didn't believe that any drug worked for anybody. And we've continued that by carving out the groups, I think, very strictly.

Harald Hampel: Can I comment on that? The BMS study, these near misses of below cut off and the discordant I think A-beta 42 amyloid PET people, if I recall this correctly, we were all negative on the APOE e4 status, or most of them. So I'm just asking, why isn't there a stratification in place to look at A-beta 4 carriers balanced versus non-carriers? Because the A-beta 4 people, they show significantly different biomarker expressions and aggravate it. So I would guess you have more people that don't miss the threshold. So the mixture of people in your phase two determines how many misses you have. Just one aspect, it's only one aspect. Another one would be age relation to biomarker expression, and education and so on, and many variables that affect biomarker expression. So this has to be pre-specified.

Rachelle Doody: But, Harald, is the solution then just to use E-4 positive individuals and carve down? Or is the solution to widen it out to E-4 carriers and non-carriers and either stratify or count on randomization to get your signal in a wider group?

Harald Hampel: It's just meaningful to look at these groups.

Rachelle Doody: It's meaningful, but I mean, is your proposal that that should be your phase two group, or is your proposal to just deal with it but include all?

Harald Hampel: I don't know, it depends on the mechanism of the drug.

Dr. Katz: To follow up on that a little bit, when we're talking about sort of slicing the population, let's say just looking at APOE for homozygous patients or whatever we're talking about, there'll always be the question about, what about the APOE e4 negative patients, and would it be even appropriate to approve a drug for APOE positive patients if that's all you ever studied, because it may be entirely unrelated to the response. And of course it could be drug-specific.

So if there's a very, very good reason to believe that, yes, this particular subset will respond to this drug, because we understand the mechanism so well, and the complimentary subset really can't respond because they're missing whatever, the drug couldn't possibly work – if there's a very strong biological rationale you could argue, okay, we don't have to study those other people. But if there really isn't, we probably would want to see those other people's studies. And if it doesn't work in them and it reliably works in these folks and doesn't, great, then you approve it for these people. But to artificially restrict it is problematic.

Rachelle Doody: What I tend to hear around that discussion is people saying we have to show a signal. If we don't, we're not going to get to carry this project forward. What can we do to make sure… So it's really more of this enrichment idea, and I think a number of groups end up making that decision because it's phase 2 and they're afraid they'll never get past it.

Dr. Katz: Well, again, phase 2 at least as it's sort of currently done is a time to learn things. So I don't think there's a problem about enriching phase 2 population if the goal is to convince upper management you've got something that's worthwhile, or something that actually is worthwhile. It's just that in further development when we're talking about approval and that sort of thing, we have to think about, well, what about the other group?

Rachelle Doody: David?

David Gelmont: I'm very conservative. I believe in homozygous patient population I don't see any advantage of having ___ prodromal _____ signal. I can see if we _____ phase 2, phase 3 study in the same patient population, if the mechanism of action in the prodromal and the mechanism of action in the moderate are one and the same, then that would be two studies, one for this and one for that, and the FDA or the EMA would approve of that. So I can see that the signal for _____ ratio would be very high when you start to mix Alzheimer's patient population with such a complicated disease as that.

Another problem is, I do believe in phase one through phase four, although at some point marketing people it's only one, one study for everything. But I do believe we learn from phase one to phase two to phase three etcetera that we cannot learn very well. So adaptive design is the new kid on the block, and I think both the FDA and _____ are trying to understand what exactly we mean and how to design such a group study. But it's not that simple and it's not that easy from both sides, the FDA and from our side. So it would be very difficult to come with agreement on this kind of stuff.

And the last point is, MTD, maximum tolerated dose, is not always the best dose. Some biologics have reshaped that, and we have to be careful that _____.

Dr. Katz: That's true, but certainly with sort of small molecules, we went searching for the inverted U across many drugs. I'm not sure we ever saw it.

Rachelle Doody: Other questions or comments? Yes, start with George.

Audience (Vradenburg): There seems to this ear, and this is a layman's ear, not a scientific ear, that some people regard Alzheimer's as the symptomatic expression of something. And other people regard Alzheimer's as a pathological state. And while I can understand sort of both arguments, I think it's important for the field to understand, when you start talking to patients, we've got to be clear about what we're talking about. Because if we demean a disease… If we say this is a disease-modifying drug but it has no effect on symptoms, we ought not to elevate that above a symptom suppressing drug that has no relationship to the pathology.

So when we talk to the public as opposed to yourself, I think we need to be clearer. We've gotten in this trouble with some of the prostate cancer. You immediately try and go get rid of it. Well, l we've gotten ourselves in a trap of sort of overreacting because we've got a disease state, rather than looking at sort of the underlying facts and progression of whatever the situation is to determine whether or not you're ever going to get the symptomatic expression which is for cancer.

And then I don't know what the right, if there is a right answer, because this is a vocabulary question of importance depending on whether you're talking to yourselves and understand each other, or whether you're talking to a patient population. We ought to be clear what we're talking about.

Reisa Sperling: I very much agree with you, and in fact when we re-did the criteria across the three groups, we actually proposed calling it Alzheimer's disease pathophysiologic process versus Alzheimer's disease clinical, which I think is cumbersome, because it's long. And I think there are competing things. At one level I think it's important in the field to recognize that there is a pathophysiologic process that may precede symptoms in some people so that we could go for earlier treatment. On the other hand, I absolutely agree that we don't want to just treat the brain changes if that doesn't have some impact on the clinical syndrome down the way.

So I agree with you this is very tricky and we need some work on the terminology, but it's important to recognize that both aspects of what the rubric of what Alzheimer's disease contains are important, and we have to figure out how they fit together. That's what we're really struggling with in all of the things today, is how do we fit the changes we can see in the brain as best we can see them with biomarkers, with the clinical syndrome? And how do we understand whether changing one of the process actually changes the clinical symptoms. So it's not just a terminology, it's actually I think a problem in how we fit these together. They must go together somehow, because they tend to come together in the brain, but we clearly don't fully understand how they fit.

Rachelle Doody: But I think there's really two aspects to what you said, George. One is the timing question. Are you treating something pre-symptomatic prodromal, or are you treating a disease? But the second aspect is, what do we expect out of our treatment? So a "disease modifying treatment" could very well have a small

treatment effect, and we could very well find marketers out there saying, "Well, you've got to be on it for two years before we know if it's working, and you're really never going to really feel any different, because it's not going to make you better, but it's going to help you not get worse." As opposed to treatments that we might offer to people that will improve their symptoms for a year or two or three or four, but not be disease modifying.

So I think there's really two different points. There's two populations or two time points at which to intervene, and then there's the expectations out of certain types of treatments, and I have made the point that you brought up many times, being rather worried about it, because people are not going to understand it.

Paul Aisen: We should remember that Lipitor did okay, no effect on symptoms.

Rachelle Doody: I'm not saying the drugs won't do okay, it's just you don't want to sell it to people as, "Now we've got the drug – here it is!" "Now we have this disease modifying drug, but, you know, you're not going to feel any different. It's going to take a couple years…" It's all in the expectations of the public.

Audience (Vradenburg): On the first round of drugs you're more likely to reduce the decline, so patients who think they might be betting better with the disease-modifying drug, I think it's going to get worse at a slower rate. And I think if we oversell these first generation drugs, we're going to get ourselves really caught in terms of what the patient population expects and what we're going to be able to do.

Rachelle Doody: Right, and then as Paul says, over time people will come to understand that the early intervention has prevented a lot worse, but not right away.

Audience (Vradenburg):   It could very well be, in most products out there, the first generation tends to be high priced and clunky performance like cell phones. But through time, the fact that you've got a first generation product teaches you a lot to get to the second generation product. So even though it may not seem valuable to patients that we're slowing the rate of decline by a little, we've got to say this is important to the field because it's going to teach us what may be the next generation product which may have greater results. It's just a public communication problem. MCI, I think there was a confusion about what was useful in speaking to the research community, and speaking to the patient population. "Gee, I've got

MCI, that means I'm on my way to Alzheimer's." If not some risk factors, I think we've learned how to understand and talk about risk factors. But I think we just have to be careful when speaking to the public.

Rachelle Doody: Michael?

Michael Krams: It's curious that we are spending an extraordinary amount of moneys on developing compounds, and yet we don't understand the disease. So would it help to maybe take part of the budget and invest heavily in understanding the basics of the disease, and then have a much more efficient approach of developing compounds? So my question really is to Harald Hampel, because you build that point. You talked about dynamic, non-linear, and complex. And yet we discuss biomarkers in two by two tables. That doesn't fit. So how, is my question to you, can you help, and can all the panel help to lift this debate from a two by two table to a more closer approximation of what the biology is when we talk about biomarkers.

Harald Hampel: I like your comment. I think there are two ways to look at it. What we are talking about is the operational way to look at it, how the research field evolves. It's very painful. Over, let's say, the last ten to 15 years, drug development and biomarker development has begun to evolve, and this is restricted by all kinds of factors – in technology development, in public acceptance, in all kinds of things that are slowing us down and also narrowing us conceptually.

The other way to look at it is, to me it seems perfectly clear that we have in sporadic Alzheimer's patients we probably have a much longer disease progression than probably in mutation carriers, which could go up to let's say 30 to 50 years, in a non-linear dynamic way through stages from the preventative stage. Which again, the brain reality is so complex, so we'd probably go through a long phase of the neuroplasticity changes that are functional, fully adaptive and reversible than at some point to a beginning mechanistic stage, molecular cellular mechanisms beginning and maybe in parallel systems involved that interact could only be solved by systems biology approach. And then at some point we are getting from this molecular cellular state into a neurodegenerative state. Maybe with microstructural changes in the beginning, then microstructural changes, and then at some

point prodromal symptoms over a 50-year period of time, just trying to make big picture.

So the current field, how it stands in neuroscience and also in Alzheimer's research, is not capable of solving this question. So we have to come to a next level of integrated, large-scale international research to solve, let's say, the big picture. But it's like the mask program, you can achieve this within a ten-year period of time, but then you have to focus your resources – industry, public/private sector, and regulators, and academics have to work together on an international basis, and it has to be streamlined to get this person to Mars and back. And it's probably true also for the Alzheimer's question, the big question. But we can't help, we have to deal with what we have, and I think there is something we have, I hope you agree, Paul, and I give this to you to add some additional comments. So appreciate what we have.

Paul Aisen: I think this is a challenging area and there are a lot of barriers to moving forward, and I think that everybody in this room also appreciates how far we've come and the extent to which collaboration has been fruitful. I think that if we set our vistas too broad, we may not get anywhere. Sometimes we do have to have a pathway to achieve reasonable goals in a reasonable period of time. I actually think we can do that here in this field in the treatment and prevention of Alzheimer's disease. I think that we've advanced to the point over these 10 to 15 years where we just have a sense of the neurobiology that's much clearer than it was, and that's a huge step forward. To the point where I really feel we have to be treating Alzheimer's disease now that is testing therapeutic agents at various stages of disease now, because we're ready to test them. It does not make sense to wait for resolving all the issues before we move into therapeutic trials.

How do we best do those therapeutic trials? We've talked about a lot of the difficulties. So the topic today is phase two trials, and personally I think the best approach is to eliminate phase two, just skip it, and go from phase one to phase three, or maybe we'd call phase three phase two. Either way.

Dr. Katz: That was sort of what I was intimating. Which is that in the old days, I think it was anticipated that you would get to the definitive studies pretty quickly.

Paul Aisen: So I agree, I think the goal should be to get to phase three as quickly as possible, right after one, or as soon as you have the tox coverage or the safety data, because you're not going to be able to rationally select the dose or see efficacy in anything other than a huge trial. So get to that trial as soon as you can.

So what does that mean about the adaptive designs? Well, I think we have a big problem because right now we don't understand… I think we understand things well enough to jump into therapeutic trials, but I don't think we understand things well enough to do adaptive designs, because adaptive designs are based on the idea that we can make decisions early. And for the same reason that I think phase two is kind of useless, I think we're not at the point where we can do adaptive designs. I hope we get there, I think it would be great if we get there, and that's again why we should build in biomarkers as much as we can into as many programs as we can so that maybe we can get there, but I just don't think we're there now.

On the other hand, adaptive is a broad term, and I certainly thing every trial should be adaptive, and every trial is adaptive, and so my thinking is you move as quickly as you can to an efficacy trial, you design the efficacy trial so you can see an efficacy signal, you have a DSMB that monitors, and you build cognitive measures into that monitoring so that you can drop doses or drop the whole trial because you have adverse cognitive affects. But you build that in sort of as monitoring, as safety/futility monitoring of your phase three rather than thinking you can do an I-SPY 2 in the AD field.

Rachelle Doody: So, Paul, the other alternative is to redefine early and do adaptive designs, but early as 9 months or early as 12 months. I think there's still a possibility for that.

Paul Aisen: Well, except that if your idea is you're going to design your trial to take you to the decision point, then by definition you can't get to the decision point earlier, right?

Rachelle Doody: No, the decision point isn't the decision about whether to go forward or not; the decision point is about which doses to go forward with and other issues like that internally within the trial.

Paul Aisen: Right, but I think you define the size and duration of your trial as your best guess at what it's going to take to determine efficacy and you've almost ruled out the possibility of an adaptive look. Again,

if we really understood how biomarkers could predict change, it could change and eventually will change, but we're just not there. So I think we're stuck, and the trial itself takes us to the decision point on efficacy, and so we can't do an adaptive look earlier.

Rachelle Doody: Unless you look at futility and you look at tolerability. So you can adapt the trial with the shell of the trial being what you said, your best guess after phase one, but you still can adapt within the trial, and it saves money.

Michael Krams: So a comment and a question. The comment, Paul, I'm convinced I can convince you that you're wrong, but what it takes is a more differentiated discussion based on data. So what I need is more time and share with you the simulation results that we have which have taken a year to work on. In a discussion like this we can't make the point.

The question, in the airline industry we don't usually send Airbuses 380 into the air one after the other letting them crash before we decide what the design should be. Nor does Boeing have that principle. What they do is they have a lot of thinking up front, such that ultimately the machine they built hopefully stays in the air. Now it's curious that in our area we have a different approach, and I still am of the opinion that there would be great value if we were to put much more effort, extraordinary effort in understanding the non-linear, complex whatever the other things were, before we get going and send these very large engines into the air.

Reisa Sperling: So I very much agree with you that we have to do a better modeling of these complexities, but I'll argue that part of the way we're going to understand them is through therapeutic trials. So the idea that we should wait and do all these natural history studies where we just wait and we look at all these biomarkers alone in 500,000 people, I would argue that simultaneously we have to try to alter some of the pieces into the biologic pathway and say what happens to the other biomarkers, and they have to happen in parallel.

The other thing we haven't talked about today, maybe because it's not the topic, is this issue of our models of how we get to these drugs in the beginning, and this is a real issue because I feel like we don't have good animal models that show us the complexity of the interaction of these biomarkers, and we need to do that. But

	since we don't have those, I would argue that we're going to have to do more of this research in humans, in people, because they have this combination of dynamic complex biomarkers and dynamic complex disease with some aspects of the disease that we know we're not modeling. Like why do neurons die that don't have tangles? Or tau related. We don't have biomarkers for that except for maybe volumetric MR which frequently goes in the wrong direction so far. So we need to, I think, do some of this work in humans with potentially disease modifying agents to really understand the complexity of these biomarkers.
Rachelle Doody:	If we have some quick final comments, we're running out of time. Dr. Ho?
Audience (Ho):	Excuse me, I had a comment and a question. So the comment was that I think one of the themes that's really come out of today is the desire to move things as quickly as possible, and we've come to a point where we understand a lot more about the disease, we have potential therapeutics on the horizon that can do this. So I think the comment was really around the endpoints, and I appreciate, Dr. Katz, your input one on the validation of these endpoints and using the guidance exactly that, as a guidance, but then having that conversation.
	And I also just want to comment on at least what is documented in the Alz Forum minutes around looking at a subtle cognitive benefit in earlier stages of disease, where, for example the ADAS cog doesn't make a lot of sense. I think that's really helpful for us in the industry to hear that because it opens the doors for our management also to be accepting of trials that use very novel endpoints that have not been regulatory endpoints.
	And then finally my question, which actually I think Paul actually asked while I was waiting to get the mic, was around the phase two and phase three trials. And it may be beyond the scope of this, but having some idea from the regulatory perspective on what are the key things that really would make a trial phase three like and whether that is incorporating an adaptive approach or not incorporating an adaptive approach, I think that would be really helpful for us from the industry perspective.
Dr. Katz:	Well, again, when you have phase three like, we use the them, phase two, phase three, but it doesn't matter what you call it; what makes something a phase three like, if we want to call it that, is

that it's adequately designed to demonstrate that the drug has an affect according to sort of the usual rules of P val .05. That's not written in stone, but mostly it is in the typical case. So it's a study that measures what you want to measure and is capable by design and analysis and conduct to be interpreted of one source of evidence contributing to substantial evidence. That's what makes it phase three like.

Sponsors come to us with a phase two study, and for all the world it looks like a perfectly good randomized control trial, but it's underpowered because it's phase two. So we say if you throw a few more patients in, it's phase three. So we don't really care what you call it as long as it's designed appropriately, conducted appropriately, and can be analyzed.

Rachelle Doody: So shall we give the last word to one of our NAPA representatives?

Audience (Vradenburg): It goes to Paul's comment that in fact we ought to be putting a lot of biomarker data into all these trials so that we can learn as much as we can, as quickly as we can. Will we do that much better if all the underlying clinical data are collected under consistent standards and disclosed so we know what is failing and what is working? And so that all the data is made public so that we can all learn as we got through these failure trials or success trials.

Dan Perry: Let me just share a few closing thoughts as they retake their seats. I think one of the things that you would agree with me after the last five and a half hours or so of this discussion is this has not been your father's Alzheimer's meeting. This has been somewhat uniquely energizing. We've had extraordinarily candid presentation by a half a dozen different companies allowing us to look behind into a world where there's trade secrets and a lot of siloed information, and I think the opening up of that curtain has been a real benefit for everyone that's been here.

We've had a wonderfully engaged audience. There are as many experts there as there are here, and they go back and forth, and I think the interaction between those is perhaps one of the best parts of a meeting like this.

As Rochelle suggested, we've been looking a lot at the distinctions and somewhat breaking down walls between patient populations,

whether it's late prodromal or early mild cognitive impairment, between phases one and two, and two and three. I don't know what it says about a meeting that's all about phase two that we end up saying that we don't want phase two, but it's a mark of the plasticity of this discussion. So I praise you for that.

Also between biomarkers and their various uses and cognitive effects we're seeing a kind of a blurring a little bit of those lines as well. And in all of this you have sitting here the head of the neurological products division of the FDA and his staff and his colleagues, and they are open to all of these rather exciting possibilities. And I think that speaks very, very well of this agency, which often in the outside world is characterized as inflexible and rigid, this gives the lie to that unfortunate characterization. So I can't thank the FDA folks enough.
[Applause]

Michael Krams gave us an extraordinarily provocative look at the way that we might think about fundamentally redesigning how we do drug development. The bandwidth for our coalition or for anyone in this audience may not be big enough for that, but those are some ideas that we definitely want to slice and dice and bring forward again. I think the idea of perhaps next year's meeting, if you're willing to look at combination therapies, how are we going to regulate that? Very provocative. Patient involvement, patient reported outcomes and that role. It's been discussed elsewhere but I think it might be ready to be brought into this forum and we'll explore that.

In all of the meetings that we've had, this now being the fourth, we find ourselves continuing to come back to the same question – how do we measure the presence and the progression of this disease in order to identify the right patient populations to test experimental therapies and to what degree do these biomarkers play a role, either in combination with cognitive tests, or in some other way, but ultimately getting us to the point where we can measure effectiveness and approval.

As coming out of all of this, we went out and recruited about a year and a half ago what we called our dazzling dozen of real experts in the field of biomarkers, and we assigned each of them to write a chapter on PET, FDG-PET, MRI, structural MRI, cognitive testing, the whole field. Dr. Sperling and Dr. Aisen were part of that team. It's out this month as a special issue of the

Neurobiology of Aging, sponsored all non-industry funds, the Vradenburg Foundation was one of the sponsors as well as the Taub Foundation in New York, and I highly recommend that you watch this as it begins to circulate. You can see either Cynthia or myself if you want to know more about this.

Also the slides that were presented today and as much of the summary as we're able to coalesce in one place will very soon be up on the ACT-AD website, that's ACT-AD.org. We will ask all of the speakers for permission to put up the slides, but we'll organize as much of it as possible.

And so I just want to end by thanking again the speakers, the audience, the ideas generated here, our co-hosts, the Lead organization and Cure Alzheimer's Fund, and for all of those that helped. And a special thank you to my colleague, Cynthia Bens, who did all of the heavy lifting in designing this program, getting the speakers together, doing all of the logistics. Cynthia, we couldn't do it without you. *[Applause]*

[End of Audio]