

WOLTERS KLUWER

Moderator: Dr. Leon Henderson
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3:00 p.m. ET

Operator: Good afternoon. My name is (Tameka), and I will be your conference operator today. At this time, I would like to welcome everyone to the Dimebon and other developmental Alzheimer Drugs Conference Call. All lines have been placed on mute to prevent any background noise. After the speaker's remarks, there will be a question-and-answer session. If you would like to ask a question at that time, please press star, then the number one on your telephone keypad. If you would like to withdraw your question, press the pound key. I would now like to turn the call over to Dr. Leon Henderson.

You may begin, sir.

Dr. Leon Henderson: Thank you very much, (Tameka). And welcome, everyone, to the (inaudible) expert call series. Our topic today is Dimebon and other developmental Alzheimer's drugs, and we'll be going through the pipeline of developmental Alzheimer's drugs. My name is Dr. Leon Henderson.

And we're very pleased to have with us today, as our expert discussing, Dr. Stuart Lipton. He is the professor and scientific director of the Burnham Center for Neuroscience, Aging and Stem Cell Research, and a professor at the Salk Institute, the Scripps Research Institute and the University of California, and a clinical neurology attending physician at UC San Diego Medical Center.

Thank you very much for joining us today, Dr. Lipton.

Dr. Stuart Lipton: My pleasure.

Dr. Leon Henderson: It's quite a time in Alzheimer's disease with several developmental drugs approaching or in Phase Three investigation. You know, we've gone through a period of time where, you know, we have some medicines out there that – acute symptoms and help us manage the disease and we hope that we're on the verge of having medicines that help modify the course of Alzheimer's disease. We've had a lot of promise and lot of setbacks along the way. It's a very challenging therapeutic area. And I just wanted to hear from you, Dr. Lipton.

First of all, a little background on your initial interest and how you developed your interest in Alzheimer's disease and where you are today and your interests in Alzheimer's disease and things that you feel we should look for in evaluating Alzheimer's disease developmentally.

Dr. Stuart Lipton: OK. Well, great. Well, first, let me start by saying I appreciate you all being out there. And it's a beautiful day in La Jolla. I'm hopeful it's good all over the world. So my background is and full disclosure with this is I hold several of the worldwide patents on memantine and – here in the U.S. – sold under the name Namenda. This work was done when I was at Harvard, was licensed through a complicated licensing agreement in this country to Forest Laboratories.

Let me say that, as an academic, I can work on any drug. So I don't think that's pleasing me, in terms of one drug or another. And particularly, you know, that drug has a modest effect. And we're always anxious to find better drugs. I have a very active practice with dementia patients. And as you all know, we need much better drugs.

So with that said, I'm excited about some of the drugs coming down the pike. I think there are certain errors that have been made in the development of drugs. And let's spend 30 second on that and then move into Dimebon. It turns out that most drugs that are developed for the brain are either found by screening or, you know, in the case of memantine and Dimebon, interestingly were drugs used for another cause. Often that latter pathway, the drugs that are already known to be safe, that's actually a great pathway to take because, as you probably know, most drugs fail in the brain not because they don't somehow work, but they either don't work at the dose that's tested in the Phase Three trial or they have unacceptable clinical side effects or at least are not tolerated because the brain is very tough space to work in. And repeatedly, trials have failed for those reasons, even trial that have gotten, you know, into very advanced Phase Three multi-center international trials in – that are in 50, 75, \$90 million have failed. We've looked back because they didn't test the right dose. And that might have been predicted. If they looked in Phase One at the dose that they were able to escalate to, it's often found in hindsight that they didn't get to the “neuroprotective” or effective dose that they had predicted from their animal models.

Now that said, Alzheimer's disease is a tough space, because none of – we all use the animal models, but none of the animal models are that good. Some of the latest are the triple transgenic mouse, which is a mouse that Frank LaFerla here at U.C. Irvin has made and that has an APP mutation, a (inaudible) mutation and a tau mutation, three mutations that, hopefully, no person will eve have to endure. But it does give a very early disease, compared to several of the other Alzheimer model mice.

But as I said, none of these models are perfectly predictive. But again, if you're going to use these models, it is good to see if the dose that's effective in the model is actually, to some first approximation, the dose that you're using in the human disease. And inevitably, that doesn't happen in the trials, and it's something you can usually pull out of the earlier trials and make some prediction. And I think it's why a lot of the drugs have failed. It's nowhere

near the level of drug that they would predict would be needed because that level is toxic for some other reason.

OK, so let's spend a few minutes and talk about Dimebon. And I think the excitement of that trial, but also possibly some of the (works) of that trial. So as you know, that's being run by Medivation in Pfizer Phase Three trials, 55 locations. But they're going to know the result in March. Hopefully, they're going to share it with us. I don't know the results. I've carefully gone over the Phase Two trials and also much of the preclinical data with Dimebon – have actually been an advisor on several capacities about that.

And I think it's fair to say, when all is said and done, as of today, February 22, 2010, we don't know how Dimebon works. It was initially thought, and it was actually reported to be a low-affinity antagonist like memantine, then it was reported to have cholinergic activity like Aricept. Then it was reported to be a mitochondrial stabilizer. And in fact, I don't think we know what it does. There are several groups that have seen effects on mitochondria, but whether these are far downstream from its actual effect or its actual primary effect, we don't know. I mean, we just don't know this. And I'm (glad) in the question session if you want to delve down on the information we have on this.

Dr. Leon Henderson: Great.

Dr. Stuart Lipton: Now it doesn't particularly bother me that we don't know how it works. There are many drugs that are approved particularly in the neurological space that we don't know how they work. I mean, we've been arguing for a hundred years how Dilantin works and 30 years how valproic acid works and Tegretol, but you know, they're out there. So I don't think that in itself is (damning), although it's often good to know how a drug works, because you can predict certain side effects and certain effects and certain bio markets to look for, et cetera. And you know, we just don't have that right now, at least with demabond.

Now let's consider a little bit about the Phase Three trial design. I think they did a couple of really good things here. They have for their pivotal trial, they have multiple endpoints that they can follow. So they don't only have the kind of usual thing ADAS-Cog, they also have an NTB, which is another battery of neuropsychological tests.

And the way I look at this is, it's kind of like that hockey game that you may have seen on television yesterday, the Canadians and the U.S. And so, the more shots on goal, usually, the better you do. And by having more than more than one readout in a trial that's pre-ordained, that is if you do a (post-talk), the FDA is not going to talk to you about approval. But if you – when you design your trials, say I'm going to look at this, this and this, I think from the Phase Two trials, these are the important things and the FDA buys into that, that can be powerful because it can give you multiple ways, essentially to get approved.

But just like that hockey game last night, it's not always shots on goal that win. The Canadians had more shots on goal than the Americans, but they lost the game. So you need one of these shots to work. That's the problem. And so they do have multiple shots. As I said, there's ADAS-Cog, there's NTB. They've also done some pre-ordained post-talk analysis. They're going to look at (inaudible) or positive and negative. So that gives them several subgroups they can look at. And if one is positive, they can try to get it approved for that subgroup, as opposed to the whole space of Alzheimer's disease. And again, this is a good idea, but it doesn't necessarily predict success. It just gives you a greater chance at success.

I think one of the problems with the trial is you can see in the Phase Two data, for the Phase Two data – were analyzed by extremely good people here in the U.S., of (Rachel Duty) and her colleagues. You know, I have utmost confidence in them. I think one of the – someone's honking – one of the problems with the Phase Two trial is that we've done it in Russia and we

don't really understand and have control of how trials are done in Russia. That doesn't necessarily mean that they're bad, it's just that we lack certain information. I know when I've done my Phase Two and Three trials here in the U.S., there's a lot of oversight, there's random scheduled – or unscheduled that is – random visits of regulators that show up at trial sites and pore over the data. And I just don't know if that happens in Russia. I do know there were visits in Russia, but they were preordained visits. They were visits that were scheduled. And so I don't feel in our Russian trial we have the control of the data that we might have in trials that are done in other places. That's not to condemn the trial; it's just a matter of confidence in (inaudible).

And I think one of the problems in looking at the data when we went over in the Alzheimer's trial. So – many of you know this, but there's a very large Alzheimer's trial center here at UCSD. It was run by the late Leon Thal. And it – there's many trials that are national trials that are funded by the NIH. And we also review results of other trials.

And so when our statisticians looked at the Phase Two data from Dimebon, it looked very good, but there was one problem that we were frankly worried about. And sometimes by chance alone, data can look a certain way, but you know, we've done hundreds of trials. And one thing we were worried about was the MMSC data. The MMSE is the Mini-Mental Status Examination. It's really – it sometimes uses and endpoint. But more commonly, it is used to enter a trial. It's a very quick – you can probably do it in two minutes – it's a 30-point scale, and we just get a rough idea of the level of cognitive decline that a patient has, and we call them mild, moderate or severe. And that helps us stratify and enter into a trial. It's very rare that we ever see a drug affecting the MMSE for two reasons. One is it's a very rough indicator and, number two, it can be quite variable in a given patient from day to day. Now that said, if you look across the MMSE, generally patients with Alzheimer's disease decline three points per year.

So if you looked at thousands of patients, the average would be that they'd lose three points of this 30 points per year that they have the disease. But as I

– again, in any given patient, it really jumps all over the place. And so we were surprised that in a relatively short, you know, six-month trial and a relatively small trial that they saw a statistically improved – a statistical improvement on the MMSE.

Now that could happen, but the problem with those data were that the error bar on the MMSE was tighter than what we had ever seen in the (U.S.) population. So our statisticians were a little worried that somehow those data – you know, something happened with those. That doesn't mean the other data with ADAS-Cog and daily living indicators are wrong, but we were just a little worried about the Phase Two trials. And you know, once your confidence is shaken, then you really need the Phase Three trials.

So what does that mean about how we look at the Phase Three trials? I'm 50/50 on this. And so it really depends if you're a betting person whether it's going to work. I wish I could be more positive. I know out on the street, I've seen data that several people on Wall Street have said 60/40 in favor of the chances. But I'm a really 50/50 person on this one because of some of the insight, as I said, in the Phase Two trial. Although I think very, very good people are running the Phase Three trial and we will get a right answer.

Dr. Leon Henderson: Yes.

Dr. Stuart Lipton: I don't know it'll be the answer we want. I'm hoping it is, because we need better drugs, but I'm 50/50 with how the trial is going to turn out.

Dr. Leon Henderson: Yes. I understand. And thank you for that cogent discussion. We actually in our model do see limited – I guess, predicted value from the Phase Two trial, and that sort of holds us down to – our model indicates a 41 percent chance. So with 50/50, that sounds about up there with ours. But do you see – let's say it does get approved and we're fortunate that it's – it has an effect either at the level of ADAS-Cog or at the level of NTB or at the level of both even, and it gets on the market, how do you view the dosing strategy and how do you view the physician acceptance rate?

Dr. Stuart Lipton: Yes. Well, it takes a while to work, as you know, at least by the Phase Two data. And the other issue is, if it does work, will it be better than existing drugs out there? And you know that – so now it's a double hurdle. It has to work, and to really gain the market, it has to be better than what's out there, and we'll see. You know, this is mild to moderate. And you know, the moderate to severe field right now is a combination of Aricept or an Aricept-like drug, plus Namenda. The mild to moderate, there's Aricept-like drugs, and I think there's room in that field, but it would have to be, I think, clearly better than Aricept, which has deeply penetrated the market to win. So it could win, but as I said, I wish the data in the Phase Two were a little more convincing. Or you know, it's not so much convincing as being not having that – the data looked a little too good, because that kind of put the fear of God in us, I think.

Dr. Leon Henderson: I understand. What about other developmental drugs? Baxter has got Gammaguard being developed for Alzheimer's disease. It's the only one that we actually have over a 50/50 shot, mostly due to its well-known profile out there already. And...

Dr. Stuart Lipton: Right. Well, that's actually – Leon, that's a really important point then – one that I – as I said, I think got me some (inaudible) with memantine is that here's a drug – like Dimebon, too, by the way – that's been in people, that is relatively well tolerated. Because amazingly in a brain trial, that's 99 percent – that's 99 percent. If you can show that something is tolerate, you know, you've already done much better than most people do. So I would give it a chance. Again, I don't know how it works, and I'm not alone. I mean, I think Relkin started this. He's done a great job, did the Phase Three trial, be complete in 2011, I believe, 360 patients for mild-to-moderate disease. I think they've got a good population. But how does it work? Is it like (inaudible)? Is it that there's antibodies against a beta and it's just that you're using gamma globulin, so you've got a lot of antibodies or – and then on the other hand, are antibodies – and we'll get into this with the Wyeth/Elan trial in bapineuzumab – do you really want to decrease A-beta? And let's talk about that for second,

OK. I don't know how Gammaguard works, so I can't say this, but I can say about bapineuzumab, here's a potential problem. What we now think in the Alzheimer's field is that A-beta is – you know, A-beta is a sticky protein. It's probably bad in certain forms, but may not be so bad in others. So what the preclinical data are now telling us is that little soluble oligomers, little tiny clumps of A-beta are probably bad, and that's because they interfere with normal processes in the cell.

But we now think that big amyloid plaques, these big aggregates that you can see under the microscope that Alzheimer's and (inaudible), you know, a hundred years ago, probably an effort of the cell to wall off the bad protein. And unless that plaque happens to be in a bad place, which can definitely happen, and Brad Hyman at Mass General has shown this most (eloquently), if the plaque is sitting on a synapse that's bad. But if a plaque is walled off and pushed out of the way, that might not necessarily be bad. It's the soluble oligomers that are bad.

So the issue becomes if you have an antibody that's stopping up a beta, where is it stopping the A-beta from? Is it going to get rid of those oligomers or is it going to create a (sink) of A-beta being leached out of plaque which are initially bad, because they become oligomers, the (four-day binder antibody)? And so nobody knows this. And so the basic science behind this is still a little bit fuzzy. OK, I mean, everybody says let's get rid of A-beta, but I think it could be the pool of A-beta and we don't know which pool of A-beta are affected by the various antibodies.

And the other is I think they're less – I think it's fair to say some disappointment in the field with the vasogenic edema that has come out of the early data. And that was largely pushed aside by the company. But – and they put a positive spin on it. But every A-beta antibody that we've seen has caused some bad side effect. And unlike Dimebon and Gammaguard and memantine, these are drugs that haven't been in people for other indications that have worked. So I think whenever we get into a new drug, no matter how

exciting it might be, there's a fantastically high probability it's going to fail because of some side effects.

Dr. Leon Henderson: Sure.

Dr. Stuart Lipton: And I think the probability goes up to 70 percent that you're going to have a problem. And they already know there's some problem with vasogenic edema. So you know I want this to work. I think, you know, people have heralded it as a disease-modifying treatment. The problem is we don't want to make things worse by some side effect. And I so I'm really worried about that.

Dr. Leon Henderson: So getting back to that disease modifying angle, you know, we've said that certainly Dimebon has been on our market or a couple of markets. Gammaguard's been out there. Do these have any hope of the disease modification? We see this purported in some of the non – so-called, non A-beta targeting (inaudible). But what is your opinion regarding that?

Dr. Stuart Lipton: Yes. I – you know, this is an interesting question. But without knowing how the disease – how the drug works, it's pretty hard to predict how effective it's going to be, right, Leon?

Dr. Leon Henderson: Sure is.

Dr. Stuart Lipton: It's kind of like you're shooting in the dark. And when you shoot in the dark, sometimes you hit the target, but you know it depends on where the target is. If there's a lot of targets and there might be, A-beta is not the only thing going on in this disease. There's A-beta, there's (inaudible) correlation with (inaudible) and others have shown there's downstream of that. There may be multiple targets you can hit and be disease –modifying.

So there's a paper from Frank LaFeral in a mouse model. Here's an example that shows that memantine in the mouse model is disease modifying. It actually prevents the downstream effects of A-beta. It's just that it may be hard to show that in a human population, it just depends how robustly effectively. Whether you can actually change the slope of the deterioration in a patient. That's what you're talking about, basically is the readout when you're looking for disease modification. So the drug has to not only be disease modifying, it has to work really, really well. And when you've done clinical trials, as I've participated in, it's hard to get a clear readout in a clinical trial. So many things happen in clinical trials – the way you enter the data, patients drop out, patients die, you have to (inaudible) the data at the end. There's – it's not like going into the lab and doing an experiment in a test tube or a Petri dish. It's very difficult to get a robust effect, even in good drugs

Dr. Leon Henderson: You know a certainly complex system. It is extremely complex. And there's a lot else going on. Patients are depressed, you know, they have other diseases. We try to control for that. Hopefully, we do a large enough trial that that kind of evens out. But there's a lot going on in the clinical trial.

Dr. Leon Henderson: Absolutely. Let me – let's speculate a little bit about Gammaguard a little bit more. You know, might it be something other than the anti A-betas in this poly (inaudible) mixture? What are the odds of that and how do we go about – how does Baxter go about learning whether there's other (inaudible) in there that can be targeted – it may extract it and, (thence), target it?

Dr. Stuart Lipton: Yes. Well, that's a great question and I'm not sure how we're going to get at that. You know, we all use IVIG for a lot of neurological indications now. Most of them are thought to be neuroinflammatory or antibody related. But neuroinflammation it's very important in the nervous system and it's very clear or becoming increasingly clear, I should say, that A-beta activating macrophages and microglia, there's a whole neuroinflammatory pathway. And it's possible that Gammaguard in some way is (quieting) those pathways. But we're really at the very early stages of studying those pathways.

Dr. Leon Henderson: Microglia pathways, A-beta pathways, tau pathways, there are other pathways that we're looking at now to sort of help us maybe understand a little bit more than folks have when they started these trials about what we should be targeting or co-targeting perhaps with future molecules and are there any future molecules you see that we should really take a look for, more so than others, in this respect?

Dr. Stuart Lipton: Yes. Well, I have a list on my desk here of a lot of programs. You know, (inaudible) I don't have a crystal ball to tell you – I guess I have 19 programs ranging from (inaudible) inhibitors, tau, (inaudible) antagonists, gamma (inaudible) (ENH3). We can go over anti polymerization, (leutanmil cyclois inhibitors), right. I mean, it goes on and on and one.

So the issue is what ones are going to work and I think we do want to have, as I said earlier, multiple shots on goal. The ultimate answer may be a cocktail. Although we are forced by FDA regulations to prove one drug at a time. I think one of the big issues here is there's something in common with all of these.

And in the last few months – and actually, I recently published a paper in science that says mitochondrial damage, like in Parkinson's disease, seems to be very important in Alzheimer's disease, seems to be the mechanism whereby synaptic damage occurs. And synaptic damage is the first thing – in fact, it's the only pathological feature of the disease that correlates with cognitive decline, as initially shown by the neuropathology (inaudible), but confirmed by many, many neuropathologists now.

So when brains come to post-mortem and you look at them, the only thing that's predictive of how bad the disease was when they get neuropsychological and cognitive testing is the synaptic dam. So protecting the synapse will be very important.

Now it's been claimed that if you – that A-beta causes synaptic damage and we had recent papers to show that A-beta does this by causing massive fragmentation of mitochondria. And if you look at a synapse, it's chock-a-block full of mitochondria. Synaptic transmission is a very high energy requiring process. So if you hurt your mitochondria, the synapse is the first to go. So I think we're going to see more and more targeting that can protect the synapse. It turns out that's probably how memantine works. It probably protects the synapse by mechanisms that are still evolving. So even though we know precisely I think how that drug works by some of our work in our colleagues by blocking (inaudible) that actually protects the energy requirements at the synapse. So it may be possible to go with some of these downstream events, even if they're not A-beta and tau focused, as long as we can protect synapsis.

Now Dimebon, if it really does protect mitochondria – getting back to that – might be beneficial. It's just in that case, we don't know if it's really working in mitochondria or some upstream effect that somewhere downstream it's protecting mitochondria. Maybe that's not critical. But I think the closer we can get to actually protecting those mitochondria, the better we're going to be offsetting probably not just Alzheimer's, but many diseases of aging and maybe even aging itself. So I think a lot of us in the field are looking for those kinds of drugs now.

Dr. Leon Henderson: Good let's get back to the bapineuzumab for a moment. You know, in the Phase Two trials, we saw the retrospective analysis revealing some punitive benefit for recipients who didn't carry a belief for the susceptibility (inaudible) there. And we saw, you know, a question of whether you know that sub-population will hold up in terms of adversity and that. What are your feelings going forward? We've sort of whittled down the eligible population already. How likely do you think this monosomal antibody is to protect in (inaudible) negative?

Dr. Stuart Lipton: Yes. I'm a little bit of a devil's advocate on this one, so hear me out. Whenever – it gets to what I was saying before, there have been many, many

trials, not just in bapineuzumab, but many trials do Phase I dose escalation, pick the best tolerated dose, you know, not necessarily the dose that worked in their animal model, so they may have the wrong dose. Then they do Phase Two. It doesn't quite work, so they do a subgroup analysis, come up with a subgroup that works, then they spend a lot of money in Phase Three. And the problem with that kind of trial is if you do enough subgroup analysis, you do 20, by chance alone, one subgroup analysis will be positive, by chance alone, because one in twenty is chance alone. So there's a big fallacy with doing such trials.

The way trials probably should be done, and some fields do this, unfortunately, in the neurological space, we haven't done this, is to do what we call Bayesian trials. The Bayesian trial in Phase Two is – it's kind of like – I'm giving a lot of sports analogies today, but this is a good one – it's kind of like the NCAA basketball tournament, right, so one plays 64, two plays 63, roughly. And so we try to do head-on-head and come up with the best game for the national championship. So in Bayesian trials, what you do is you take various doses of your drug and try to figure out the best dose to do a focused Phase Three trial that's very likely to work because you've (vetted) all of these other concentrations in phase two. The problem is we never do that. That would mean Phase Two would cost more than Phase Three. And so, we don't do it. And as a result, we really rely on this subgroup analysis which is post-talk in Phase Two, and then we get to Phase Three and we fail. And I – you know, again, past performance doesn't predict future – it sounds like a stock market analyst here – but this happens over and over in these trial unfortunately. And so the subgroup analysis often isn't helpful, although we use it.

Dr. Leon Henderson: Yes. And certainly we do in our model look at designed features where, although not necessarily predictive, is a lack of prediction is there and doesn't really accord, you know, extra confidence in these trials moving forward. So I take it that you feel the benefit/risk ratio, even in (inaudible) negative may not be all that it's cracked up to be.

Dr. Stuart Lipton: Well, I would have been happier if it were (inaudible) positive and you had a bigger chance for the disease. But you know, I – that's just – you know, so now you're taking people with less risk and saying they have more benefit. So I'm – you know, that's not what I would have predicted, although that's what they found in the subgroup analysis. So I – you know, I don't know.

Dr. Leon Henderson: Do you think there's any – well, what do you think of – are the benefits perhaps of active immunization? Because I know that they have products downstream that look at actively immunizing folks with A-beta.

Dr. Stuart Lipton: Well, as long as we can avoid encephalitis and vasogenic edema, then antibodies will have a chance. But so far, we seem to be introducing more problems, rather than less problems, and I just don't think we've gotten over that hurdle with the antibody therapies yet. Certainly, you know, for (inaudible) and other places non-nervous system, there's been a great success in antibodies. But the brain is a very tough space.

You know, there's also antibodies that work outside the brain. But that gets back to the (sink), right, the (sink) of A-beta. And if you're pulling A-beta out of the brain, you have to worry that you're pulling it out of plaques (inaudible) which can make things worse, got it? And so you could argue let's go the peripheral route and avoid direct effective antibody in the brain, but that may not be the way to go either because of the kinetics of the different pools of A-beta.

Dr. Leon Henderson: Got it. So anything on – let's see, gamma, secretase or other secretases that may make it more promising or are we just in a sort of wait-and-see mode for everything really downstream?

Dr. Stuart Lipton: Well, again, these all come up with that they're new kinds of drugs, and I'm not so worried that they don't work. I think they might work. I'm really worried about clinical tolerability in all of these drugs. I mean, we can run the list ranging from alpha secretase inhibitors. I mean, there's a lot of drugs

here. But anytime – I mean, there's 5-HT(6) as receptor antagonist. There's (inaudible). All of these being new entities and the brain being such a difficult area, it's very difficult to predict success. I know investors don't like this. But I think if you – you just have to really take these with a grain of salt. A lot of them have excellent science, but we're not talking science, we're talking clinical tolerability. This is very, very difficult in the brain unfortunately.

Dr. Leon Henderson: Yes. And to wit, we do have, you know, very low (inaudible) indices on the majority of investigative drugs here in the Alzheimer space, probably one of the highest outside of Gammaguard is really Dimebon which is at (41c) and (Lilly) as a (35D) right now. And downstream from there, all of the secretase inhibitors and down the line have less than 35 percent.

Dr. Stuart Lipton: The one lesson I take out of this is when they show you how the trial design, ask in Phase One, did you reach the concentration that worked in your preclinical models? And was that dose clinically tolerated in human beings? OK? And that question is almost never asked by investors. I think if we started to do that and hold the big pharma feet to the fire and little pharma feet to the fire on that one, that a lot more drugs would be killed.

And as you know, if you're in a little pharmaceutical company, if you don't kill a drug, I'm not so worried about the ones that go to Phase (Three). I'm worried about the drugs that aren't killed that should have been because often, it's a one-shot deal and you fail, you're out of business. And so I think we really have to look at these Phase One trials and say, did we get at a clinically tolerated dose, a concentration that worked in our preclinical models? And as I said, we almost never asked that.

Dr. Leon Henderson: And that's certainly limiting to the predictive value going forward, indeed. I want to make sure that everyone has – since we're really coming upon the Dimebon Phase Three trial or result, at least, the top-line variety, I want to make sure everyone had their questions answered regarding that compound

and any others, actually, at this point. So Tameka, can you poll for questions for Dr. Lipton, at this point?

Operator: Certainly.

Dr. Stuart Lipton: I just want to make sure that everybody gets their questions in, if they want to ask questions. It's sort of a tenuous time, you know, certainly where we're hoping that we have some more in the arsenal against Alzheimer's disease. But we have such limited predictive value, that you know we have a lot of (toss-ups) here.

Operator: Certainly. At this time, I would like to remind everyone, in order to ask a question, press star, then the number one on your telephone keypad. We'll pause for just a moment to compile the Q&A roster.

Dr. Leon Henderson: So Dr. Lipton, while they're compiling the Q&A roster, one of the questions that always comes up before every (ICAD) meeting is, you know, are we able to – are these drugs really not working or are we unable to detect that they are working? What are your thoughts regarding that, in general, and in specific instances?

Dr. Stuart Lipton: An aside view of that, Leon, is what we say is statistically working, is that really relevant to the everyday life of the patient?

Dr. Leon Henderson: (Inaudible).

Dr. Stuart Lipton: You know, I think that is the hardest one. I mean, maybe that is – you know, that's the – as a clinical neurologist, that's the one that's most relevant for me. To the FDA panel, that's – you know, often statistical significance is good enough. So you might still get on the market, but whether we really have

something that's going to change the disease that's always the bugaboo. So activities of daily living is a great way to look at that, but it's very hard to make those moves.

And you know, one thing, when they analyze the Namenda trial, the – and I had nothing to do with the analysis, by the way, I was just an independent visitor at this meeting telling people how the drug worked, they said that a fair number of people that weren't recognizing their loved one or their spouse or their caregiver began to recognize them again. And actually, that's the kind of thing, although it doesn't cure the disease really helps, because it decreases the level of care needed in a patient and then also if you're the caregiver, that's (inaudible).

So if we can get drugs that do that kind of analysis, that's going to be pretty good. I think that's where we need to be. You know, to decrease the level of care, otherwise, as you all know, by 2050, we're going to be spending most of our gross national – gross domestic product on care of Alzheimer patients, and we're all getting into that age group. So that's where we need to be. We need to really, really at least start to improve cognition.

Dr. Leon Henderson: Yes, a lot of folks last year at (ICAD) seem to be focusing on, I guess, refining tools such as ADAS-Cog or NTB, you know, sort of trying to get some of the noise out of the system in those and see if we can refine measurement. Do you think that's – continue to be a valuable pursuit?

Dr. Stuart Lipton: Leon, it's just in the Alzheimer field. I think in all – in many, many neurologic disease where we look at neuropsychiatric, neurological intervention. I we want to (inaudible) psychiatric inventories. We want activities of daily living and then we're always trying to refine the batter. No question about it. I think one of the – the big issues in this field, and we probably don't have time on this call to do it justice, is whether we can come up with a biomarker that's predictive. And you know, my colleagues at Washington University, such as David Holtzman, are now saying that if you

look at the A-beta to (inaudible) ratio and the CSF, we may be able to get some biomarker indicator of the disease, PET scanning with agents that look at plaque. The caveat there is that plaque don't correlate with the disease. You know, at least with the disease process it's define by neuropsychological testing. But clearly biomarkers are going to really improve our testing, but we're still in the early days of that. Although there's a lot of good groups working on that.

Dr. Leon Henderson: Indeed. (Tameka), how are we doing?

Operator: Your first question comes from the line of (Dan Winethrob).

(Dan Winethrob): Hi, Dr. Lipton. Thanks very much. I wanted to go back to Dimebon for a minute and ask you about – you talked a lot about the efficacy and whether that's going to be acceptable. What do you think about the safety and Alzheimer's disease, compared to other indications of (inaudible) and the practicality of the drug and how it has to be administered?

Dr. Stuart Lipton: Well, I – you know, I think those are the strengths of Dimebon, that it's been out there as an antihistamine for, you know, I don't even know the number of years. Many years. And that 20 milligrams orally, that's three times a day, I mean, that is a problem because unless you have a caregiver with you, it's tough to take things three times a day. So I think a lot of the other drugs you try to move to once a day for that very reason. So because of the multi-dosing, you really need something that works well, if you're going to compete with the once-a-day dosing of the other drug. That's an excellent question.

As far as tolerability, to my knowledge, it's pretty well tolerated. And I think as I said, that's one of the real benefits of having a drug that's been in patients for another reason. So I think they're on pretty firm ground with tolerability. Efficacy, I think we have to wait and see.

(Dan Winethrob): Thanks very much.

Operator: And there are no further questions at this time.

Dr. Leon Henderson: Thank you, (Tameka).

Dr. Lipton, could you just for a moment, tell us the status of how we're doing with therapeutics directed at tau protein?

Dr. Stuart Lipton: OK. Let me get to my – yes, so you know there are drugs that stabilize tau that are used for other indications. (Inaudible) are very, very toxic. But the University of Pennsylvania group, you know, a fantastic group there with John Trojanowski and Virginia Lee, were really the first to show and really deserve the credit for setting the (inaudible) temporal dementia, but important in Alzheimer's disease. But to my knowledge, a lot of those drugs, which are microtubule stabilizing agents and that we often use them as anti-cancer drug. And so I think we have a tough war to hoe to come up with a new set of drugs that are going to be well-tolerated. Yes. So it's a difficult target, although I think everyone agrees that it's a worthy target.

So in (inaudible) you know, here – another one – you know, so let's look at this. What do we know, known pathways, that affect tau? Well, it turns out that that (inaudible) tau is affected by the GS Phase Three beta pathway and many companies have been looking at that, Astra Zeneca and others. Lithium (inaudible) pathway. The problem is lithium has a lot of side effects. I mean, lithium obviously is used for bipolar disease, but none of my patients like it. And so I think when you're talking about dementia, we need to come up with other drugs. But there are a series of peptides that affect the (GS3– AKT GSK3) beta pathway that are approved for other indications and haven't been well-tested in Alzheimer's disease. But I think some of those – some of them (inaudible) personally working on, they may have a chance in this sphere, because they're useful in other disease. Again, taking that path gets rid of this

whole issue of side effects. And so you know I think those may have a shot. Whenever you start with a new drug entity, you're 15 years out. So if we're going to start with new drugs, I think that program is going to be a long time in coming.

Dr. Leon Henderson: Yes. I think Allon therapeutics is working on tau mediation as well as the – some folks at Tel Aviv University as well. What about ampa?

Dr. Stuart Lipton: Ampa receptor antagonists?

Dr. Leon Henderson: Yes.

Dr. Stuart Lipton: Or ampa?

Dr. Leon Henderson: Antagonists.

Dr. Stuart Lipton: Yes, there's two ways to go. Ampa, from the work of (Leonard Mukhe) has shown that ampa receptor is another type of glutamate receptors in addition to NMDA receptors may have a role in inuring synapses in a (amiloid) beta possibly talemdia system.

Again when you look at that there's another school of thought that thinks you mildly increase (tallc) for cognitive enhancement. I'm sorry; moderately increase the (Amperis) receptor activity for cognitive enhancement. But your poised at disaster because it's very clear that glutamate receptors in general are very important in synaptic communication, that's how (excitatory synapses) communicate with one another but their poised on destroying the (synaptic if they) are over activated.

So these are very tough targets unless you can figure out a way of a drug interacting with the target only blocking excessive activity. It turns out that's how (melatine) works in the NMDA receptors. I know people are trying to

come up with AMPA receptor antagonists that do that, but there aren't any to my knowledge that do that yet.

So that's a (case where) that we know the kind of drug we need to make but we just have to come up with the right drug; avoiding normal activity only abating pathologically increased activity. So there's a chance there but we're still in the early days, I mean we've developed a novel (inaudible) but still in the very early days.

Male: And, you know getting back a little bit to the biomarker and maybe biomarker combined with imaging strategies, you know how do you see these modalities being brought to bear both on drug discovery and clinical activity.

Male: Well so in terms of clinical trials, enough phase two and phase three studies have to use these trials and whether the trials are successful or not show that the biomarker correlates with disease outcome and for the FDA to get comfortable with that. And that's a process sort of field has to move on.

And I still think we're several years away from that, unfortunately. Although there have been several white papers delivered to the FDA, I know one from Harvard Business School that was requested by the FDA which is clearly put them on notice that trial need to move in this direction. But the problem with that is the whole field needs to move in that direction so its kind of a mass action. And I think we're still a bit, a bit away from seeing that. I do think it's really important that these trials try to put in secondary endpoint in as many biomarkers as they can. Not just for the trial at hand but for future trials because that's going to help all trials eventually.

Male: And before I conclude I'd be remiss if I didn't ask you about the (amiloid) hypothesis, I mean, I know once things started to fail with (anti-amiloid) agents, you know people began to say, you know is this a dismantling of the (amiloid) hypothesis and so forth and so on. And from what I understand, you know as you speak about the (algameers) versus other types of (ABATA moditiys) it feels like, and correct me if I'm wrong but it feels like the (amiloid) hypothesis is still alive and kicking but needs refinement in terms of our understanding of the true biology. And I'm wondering if we're seeing

anything in the translational literature that would suggest that, a way to more rationally make developmental drugs, you know that target this.

Male:

Great question, you know I think not only in the Alzheimer's (sphere) but in most nerve degenerative disease what we wrestle with is the following problem. There are some very rare less than one percent cases of genetic mutation that cause the disease and that's true and (amiloid) precursor protein. And so its estimated to be less than one percent of the disease has a genetic defect and may have increased (amiloid) data and we're pretty confident that (amiloid) has something to do with it.

The problem is this other 90 to 99 percent that is our quote unquote sporadic or idiopathic cases. Its funny when I went to medical school people called these idiopathic because we're all idiots, we don't understand the disease. And there's probably some (paraplegia) of genes that make you susceptible on how the environment plays out on that range of genes that you have to create the same (phenotype) as these very rare genetic mutations we're really just starting to see.

Now, having said that I need to give one more disclaimer (Dennis Selco) was in the lab next to me back in Boston when I was in Boston for 25 years as part of my time there (Dennis) was literally next door and in fact I moved into his lab and he moved elsewhere. And is a very good friend, you know that aside I think there is merit to the (amiloid) hypotheses but its probably not the only mechanism that's going on in Alzheimer's disease. That doesn't mean if we interfere, that doesn't mean that it doesn't make sense to interfere with that pathway though. That may give us a lot of traction on the disease, but it's very likely there's a lot of other things that feed into that pathway that we can probably do equally well or better.

The key thing is can we develop a drug that's tolerated by the brain. And this is very very tough. No matter what pathway you propose if you can do some good and get some clinically tolerated drug. Even if we don't know how it works like the (Demabon). You know, I think if you can get a lot of traction with the disease.

Male: How are we doing in terms of, for instance (micro array analysis) to determine which genes maybe at play in this condition or pathway analytic methods.

Male: Yes well now it's getting more complicated, because I don't know if you want to go here but I'm going to tell you the dirty little secret of the human genome. So we know the genome since 2000, right? But it turns out we know four percent of the genome. We know DNA that encodes for genes. It turns out that 96 percent of the genome, what we thought was junk seems to be composed of genes that control those genes. And so now we're talking about micro RNA's and small RNA's.

RNA biology is exploding and we're starting to find that there are errors in Micro RNA's that can cause diseases, which means we don't know squat about the genome. So just looking at an array of that represents the proteins that are encoded probably is not going to give us the overall information of what's encoded and what's causing or contributing to diseases. So it's probably much more complicated than we first thought.

Male: So you're saying that every jumping off point is just a jumping off point?

Male: Yes, now that doesn't mean that personalized medicine may not come to fruition, lets end by saying one thing that we're all very excited about is taking induced (plural potent) stem cells that is, you know skin cells that we convert to a stem cell or maybe even directly convert to a neuron or a (age1) cell and we take those from a disease patient and then we have disease in a dish. Now this is not the same as being in the human brain, but its a much more tractable way to study the same cells that are affected in this disease, so many of us are very excited that the new way to start looking at drugs will be to take a patients skin cell make it into an (induced plural potent) skin cell making it into a neuron in a dish and trying to study what drug helps that person's neuron. I think we're going to start moving to that kind of drug discovery but it's a slow process.

Male: And that's going to be a topic for a lot of future discussion as we've just started looking at stem cells and so we hope to invite you back fro that particular discussion as well.

Male: So I'd be honored.

Male: And (Taneka) if you can pull once more for questions as we close, I'd appreciate it.

Operator: As a reminder, as a reminder if you would like to ask a question or make a comment press star one on your telephone keypad.

Male: The brain is a difficult place.

Operator: And there are no questions, sir.

Male: And I'd like to thank you very much Dr. Lipton. It's been a wonderful discussion today. And we look forward to going over the initial (Dermabond) Phase 3 data with you when they come out as well.

Dr. Stuart Lipton OK. And I'm keeping my fingers crossed.

Male: Absolutely.

Dr. Stuart Lipton OK. Very good. Thank you very much.

Male: Thank you, Dr. Lipton.

Dr. Stuart Lipton Have a good day, everybody.

Male: Enjoy your day.

Operator: This concludes today's conference call. You may now disconnect.

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