Alzheimer's Talks Transcript
MINDSET Trial
with Dr. Lawrence Friedhoff
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Note: This transcript has been edited for content and clarity

Welcome to Alzheimer's Talks, a monthly teleconference series presented by UsAgainstAlzheimer's where we connect you with leaders who are working to stop Alzheimer's.

My name is Stephanie Monroe, and I'm Director of African Americans Against Alzheimer's, a network of UsAgainstAlzheimer's which is an entrepreneurial and innovative organization, transforming the fight against Alzheimer's.

I want to thank you for joining us today to hear about the MINDSET trial. Our guest today is Dr. Lawrence Friedhoff from Axovant Sciences. Dr. Friedhoff has worked in pharmaceutical research and development for more than thirty years. He has led teams that developed and obtained approval for six new drugs, including donepezil (commonly known as Aricept) and he is also the author of the book *New Drugs: An Insider's Guide to the FDA Approval Process for Scientists, Investors, and Patients*. Dr. Friedhoff also unfortunately knows all too well the devastation of Alzheimer's disease, as he has been an Alzheimer's caregiver for his mother.

Today Dr. Friedhoff will talk about the clinical trial called MINDSET, which is currently enrolling participants.

We have at least 200 people registered from 37 states and the District of Columbia and another 630 people who couldn't join us today, but have asked for the recap materials. We will send everyone who registered a copy of the recording and a transcript about a week after the call.

If you have a question during the call, please press *3 on your phone. By pressing *3 you will be placed into the question queue. Please have your question ready to share briefly with a member of our staff or, if you are listening to us online you can type your

question in the box, and we will get to as many questions as possible after the opening presentation.

Thank you very much for your attention and now, it's my honor to present Dr. Lawrence Friedhoff. Dr. Friedhoff….

Dr. Friedhoff: Good afternoon to those of you for whom it's afternoon which it is here in New York City. Before I tell you about the MINDSET trial, I want to tell you a little bit about me. You heard a little bit in the introduction, that I've been in drug development for many years now and have a mother who developed Alzheimer's disease and subsequently died of it. I first became interested in dementia drugs when I was a young man in medical school and I was a house officer. I was an internist and as a result, many of my patients were elderly and suffered from dementia and related diseases so I soon learned that there was a big need for treatments for dementia.

Early in my career, I was asked to start a drug development organization by a company that had never gotten drugs developed on its own before, and step one of that process was to look around in their portfolio of molecules to find something that I thought might be able to help patients. And just by coincidence, I found one potential treatment for Alzheimer's disease that I thought was quite interesting and that had been terminated very early in development. The reason it wasn't developed further was because there was a lot of pessimism about this drug, because it wasn't secure, and also because there wasn't the big market for Alzheimer's disease drugs in those days, primarily because there were no treatments for Alzheimer's disease, and so people were quite pessimistic that one treatment could be developed.

But I got a small budget and I hired a small team of very talented people and five years and two months later we actually submitted our application to the FDA, which approved Aricept seven months later. So that was really a turning point in the treatment of Alzheimer's disease because before that, there was really no treatment that could be used by most patients anyway that was effective in improving the function and cognition in Alzheimer's disease.

Following that approval, in the commercial success of Aricept, there was much more recognition of Alzheimer's as a disease that could be treated. As a result, there was greatly increased investment in finding a cure for Alzheimer's disease. This led to a very large overreaction and a series of very large expensive clinical trials and development programs, many of which I think were based on very minimal justification in terms of

early scientific studies, and as a result there were lots of expensive failures particularly looking for cures for the disease, which is a very lofty goal, very difficult to achieve.

Now I think research has turned back towards what we call neurotransmitter targets, targeted drugs like Aricept. So Aricept is a neurotransmitter targeted drug. What does that mean?

Neurotransmitter targeted drugs are based on the fact that patients with Alzheimer's disease have lower levels of certain critical neurotransmitters in their brain, like a neurotransmitter called acetylcholine. Aricept works by blocking the destruction of acetylcholine and thereby raises brain levels of the neurotransmitter. RVT-101, a drug that our company is developing, increases the release of acetylcholine. So if you think of the brain as kind of like a bathtub, and it contains a certain amount of acetylcholine, Aricept works by slowing the drainage of acetylcholine out of the brain, and RVT-101 works by increasing the amount coming into the bathtub from the spigot, and so together they work better than either one alone; at least, that's what the evidence suggests quite strongly so far.

So let me tell you a little bit about RVT-101, because I believe it has the greatest potential to obtain FDA approval over the near term. There are a couple of reasons for that. First, as I mentioned, it acts to amplify the benefits of Aricept and likely other similar drugs that are already known to be useful to the treatment of Alzheimer's Disease. So because it's acting in the same kind of mechanism, it's much more likely that it will provide the same kind of benefits as the already-approved drugs like Aricept. There are also results from a very large, very well designed clinical trial showing strong evidence of benefit on the endpoints the FDA considers important in the treatment of Alzheimer's disease. That's very critical and very different from other products that are in development, in my opinion.

RVT-101 has been very well tolerated in clinical trials so far; there are over 2,000 patients who have been studied in clinical trials of this drug. It's a once-a-day pill so it's very easy and convenient to take. Now, as I mentioned, these are pretty encouraging early results and I think that's the main motivation for participating in the clinical trial. In particular, when I say that the results are promising, let me make that concrete. The FDA and other international regulators have told us that a single additional clinical trial may be sufficient to obtain FDA approval and approval by other regulators around the

world. This is less than the two clinical trials that are usually required and we believe that the difference is based on the very strong encouraging results from the prior study.

So that one clinical trial—that we are hopeful will provide the evidence to get this RVT-101 approved—that clinical trial is currently underway, and it's called the MINDSET study. Participation in this particular study is easier than in many other Alzheimer's disease trials for a couple of reasons. First of all, it's a pill, it's oral, it's given once a day, as opposed to intravenous infusions that are required for some other studies.

There are minimal to no scans and MRIs required; in some studies there are a lot of them that are required. And in many cases, transportation to and from the study site is provided free of charge. And finally, RVT-101 appears to be very well tolerated, thus far.

So this is a six-month trial; it's six months of double blind placebo controlled treatment, followed by one year, when patients who complete the double blind trial are given active RVT-101. The RVT-101 placebo in the double blind trial and RVT-101 alone in the extension trial are given on top of donepezil in the double blind or many other drugs can be put on top of it in the open label extension trial. So that means that everybody who went to the placebo controlled trial is guaranteed active treatment, after the double blind treatment is over. I think that's another advantage of this study.

Now, why would people want to participate in clinical trials, MINDSET or others? MINDSET is not the clinical trial for everyone, and you should consult your own health care advisors and the investigators of this trial to see if it's right for you or your loved one. But here are some reasons to consider participating in any clinical trial. Number one is early access to potential new medicines. Of course, the evidence supporting their efficacy and safety is less than for approved medicines but you get access to them far earlier than you would if you waited for them to be approved, which takes a number of years, sometimes many years. You also receive free care by expert Alzheimer's doctors, and are part of the process of providing new medications to other patients and to future patients when they come along, long after all of the people on this call are no longer worried about Alzheimer's disease.

So, that's a description in very general terms of the clinical trials, my background, and the MINDSET study. I'd be happy to answer questions about it that people have.

Stephanie Monroe: Thank you very much, Dr. Friedhoff.

Before we get into some specifics about this very exciting MINDSET trial, I want to ask you a little bit more about your background and your engagement around clinical research. Aricept came on the market almost twenty years ago. Can you explain to us how the treatment landscape has changed since then? I've often heard in the community that almost everything that we know now about Alzheimer's we've learned about through clinical trials that have happened in the last seventeen years. What do we know now that we didn't know then?

Dr. Friedhoff: Well, it's very interesting because if you read in the press about Alzheimer's disease, everybody recognizes it's a disease, a public health issue, and it's a major cause of death. But back when we were getting started with the Aricept program, people very rarely used the term Alzheimer's disease. It was called senile dementia and it was considered just what happened when people got old, and that there really wasn't much to be done about it. That was one of the reasons why the cholinesterase inhibitors, of which donepezil is an example, they've been around since the 1930s and it took a very long time for people to come along and recognize that this is actually the reason there's a possibility that you could develop a drug that can treat this disease.

One of the things that the commercial success of Aricept has resulted in, is a big, big increase in awareness. Once there's a treatment available, then it's worth it to make the diagnosis and so now we know that there are a lot more people with this diagnosis than we knew about back then. And there's a lot more interest and a lot more optimism about creating drugs. So there's been an enormous amount of research. Unfortunately, clinical research has not been terribly productive. It did produce RVT-101 so there have been some successes, and there are other drugs that are similar, that have shown similar results, although we don't think they're as well tolerated.

There's a lot of understanding of the path of physiology associated with Alzheimer's disease, so we know a lot about the changes that occur in the brain. The problem, in my opinion, is that we really don't understand the cause of this illness. And because we don't understand the cause, there aren't good models in test tubes or in animals. So clinical trials are really the way that we figure out whether drugs can help patients or not. Clinical trials in Alzheimer's disease research are much more important than in other forms of research on other diseases. Unfortunately, ever since the last drug, Namenda, got approved thirteen years ago, mostly what we've learned is what doesn't

work. We d know the 5-HT6 antagonists, they seem to be quite promising, RVT-101 is one of those. So there has been some meaningful progress.

Stephanie Monroe: Fantastic. I think this speaks very clearly to why we really need lots of people involved, of various ages, various races, gender, because we want to make sure that these medications work well for everyone. In fact, we learn about how the disease shows itself and what the characteristics are, in people of different races.

It's been my pleasure as director of the African American Network to be partnering with Axovant this year, in particular in going out into key cities with a strong African American demographic and using the play *Forget Me Not* to be able to present information about Alzheimer's and about its diagnosis, because unfortunately only 40% of people with the disease actually ever get diagnosed and we know that if they're not getting diagnosed, they're certainly not getting treatment and unfortunately they're not engaged in clinical research. We're so thankful to be able to partner with Axovant on this, and in spreading this important message that Alzheimer's is not a natural form of aging as we thought it was twenty years ago.

It seems like our mindset about Alzheimer's has changed. Is that what led Axovant to calling this latest trial MINDSET? Can you share with us where that name came from?

Dr. Friedhoff: You know, that was a group decision by the people in the company. I think your explanation is probably as good as any. We just wanted something that was memorable and that reflected our change in mindset in our determination to get this drug through the clinical trial that we think will lead to its approval. It's not a simple matter. This is a very large trial and it's part of a very large development program involving probably close to 1,000 people one way or another all over the world. And so it takes a certain mindset in this large group of people to bring this thing over the finish line and of course, every day that we can do it quicker is a day that potentially patients can benefit from it, and so we're very cognizant of that, every second that we're working on this.

Stephanie Monroe: Dr. Friedhoff, very exciting that you have already seen 2,000 people studied so far with RVT-101 and that the results are promising and encouraging in terms of its ability to improve cognition and function. During the trial that has gone on up to this point, have you seen differences in how women versus men are responding to the medication?

Dr. Friedhoff: Not really. In biology, no two numbers ever come out exactly the same. We're not machines. So, not really, no. The results seem to be the same. More women are affected by Alzheimer's disease than men, so there are generally more women in the completed clinical trials than there are men, so we actually understand the effects of the drug in women a little bit better than we do in men, because there are slightly more women who are affected by the illness. So this is something of particular relevance to women.

By the way, I would be remiss if I didn't mention how people can find out more about this study, we have a website: www.alzheimersglobalstudy.com. Or, there's a phone number: 1-855-241-6288 for people who really want to find out the information that you need in detail.

Stephanie Monroe: Absolutely and we are pleased to be featuring the MINDSET trial as one of our featured trials on the UsAgainstAlzheimer's website. People participating in this call will also receive information by email about how they can get in touch with you and get more information about this very important trial.

On the phone with us right now is Meryl Comer who is a wonderful author, caregiver, and leader in this Alzheimer's space. Meryl has a question so we'd like to open up the line for Meryl Comer.

Meryl Comer: Thank you. Thank you, doctor, for Aricept. Those of us in the caregiving community who have used it, it has given us relief and helped us care for our loved ones in our home.

Two quick questions about the MINDSET study. Many of us may be interested, but what are the inclusion and exclusion criteria, so that we respond properly? My second question is: If we were able to get people to diagnose earlier, would the efficacy of these modifying therapies like Aricept and this new compound have a longer life in terms of their ability to help people?

Dr. Friedhoff: There are a fair number of inclusion and exclusion criteria and you can see some of them on clinicaltrials.gov or by going to the website or calling. But briefly, patients have to be on stable donepezil therapy; they can't be on Namenda; they have to have mild to moderate Alzheimer's disease; and they have to be in good general health, that is, for a clinical trial, it's important that patients are sufficiently healthy to complete the study and don't have illnesses that would interfere with the evaluation of

efficacy. That allows us to do as small as possible trial in the quickest period of time. Eventually when it's approved, everybody can take it if their doctor thinks they need it.

So your second question was about whether these kinds of drugs would be effective if given earlier in the disease. Now you're asking me to guess. We scientists call that speculating, I guess it's just guessing, and my guess is that, yes, I think that this class of drugs can improve cognition in a much wider group of patients than just Alzheimer's disease, and in a wider band of efficacy. For example, Aricept is also approved for treatment of severe Alzheimer's disease and there are various studies showing improvement in cognition for these neurotransmitter drugs in earlier and less demented and even non-demented patients. So my guess is, and it's just a guess, is that, yes, if you could figure out the way of measuring that fit in patients who are less affected, you see it from this class of neurotransmitter drugs and I think because of that, it would probably delay the time to actual diagnosis of dementia, if given early. But it would take two clinical trials, approved by FDA, to allow me to say that that's a fact, rather than a guess.

Stephanie Monroe: Dr. Friedhoff, we have a question from one of our listeners which I think will also be asking you to make a guess or a good scientific analysis, potentially, from Del Muzzillo. He's asking: Do you think there will ever be a single medication or does Alzheimer's require, in your estimation, a multifaceted approach?

Dr. Friedhoff: I think that's really a great question. Ever, that makes guessing a lot easier, right? So, ever? I think the answer that anybody working in this field would have to give you is, yes. I think someday we'll figure out what causes this disease, and someday, maybe before or after we figure out what causes it, we'll find a way to prevent it, at least in most patients. When that will be, I'm not sure. I'm not optimistic that that's going to happen in the next three or four years, but it could. We just don't know.

I think while we're trying to find a single pill or single medicine that can be used to treat this disease, one way of doing that is to develop a pill that contains both donepezil and RVT-101, and we're doing that. So we hope to get that single pill approved; it will contain two different drugs but it will allow patients to take a single pill and get those two different drugs. So in that sense, I'm optimistic that we'll have a single pill that can treat Alzheimer's disease better than donepezil does now.

But I think while we're hoping for big advances, we can't neglect the fact that there are an awful lot of people who have this illness now and these people, I think, would

appreciate treatment while they are still here to benefit from it. And the earlier they get benefit, the longer they get to benefit from it. So I think that in the short term, we're going to treat Alzheimer's disease the same way we treat Type II diabetes or hypertension or HIV infection or other serious illnesses. For hypertension, we often start with one drug and if that doesn't work, we add another on top, and if that doesn't work we add a third one on top. Same thing with diabetes; most people are on multiple therapies. And it's easy to say, well, let's just cure this illness. But remember that these illnesses that I'm talking about, they were acutely fatal diseases years ago. And combination therapy with multiple drugs has turned them, by and large, into chronic illnesses that people live with for decades in relatively good health.

So, I think the prudent approach is to say sure, we're trying to find a cure and a treatment that prevents Alzheimer's disease—even here at our company we have some good ideas about how to do that—but that's going to take a little bit longer and in the meantime, it's my personal opinion that treatment for Alzheimer's, and other forms of dementia for that matter, are going to follow the pattern set for other serious illnesses and how we treat them; that is, we'll have multiple drugs, each will help in one way or another, and some may help a lot and some may help a little, but when you add them all together hopefully, in perhaps the foreseeable future, we'll turn this into an illness that can be halted at a reasonable level of disability so that people have a long period of good quality of life and eventually die from something else as happens often with Type II diabetes or hypertension or hypercholestorelemia or many other illnesses that we manage chronically, especially illnesses of elderly people—of whom I am now one, by the way.

Stephanie Monroe: Dr. Friedhoff, we're getting a lot of people who are interested in some specifics, so let me just quickly run through some questions that people are asking specifically about MINDSET. At the end of the call, we will repeat how you can get more specific information about the MINDSET trial, either by going to www.alzheimersglobalstudy.com or going to the UsAgainstAlzheimers website and looking for MINDSET under our featured trials section.

So one person, Arthur Hartz, is asking: Can a person who is being treated for Stage One malignant melanoma, be included in this trial?

Dr. Friedhoff: I think that that may be possible. As I mentioned, the key criterion for this study is we want people who don't have other health issues that would interfere with the

evaluations of the trial. I would love to enroll everybody but if we do that, the trial could fail and we'd have to do it again, which would mean several years of people waiting. I think the thing to do is to go to the website and find a clinical trial site and let them complete the evaluation. I'm not an expert in malignant melanoma, but my understanding is that this is a pretty curable illness at that stage and if that's true, then it may be possible to be part of this trial.

Stephanie Monroe: I know this information will be on your website, but do you, by off chance, know if the Mayo Clinic is participating? A couple of our callers are interested in that.

Dr. Friedhoff: Unfortunately, they are not participating in the MINDSET trial. We have some studies of dementia with lewy body that they are doing or that we hope they will be doing; we are in talks with them now. But we have a large number of sites and so there's probably a site that's near enough to your caller that they would be able to participate and we can, in many sites, provide free transportation back and forth. People may be able to go to sites that are a little farther away than they would anticipate based on having to take the bus or drive themselves.

Stephanie Monroe: I know that you said that RVT-101 is a once a day pill. Can you tell us how often a person who is in this study would have to go in to the clinic for a visit?

Dr. Friedhoff: I think it's basically once every six weeks for most of the trial, and then longer during the extension trial when everybody is guaranteed to get active drugs. This is relatively easy compared to many other clinical trials, as I mentioned before. We're mostly just interested in how people are doing at home so there are a lot of questions for the caregiver about how patients are functioning in the house and what the burden on the caregiver is, and then there's a little bit of cognitive testing, takes no more than twenty minutes, I think. You have to remember words and things like that. There aren't a lot of scans, there aren't a lot of manipulations of the patient. It's relatively benign compared to other studies that I've heard about.

Stephanie Monroe: Thank you so much. Another quick question from one of our callers, Bill Ihlenfeldt, he's asking whether a person who is taking Namenda and Aricept would be able to stop the Namenda in order to participate?

Dr. Friedhoff: Yes, the short answer to that is yes. There's a time limitation on when the last dose of Namenda was taken, but that can be done. If the patient has mild

Alzheimer's disease, Namenda is not FDA approved for that indication so there's probably, at least in my opinion, not a big reason to take it if you have mild Alzheimer's disease. But this is something that the patient should discuss with their doctor. But it's certainly possible. And then, once the double blind portion of the study is over, if they want, the patient could restart their Namenda so they would only be off it for six months.

Stephanie Monroe: So for a person to qualify for this study, I assume they have to have already had the diagnosis of Alzheimer's. How long do they have to be on Aricept in order to qualify for the study?

Dr. Friedhoff: Four months. Two months on a stable dose. They don't necessarily have to be diagnosed with Alzheimer's disease; we have many patients—we often do screening for Alzheimer's disease, events where people learn about Alzheimer's disease and then, at the end, they can get screened and if they seem to have Alzheimer's disease, they are asked if they want to participate in the trial. So, no, people don't have to have a diagnosis of Alzheimer's disease. But in order to enroll in the study, they have to be on donepezil for four months so if they are not on it, they would have to get that diagnosis and then start on it.

Stephanie Monroe: Thank you so much. I now want to pivot to a couple of general questions that have come in ahead of the call, some general questions about Alzheimer's for our listeners. Nita Jones, from Virginia, asks, she hears a lot about the different phases of Alzheimer's disease. How do you tell which phase a person is in? Whether they are mild to moderate, end stage, early stage?

Dr. Friedhoff: There's a test that we do, called the mental status examination, that can classify people into mild, moderate, and severe Alzheimer's disease. That's what's used in this clinical trial. I think you can get a general sense of what mild, moderate, and severe Alzheimer's Disease are like. Mild Alzheimer's disease sort of overlaps with cognitive impairment that's not Alzheimer's disease, people who are having memory problems that don't seem to be the kind of thing that normal people have but they don't have very difficult problems with thinking and function. Moderate is a more profound deficit, so now patients clearly have an illness and it impacts on their ability to function at home. Severe Alzheimer's disease is what it sounds like; it's a bad, bad situation where people are quite disabled. If people go to the screening, or consult a physician about their particular case, they will learn from a trained professional which, if any, of these stages they have.

Stephanie Monroe: The next two questions are questions that we often get when we are out in the public presenting information, doing community forums about Alzheimer's disease. One question pertains to the genetic link, ancestral link, potentially, with Alzheimer's. Carol Edwards from Nevada is asking: If my brother and mother had Alzheimer's, how likely am I to get it?

And the next question from Marilyn Herbert, from Michigan, is: What part diet plays, and sleep, and what about stress? So genetics, diet, sleep, and stress.

Dr. Friedhoff: Okay. So, genetics. I'm not an expert in this field, my expertise is in drug development. But genetics clearly plays a role in the risk of Alzheimer's disease, so having first degree relatives who developed Alzheimer's disease definitely increases the risk that a person will have it. There are certain relatively common genes that can be easily tested for, so if a person is really interested, there's the gene, APOE, which I think can be tested for relatively easily, that depending on which of the different genes you have, can either be protective or be a risk factor for developing Alzheimer's disease. So if someone's really worried about it and wants to get a definite answer, that's one thing you could look into, genetic testing for APOE. Then there are less common genes that are associated with the development of Alzheimer's disease as well that could be looked at. So that's genetics.

Diet, sleep, and stress. Lifestyle, again, I'm not an expert in this, I believe there is some association between lifestyle characteristics and the risk of developing dementia just like these things are related to the development of a lot of the illnesses of old age. So very sedentary people who are overweight and so on and so forth are at risk for a lot of bad things, and some of these bad things are also associated with dementia and/or Alzheimer's disease. So I think the short answer on lifestyle is yes, try to get a good night's sleep, try to eat a healthy diet, and try to exercise. That's just good advice in general.

Stephanie Monroe: We've often heard that if it's good for your heart, it's good for your brain and the most important thing for folks in terms of diet is make sure you've got lots of color on your plate. That was a great explanation that one of the doctors during one of our community outreach presented to people. Have lots of variants in terms of vegetables and everything else that you would eat. So we've got a question from Will, who's asking, and this is actually a new term I haven't heard of before: can people with atypical Alzheimer's qualify for the study?

Dr. Friedhoff: I think it depends on what exactly atypical Alzheimer's disease means to the person who made that diagnosis. Again, this is the kind of thing that's very hard to answer over the telephone and I would recommend that anybody who's interested in the trial, just give a call. The other thing to remember is that even people who don't qualify for our study may qualify for another study that's being done. So if you call up a site that's near you and you don't qualify for that particular study that you're calling about, you may be able to find another one. At some of these sites we're doing studies of patients with dementia with Lewy bodies, which I suppose somebody might consider atypical Alzheimer's disease.

Stephanie Monroe: Thank you so much for that. Apparently, we've got some very interested scientists on our call. Bob Carrico would like to know if you can explain the mechanism of RVT-101. He says that it seems to be different from both Aricept and Namenda. Can you respond to that?

Dr. Friedhoff: Sure. RVT-101 binds to two receptors. The first one is a 5-HT6 receptor, that's a receptor that is activated by a neurotransmitter called serotonin. Blocking that receptor is what results in increased release of acetylcholine in the brain. As I mentioned before, increasing acetylcholine in the brain is the same thing that Aricept does; it does it by reducing destruction of acetylcholine. RVT-101 does it by increasing release of acetylcholine. Now, one of the things that limits the effectiveness of cholinesterase drugs like Aricept is that they increase acetylcholine levels not just in the brain, but in other parts of the body as well. So, if you give large doses in an attempt to increase the efficacy of these drugs, they produce diarrhea, nausea, vomiting that can be quite significant at very high doses. So the doses are generally held to moderate levels, where the drugs like Aricept are quite well tolerated especially over longer term. The good thing about the 5-HT6 receptor is that it's present really only in the central nervous system so activating or blocking that receptor doesn't cause side effects in the GI tract and the other things that the cholinesterase inhibitors do. So, it's a way of amplifying the effect of the existing drugs but just doing it in the brain, not in the gastrointestinal tract where you get all these side effects that the cholinesterase inhibitors can produce especially at high doses.

RVT-101 also binds with somewhat less power to a receptor called 5-HT2A receptor, which has been implicated in behavioral disturbances, in dementia in particular, and so we think that there may be some benefit on behavior that would be through a mechanism that's different than what the cholinesterase inhibitors do in Alzheimer's

disease. So it may have two mechanisms of action, and we're going to evaluate higher doses to see if that 5-HT2A antagonism is a part of the benefit that we can get by raising the dose.

But it's a 5-HT6 receptor antagonist, we believe that's its main mechanism of action, and blocking that receptor increases release of acetylcholine and some other neurotransmitters as well, and we think that's how the drug works.

Stephanie Monroe: Great. Dr. Friedhoff, this is fantastic. You are answering very difficult questions and we really appreciate that, and making it clearer for all of us.

We have Joel from New Jersey who wants to know whether the information contained in MINDSET has been IRB approved but I think in answering that question if you could just explain to our listeners a little bit about the role of the IRB in the approval process; we know that especially in the African American community and I think in the general public there's a fear sometimes of participating in clinical research, but once people learn about the layers and layers of approval and protections that exist for human subjects, that fear dissipates. Could you describe a little bit about the IRB approval process and whether MINDSET has been approved?

Dr. Friedhoff: Sure. Let me address the more general question first which I think is probably pretty important. When people participate in a clinical trial they're participating in an experiment. And an experiment means that we're not absolutely sure of what the results will be, if we knew for sure what the answer would be, we wouldn't be doing it. So there is some level of risk of taking a new medication that hasn't been on the market for twenty years. So, how do you balance that risk and how do we try to manage that risk? There are, as you mentioned, multiple layers of protection.

The first is within our company, as you might imagine. We're in the business of helping people not hurting people so we're very very cautious about the kinds of experiments that we do, about the kinds of studies that we do. We have a process within the company to be sure that we've evaluated not just the human safety data but the animal safety data, the way that the drug is manufactured, to be sure that what's in that pill is exactly what it's supposed to be, and that we're satisfied that we've done everything possible to reduce the risk to an absolute minimum.

The second layer of protection is the Food and Drug Administration. We are a very, very heavily regulated industry. The FDA is quite serious about making sure that we stick to

the laws and the regulations; they check everything we do and we couldn't initiate this clinical trial without the approval of the FDA and in fact, we have the most strict form of approval from the FDA. It's called the special protocol assessment, and it's the kind of assessment that the FDA does for a trial which is potentially the basis for getting a drug approved, so anybody who's read about the FDA knows these guys are pretty serious. You'll find many pharmaceutical companies that complain that the FDA is too rigorous; our company is not one of those. We think that the FDA people know a lot about drug development, probably more than any company can know and so we very much appreciate their advice and guidance on how to do drug studies.

In addition to us and the FDA, there are organizations called institutional review committees, so each investigational site, each doctor really, who is participating in our trial has to go to an independent body of experts who again review all of the information from the animal safety studies and the animal efficacy studies and the results of the earlier clinical trials, and look through all the materials that are presented to the patients, so in other words, the consent forms, the advertising, all of that has to be reviewed and approved by this independent committee.

All of those organizations are dedicated to protecting the welfare of the patients in our trials. I think if nothing else, people who are considering participating in a clinical trial can rest assured that this is not something that is done in a casual way. As I mentioned, there are multiple levels that check to be sure that what we're doing is ethical and appropriate and absolutely minimizes the risk to patients, which is not to say there's no risk but these entities, including us, are quite serious about being sure that we do good, not bad, things to people.

Stephanie Monroe: Absolutely. The protecting humans part is really important because I really want, in our work that we do at UsAgainstAlzheimer's, to be part of the solution, to be part of finding more effective treatments and hopefully a cure for this disease.

If I could ask you, Dr. Friedhoff, to put on your other hat—your personal story and your mom, so many of us, too many of us, have these stories. My dad is currently actually quite stable taking Aricept but we as a family are working through dealing with that issue. I've got an aunt who has Lewy body dementia so we're going to be very interested in the work, and maybe have you back on the show to talk about that at a later time. But if you could say one thing to family caregivers and those who love people who are living with dementia, what's your advice, what would you say to those folks?

Dr. Friedhoff: So this is just based on my personal experience, which is different for everybody, but the thing that I tried to remember when I was involved in taking care of my mother was that, although parts of her were clearly gone especially at certain times, if I was just patient and sensitive and thoughtful enough, I could see that somewhere inside of her, she was still there. The things that really made her *her* were still there. You didn't see them all the time, you didn't see them in the same way, they weren't manifest in the same way as when she was younger and was less sick, but she was still her and I could see that. That's number one.

Number two, there are things that can be done and we did do them including considering these kinds of experimental treatments. And lastly, just remember that there are people all over the world, in our company, and elsewhere, in academic institutions and other companies, who are working all the time, day and night, helping to find—and finding—new treatments and so you just never know when something new will come along and when there will be even more hope for helping patients with this disease and with other forms of related dementias as well.

Stephanie Monroe: Thank you so much for those words, Dr. Friedhoff, and thank you for so much for your decades of service to our country in terms of looking for treatments for this really important disease.

Again to our callers, if you would like more information on the MINDSET rial you can visit their website at www.alzheimersglobalstudy.com or give them a call at 1-855-241-6288. We will also be including this information in our recap message and on our website. If you have not already joined UsAgainstAlzheimers, please go to www.UsAgainstAlzheimers.org and sign up. We'll send you a recap of this call, invitations to future calls, and important updates and simple ways that you can get involved. I hope that you will join us.

Thank you to everyone on the phone or online for participating in these Alzheimer's Talks. In about a week, we will have a copy of the recording and a transcript on our website for you to share with your friends. And as always, please stay on the line if you would like to leave a message for us or have a question or comment. We're particularly interested in what you would like to discuss on future calls. Thanks again for joining us today and have a good afternoon.