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PRESENTATION

Cory William Kasimov *- JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

All right. Good afternoon, everyone. My name is Cory Kasimov. I'm the senior biotech analyst at JPMorgan. It's my pleasure to introduce the next company. I'm glad Jamie stopped talking to give him his full allotment, but we have Sage Therapeutics and the company's CEO, Jeff Jonas, with us. Please note that following Jeff's presentation, there will be a breakout across the hall in the Georgian room.

With that, I turn it over to Jeff.

Jeffrey M. Jonas *- Sage Therapeutics, Inc. - CEO, President & Director*

Good afternoon, everyone. Thanks for coming. Just before this started, I was given the opportunity to cut off Jamie. I wisely declined. The -- so this is our safe harbor. And again, we're going to be making some forward-looking statements today. Refer to our filings for further details.

I'm going to begin today with a little bit of an overview of what's made Sage -- what's driven the folks at Sage. What we think -- what our vision really is and has been, and why we're doing what we're doing. And I'm going to start -- focus on depression and psychiatric treatments. And what you see here is a slide of the 29 new therapies that have been approved in this country since the early 1950s. I've worked on some of them.

And there are a couple of important takeaways when you look at what's gone on in the CNS space. And the most important, the most important is virtually all of these, in fact, all of the drugs before, what we're calling the second wave in 2019, are based on a single hypothesis, and that's the monoamine hypothesis. Every drug, whether you like them or not, I've worked on some of them. SSRIs, SNRIs, tricyclics, MAOIs have all shared an approach, unified by this monoamine hypothesis, nothing new. Think about other areas of medicine. Cancer, immuno-oncology, where we have so many new targets. The difference is really astounding when you think about what's gone on in depression, a wave of like drugs versus what we've seen elsewhere in medicine. And this is a theme I'm going to return to in a little bit.

This is important for a number of reasons. First, the disease model and the disease treatment model for psychiatry hasn't changed literally since Sigmund Freud. It's a chronic disease model. The drugs we use are very similar. They take 6 to 8 weeks to work. They have a raft of side effects. The majority of people do not sustain improvements on those drugs. Why is this important? Because depression, despite all this innovation, not lack of innovation and investment, depression remains a key public health menace. 50% of people with depression will try to commit suicide. And despite all the work, these 29 approvals, the rates of depression have gone up. I don't have the suicide rates going up. They go up as well.

We haven't made a dent in this disorder. The treatment options have been largely the same, and the treatment model has been largely the same. So that's what really drove us when we started Sage. We thought this is an opportunity for a new company to look at innovative therapies to address important public health issues to develop new molecular entities, not repurposing older drugs with new mechanisms that could potentially change the way people think about brain health. We've had a good track record to date with the first and only -- we've had the first and only product

approved for postpartum depression. We have 5 new chemical entities in -- clinical candidates in the clinic for 8 indications, and we have developed -- our discovery group has developed in-house more than 6,000 proprietary compounds. This has led us to establish Sage as, we believe, a leading multi-franchise company in CNS.

We have products with near-, mid- and long-term opportunities. And I'm going to take you through this as we go -- in the remainder of my talk. But suffice it to say, we've utilized a method of development that we think is unique, where we think that the product candidates that we're putting in depression, neurology and neuropsychiatry all have reasonably de-risked -- proof of principle is already established. Sorry, I didn't mean to do that. I can't go backwards. So imagine that slide.

So you see the 3 franchises, and I'm going to turn now to depression. We've begun this with a somewhat lofty goal. We would like to make psychiatry medicine. Some of you know that I'm a recovering psychiatrist. I've been doing this 30 -- for more than 30 years. I've worked on a lot of the psychotherapeutics that are currently available. One of the enduring facts of psychiatry is the assumption that all psychiatric patients have chronic disease and must remain in the system, in the mental health system. That's the only choice they literally have today. If you're on a tricyclic or an SSRI, you're on it for months to potentially years.

People are often afraid to stop their medicines. The side effect profiles are very similar. The onset of activity is slow. The onset of side effects is rapid. We think it's important to offer a different alternative. Sometimes people say, how are you going to get rid of SSRIs. And our answer is, you don't have to get rid of SSRIs. You simply have to offer a different treatment option. Let patients choose a different option, stay on the drug for months to years or if, for example, if 217 were approved, have a drug that works rapidly. You'd use it as only when you need it, and then you go back to life and work. You're not a chronic depressed patient. You're a person with an illness that you manage by yourself.

We believe that if patients are afforded that option, we can go a long way to reducing the stigma associated with mental health and actually enhance compliance of people who have this type of disorder. We've taken a very important first step in this journey with ZULRESSO. ZULRESSO literally is the first of a new generation of antidepressants. Now this was invented by -- in Sage -- developed by Sage scientists. But I'll tell you, it is not an easy thing. If you think about the assumption that all diseases -- all psychiatric diseases are chronic, you have to step back and think about this from a medical standpoint. All diseases are chronic until we have a good therapy for it. When we have good treatment, the diseases are no longer chronic, and we know the history of medicine is filled with diseases that were once chronic. I mean hepatitis C is a great example that, with good therapies, no longer are considered chronic disorders.

ZULRESSO, we believe, has that type of potential. If you think about what we offer women, it's a 60-hour infusion. We know women's mental health and mental health are often second class diseases, but here's what we're offering, 60 hours in and out, majority of patients responding, going home to their families, their lives and their loved ones. It is, however, a journey. We are trying to change a treatment paradigm. We're telling people, you don't have to be on SSRIs, you can come into the hospital and get treated. So to do this, and we've often said this, this is a journey, not only for the patient but for the company.

This is a product being sold under a REMS, takes 6 to 9 months typically to get a site ready, sometimes more. We've been making good progress doing that. We know we have extensive demand. We've established that. Very importantly for us, this is the first foundation of our journey as we move forward with our next product, which I'll talk about in a minute, which is our oral therapy. But even what we've seen today with ZULRESSO has been encouraging. We have more than 75% of lives covered today. Why is that important? Because that shows that we're beginning to shift the mindset of payers, who we all know are important, to think about treating depression like a medical disorder.

Urgency, getting people better quickly, payers recognize that that has value. And we also have to take care of the patient. We have to shepherd them through this process. So we've established Sage Central, which basically provides customized management service for patients to help them understand the options and opportunities that are in front of them, if they want to seek treatment for postpartum depression. So ZULRESSO, though, most importantly, sets a foundation for this company. It gives us operating leverage and learnings in advance of our next product. And that, of course, is zuranolone or SAGE-217. ZULRESSO has begun by changing the depression landscape. Our goal is very lofty with 217. We would like to change the way people think about treating depression, the way people with depression think about themselves and offer a different opportunity for people with depression.

We've developed a program, the Landscape Program, that's from our marketers, I intend to use numbers, but we call this the Landscape Program, and it really is attempting to change the landscape of the way people think about depression. We believe this is a comprehensive program. It's very different than the other types of programs you often see in the central nervous system space.

Now let's be clear, CNS development is hard. Most of us are used to looking at immuno-oncology, cancer, you have hard endpoints. You can measure things. In depression, you're talking about rating symptoms in patients. And we're also talking about changing a disease treatment model. How do we do that? Well, we've done that by a combination of acute intervention studies, and those are the studies on the left-hand side, 201, 201 and 301 and then maintenance studies and 303, which is the SHORELINE study, which is the largest prospective naturalistic study ever conducted with an antidepressant medication.

Our goal is to not only inform doctors about how the drug works acutely, what the safety profile looks like, but how they might think about using the drug on label if and when the drug is approved. It's a very broad program. It's different than what you've seen for other antidepressants and certainly different than what we see, say, in the orphan space. And that's important to remember because when you're doing drug development for large populations, it's a learning process, and I'll talk about that as we move forward.

So the first 2 studies, the 2 pivotal studies that we conducted were the MDD-201 study in major depressive disorder and the ROBIN studies in postpartum depression. And there are a number of things that you can see from these data. These are both pivotal studies -- have been under the breakthrough program. There are some commonalities that you see. Now remember, this is a mechanism that's a GABA positive allosteric modulator. This is a drug that calms down neural circuits in the brain.

What do you see here? What's exciting to us, as drug developers, one is rapid onset. Separation from placebo within a matter of days. Now we've already seen that with ZULRESSO, literally within the first day, separation from placebo. This is now replicated with zuranolone in these 2 studies. What you also see is a large effect at the primary endpoint at day 15. These are 2-week treatment periods. What's exciting for us also is that you see basically patients who get better tend to stay better over the course of the follow-up period out to 45 days. You can see the adverse events noted on -- below. It's a very well-tolerated molecule. It has a unique -- has a unique profile in terms of tolerability, very distinct from what's currently available in the market today.

The most recent study was the MOUNTAIN study. Some of you may have been aware -- followed the news on this. This is a study that importantly, or not for us, it just missed the primary endpoint at day 15. And as I said earlier, you have to learn from studies. And for us, this is a drug development lesson for us. What did we learn from this study? First, the patient curve looks startingly similar to the other 2 studies, very, very similar. Secondly, early separation and significance from placebo at every time point, but the final one, where we skim, basically, skim significance.

We have an extremely good tolerability profile. Again, rapid onset and as you take a look at this, very importantly, from a drug development standpoint, an inactive dose. The 20-milligram dose is not active. As a drug developer, that's something that we'd like to see. That suggests activity in the 30-milligram that you've seen in the other 2 studies. So taken as in sum, we think we have -- this is an iterative process, and there are some learnings that we've gathered from this program. Let's see if I can do this now. Yes. Sorry, I'm having trouble with the remote.

What do we know? The first and most important, there is a consistent activity and tolerability profile demonstrated across 3 studies. Then if you look at the ZULRESSO data with the same mechanism, a similar profile with the intravenous molecule. If you look at the tolerability data, which I showed earlier, we believe that we have potential to enhance and increase the dose to get even potentially more efficacy.

And finally, and most importantly, for Sage, the data continued to support, when you look at the durability, our attempt to change the treatment paradigm and offer an option for patients to have treatment-free intervals. We -- this is a breakthrough program. And as we've said publicly, once we had these data, we'd go to the FDA, we do have a meeting scheduled with the FDA in the first quarter. To preempt questions in the one-on-one, we will not give out the date of the meeting. We'll report on it when we have the minutes. So don't ask me on the one-on-one, but -- because that's always been our policy. But the meeting is, in fact, scheduled. So that's for you too, Cory. Because I know you're going to go there.

So let me turn now, in the remaining time, to the other 2 franchises. The first is neurology. We have an approach at Sage in looking at CNS disorders, it's really driven by our belief that human data is important to drive development. That is the most important way to understand how a drug acts after Phase I.

So our next molecule is a molecule called SAGE-324. This is another positive allosteric modulator of GABA. It's distinct from 217 in some very important ways. It has a very long half-life, it's less sedative and it's quite active. So we think this drug has the potential to be a long or a chronic pharmacotherapy for an assortment of neurological conditions, such as the essential tremor, epilepsy and Parkinson's disease.

When we looked at this drug, we had some human data previously to suggest potential indications. And the area that we decided upon was essential tremor. This is the most common movement disorder in this country. As many of you know, there aren't really very many effective therapies. People will take anything from using alcohol to primidone. It's an area of significant unmet medical need. But what this exemplifies for us is the way that we do business at Sage.

Here is a slide on the y-axis that shows reduction in tremor. This is total plasma concentration. And these are 2 studies, one with -- a controlled study with brexanolone or ZULRESSO and one with 217 open label. What you see here is a highly predictable dose response with 2 molecules, 1 intravenous, 1 oral that show meaningful reductions in tremor, more than 50%. Importantly, these are not dose optimized. Thank you. Excellent. Not dose optimized studies, 324 is our next -- I'm going to see if that works. I'll try in a second. I'll know in a minute. It's very exciting. Really, where is Jamie when I need him.

So 324, this is a single dose of a long-acting drug. And what you see here is, again, is a very profound decrease in tremor intensity and this incidentally is measured by accelerometer. This is a physical measurement of tremor. And again, tapering off with time. If you -- we don't have -- didn't have the room to show it. But if you looked at the drug levels, they would be almost mirror image. This is a well-behaved molecule that's very active that we believe has real potential for Phase II in essential tremor. And that program will begin this year. And now it works. Thank you.

The last franchise I want to talk about is neuropsychiatry. This is a completely different area for us and a different molecule. We've talked about GABA on the one side, which is sort of a brake pedal on the brain. Now we're talking about the NMDA system, which is an accelerator of brain activity. Sage scientists, with collaborators, discovered an endogenous modulator of NMDA called 24S-hydroxycholesterol. That is a drug that has helped form the scaffold for our drug development process in NMDA program, leading to 1,000, literally thousands, of potential molecules.

Why is this important? Because this receptor family has lots of functions. One that we are intrigued by is its effect on cognition and behavioral processes. We -- all of us realize that this is an area of significant unmet medical need and our lead compound, SAGE-718, we believe, has the potential to make a meaningful difference in the lives of patients. This, again, exemplifies how we do our development. We want to look at cognition. So it's fair to say if you -- a mouse model, mice don't forget to balance their checkbooks. They don't forget to pay their taxes. How do you find out what a drug really does. After you finish Phase I, it's important to go into people. So that's what we did with 718.

So this is a test called the two-back test, and we can talk about it in the breakout, if you like, but it's a measure of working function and cognition and executive function. And voluntary control of behavior, basically, learning and processing. It's a very annoying test, if anyone's ever taken it. You have to deal, basically, you deal out cards, you ask the person to remember the third card back and you keep on doing it until they get very angry at you. So it's a very difficult test. And as you go forward, the burden of the test increases, it's harder to do as you get bored and annoyed. Yes, more technical terms, but that's really what it is. And if you look here, that didn't want to do that. If you go back, there you go. Thank you. These are the normal.

So these are 2 studies. I want to make there 2 different cohorts, but I put them together for ease of discussion. And the data here are really intriguing. Because we really didn't know what this would do. This is the first time this type of molecule has been put into man. Normals, very little effect. Here, by the way, is better, the higher you go. And here what normals are dosed, you see a rapid increase in enhancement of their performance as the burden, cognitive burden increases. It's a really intriguing finding. And it gets significant at day 2 and persists through the course of the therapy. This, frankly, was a little bit unexpected, especially, the nature of the response. So it's quite intriguing.

And what was also really important to us is that this did not look like an amphetamine effect. It appeared to be a processing benefit. So we then asked the question, where else might this be applied. Now we had biomarker data that already suggested that Huntington's disease might be an applicable indication. So we then did a second study. So I'm just -- again, this is a separate study of 6 patients with mild-to-moderate Huntington's. And what you see here was very interesting to us. It's really quite intriguing. You see a rapid numerical improvement in their performance by day 2, reaching significance at day 8 and maintained through the course of their exposure. We believe this is a unique finding. The other interesting finding that we achieved here was seeing that the AE profile was extremely benign. We had very few side effects with this program.

So that, of course, leads to another conclusion, which is, we have room to increase the dose and potentially enhance the effect. So when you think about this, what can we do with this molecule. And there are a lot of potential. But if you look at the populations where this might have utility, you're talking from narrow populations like Huntington's to broader populations where we think this biomarkers support. It's Alzheimer's disease, mild cognitive impairment, ADHD, are all potential indication for this type of molecule. We've made a decision that these data are so unexpected, and we haven't shown these data before, especially the Huntington's data, and so interesting that we're going to look at a cohort of different disease states over the next year looking at dosing and different diseases to see where we can optimally apply this molecule. We think that's the prudent way to approach development versus rolling the dice with a single double-blind study before we optimize dose and before we fully understand the impact that this drug might have on cognition.

So if you look at the efforts of the Sage team, we have thousands of molecules that we think many of which are pharmaceutical-grade that we brought molecules forward, we think, quite efficiently, because we've used this probe mechanism of going first in humans, and then moving forward into clinical trials. And it's really allowed us to create what is really an extensive, what we think is a leading brain health portfolio today in the industry. That, we believe, will yield a really catalyst year in 2020. And again, I know we'll have time to speak about this on the breakouts, but we think that there'll be a number of events in 2020 that we're looking forward to. We're very optimistic about where we can take Sage in the future. We're in great financial position. We have almost $1 billion in cash. We have a great pipeline of molecules, a great team so -- and again, so we're looking forward to 2020. I'm going to stop now, look forward to people talking in the breakout, and thank you very much.

(Break)

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

But firstly, thank you all for waiting. As you know this is webcast today. So thank you all. I'm Jeff Jonas. I'm the CEO of Sage, I'm going to let everyone introduce themselves.

Kimi E. Iguchi - *Sage Therapeutics, Inc. - CFO & Treasurer*

Hi. I'm Kimi Iguchi, I'm the Chief Financial Officer.

Michael Cloonan - *Sage Therapeutics, Inc. - Chief Business Officer*

And I'm Mike Cloonan, the Chief Business Officer.

Stephen J. Kanes - *Sage Therapeutics, Inc. - Chief Medical Officer*

Steve Kanes, Chief Medical Officer.

QUESTIONS AND ANSWERS

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

So I'll start and people can chime in with questions. Since you won't give us the exact date. The FDA, we say in January, February, March, (inaudible). I wanted to ask, though, for sort of next steps of 217, you talked about exploring potentially higher doses now. What have you looked at before? And how high do you think you can safely drive this dose?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

So we've looked -- do you want -- should I repeat the question? Okay. So the question is, what -- our thinking about dosing. There are a couple of ways to think about that. We know we can go higher. We've had -- I think we've had...

Stephen J. Kanes - *Sage Therapeutics, Inc. - Chief Medical Officer*

60?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

60, up to 60 milligrams already. We have more than 5,600 patients overall treated with the drug. So it has a really good tolerability profile. So we think we can push the dose higher. That's something we'll be looking at now based on exposure and population PK data. The one -- I think there are a couple of takeaways here from -- again, this is my drug development hat. And I'm going to turn this over to Steve for some further comments. One is, we've shown that we have an inactive dose, which is actually pretty useful. And then we've shown we have what we believe is an active dose. That's the 30 milligrams. So that's your basis, but that's a basic requirement, right? We have a minimally effective dose, we believe. We think we have room to go up based on the tolerability profile. We've demonstrated it in 301, and we've had multiple exposure at higher doses. So we're pretty comfortable. We have room to increase.

I'll turn this to Steve.

Stephen J. Kanes - *Sage Therapeutics, Inc. - Chief Medical Officer*

Yes, one of the things, particularly in psychiatry, it's useful to have as more than 1 dose when we do the 301 study. We studied the 20 and the 30. Jeff showed the data during the presentation. The 20 itself is inactive. And so I think it will be important overall to be able to explore at least 1 higher dose. We're looking into what that would be right now.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Can you remind us in the earlier studies and work with 217, what you saw in terms of the adverse event profile, how it might have differed for higher doses that you're exploring?

Stephen J. Kanes - *Sage Therapeutics, Inc. - Chief Medical Officer*

So the overall...

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

Repeat the question.

Stephen J. Kanes - *Sage Therapeutics, Inc. - Chief Medical Officer*

Oh, I'm sorry. So the question is, what is the adverse event profile and what have we seen moving on to higher doses. I think it's important to recognize that when you go through an early phase development program, often, you dose to the highest tolerable dose. That sort of represents as far as you want to go in terms of dosing. At Sage, our early phase studies were done with an oral formulation. That's a solution, gives very high spikes of exposure. So it really gives us an idea of what the safety profile of the molecule is in and of itself. What we've seen as we go higher is increasing rates of somnolence and sedation, not surprising given the mechanism.

But overall, as we've proceeded with the development program, particularly with the capsule formulation that we're using now, the rates are very, very, let's just say, manageable and relatively low. So the amount of somnolence, sedation and so forth that we've seen in trials has been about 10% to 15% overall. The most recent trial is a little bit lower. And these compare very well to available antidepressants and many drugs that are seen in the CNS space. So it's one of the reasons why we think we're able to go at a higher dose.

Beyond that, and I'll just sort of tee this up. One of the things we're interested in doing is understanding the potential role of somnolence as a potential benefit for patients with depression. As we all know, many patients with major depressive disorder have disruptions in sleep, and we're actually doing a study specific to explore the potential utility for improvement of sleep in patients with depression.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

So with accrual pause in 2 of the Phase III studies for potential protocol amendment. Is that -- are you waiting on getting feedback from the FDA at some point later this quarter before you make those amendments? Is this -- there are other things that you're considering, maybe what are some of the changes aside from dosing could make the (inaudible)?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

Yes. I think it's a couple of points. Some of this is sequencing. And we think some of these are not of regulatory impact. So for example, we may look at altering some of the inclusion criteria to moving -- moving up to 24 from a 22 to help prevent upscoring. We may do some of that. 303 is fully enrolled, but we -- and so that's something where we may add another cohort at a higher dose, just as an example. But we don't think that a lot of these will require regulatory input. We don't believe so. So mostly inclusion and probably dosing, but we're pretty comfortable today. I'm actually confident that the 30 milligrams is an active dose.

So the question for us is the -- is in terms of looking at higher dosing, that doesn't have to be, in theory, part of a potential file. That could be something that's added on as part of life cycle management. But we don't know in terms of -- we don't have a filing pathway yet. So of course, that's the case. But we don't think that's necessarily a regulatory requirement. We think that's something, as Steve said, that will be useful for clinicians. But the amendments per se, I think most of them are the things that we've discussed, which is why we -- when we first announced the 301 data, we were very careful to say, this is what we thought about. We weren't trying to do subsets, we really were trying to explain, here's how we saw the data as drug developers, here's what we thought was going on in that particular study.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Okay. Can you be more granular with the timing for the 303 or the SHORELINE Study that will have data this year?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

We haven't put out a final digit. Sorry, the question is, do we have a time line for the 303 study? That's our naturalistic real-world study. So we haven't made a determination when that will be released. I think if you look at a study like this, this is not just this particular study. In general, there are different types of analyses to which this might be amenable. So we'll have to make a decision based on what the agency would like to see first

because that's likely to be the first cut we do, what the agency will want to see. But the kind of data you can expect out of this, and we don't know what sequences will be, is the overall initial response rate, what percent of patients make it to a follow-up period, what percent of patients require another treatment and what happens after the first treatment of patients.

And you'll have a duration of treatment, a gap between patients, when they got their therapy and when are they -- how long it was before they needed another treatment, if at all. So that's the kind of data we'll see. But -- you're looking at this almost a Kaplan-Meier type of approach. So there's a variety of analyses that we could subject this to. So we've been very careful, so far, not to do anything. I think the first release, when we do it in 2020, we don't have a date, is likely to be the most straightforward analysis of what was the overall response rate, how many patients required a retreatment and when.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

And then one of the most frequent questions we got post the MOUNTAIN Study was this perspective of that size. Can you speak to effect size of the clinical trial versus the real world and whether you could read from one to the other?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

Do you want to do that or do you want me to...

Stephen J. Kanes - *Sage Therapeutics, Inc. - Chief Medical Officer*

Sure. So there's a couple of things. In -- oh, the question is, can you talk about effect size versus effect? And this is a really important question, and it's sometimes -- particularly in psychiatry, it's one that's -- it's often easy to confuse the two. What we look at are 2 things. One, effect size, that's the difference in the drug response versus placebo. It's a technical question. How large do you have to make the study, how big the groups have to be, how long do you have to treat patients. Those are what we use to go and design trials. That's number one.

The other is effect of the drug. And that's -- it's a related but different concept. Here, we're looking at what's the overall improvement that patients experienced during the treatment and perhaps more importantly, do those patients sustain that treatment after the drug is gone. Those are 2 very different things. You can have a small overall improvement but a 2-point difference from placebo, or you can have a very large and dramatic effect and still have a 2- to 3-point difference from placebo. So what we've seen consistently with 217 and with ZULRESSO before it is a very large and very rapid drop in symptoms and those that are maintained and sustained well after the treatment has continued. That's one of the things that when the drug, if it's ultimately approved, will translate into what the rational benefit is for patients.

I'll just say, what we've seen, even in 301, while we didn't hit the primary endpoint, we did see statistically significant differences on Day 3, Day 8, Day 12. So we saw a very rapid and ultimately, sustained improvements in those patients. So it's one of the reasons why we continue to feel very confident that there is -- that the overall Phase III program that we've put together will ultimately support registration.

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

The other thing I'd add, and I think you've sort of alluded to this, is when people talk about effect sizes, we're achieving an effect size within days versus what you normally see an antidepressant therapy from 6 to 8 weeks. And I think that's part of the -- these options we're talking about, which is it is important to get people better, faster. The rest of medicine, that's a well-established principle, right? You can -- if you have a broken leg, you can lie in bed for 8 weeks immobilized or you can put a cast on and go around your business. So the belief that depression should be treated rapidly and urgently is one that we think we can establish that as a new treatment option for patients. So I think that's the other thing. It's a little apples and oranges when we talk about effect sizes because we're doing this in days versus weeks.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

I assume you need to wait for this meeting with the FDA. But is one of the scenarios that you believe is on the table to separate postpartum depression and MDD for 217 and file (inaudible)?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

Yes. I think we're reluctant to speculate. I think we're going to explore multiple pathways with the agency when we meet with them. I don't think it's productive to speculate. I think all we can say from our perspective is that we think we have a drug. We understand we didn't hit the primary endpoint, but with 30 milligrams, it's clearly active. It's consistent. We've replicated overall the findings. So we're optimistic about the future of the product. I think beyond that, I think it's -- we shouldn't speculate what will happen with the agency. And we won't tell you when we're meeting with them either.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Okay. So let me ask you another question then. Switching gears, I wanted to ask about the Huntington's data that you had. I guess maybe, first, it would help to hold the -- what was it, the two-back test, if you can explain a little bit how it works?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

Jim, come on. You want to do it?

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Do you want a reinforcement? Jim can answer the question.

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

Jim? Yes. Jim, so we're going to talk about -- we want to talk about the Huntington's data. So Jim -- take that microphone. Thank you. This is a science. I can explain it, but Jim will be accurate.

Jim Doherty - *Sage Therapeutics, Inc. - Chief Research Officer*

Yes. So the two-back test is a test of executive function, essentially. And Jeff talked about it in the presentation. It's a card-based test. You -- and it works well with video screens and things like that. They show a playing card. There's a pause. You're shown another playing card. There's a pause. You're shown a third playing card. And then the question is, what was the first card, right? And you can step through sequentially. And one of the values of the test is you can titrate just how hard it is, right? You can either lengthen the pauses or ask people even longer sequences. So the value is it's probing the sort of complex construct.

When we think about executive function, we're all pretty clear what it means. You're able to sort of do a robust planning. I'm going to go to the store, and then I'm going to do this and I'm going to do that. But what we're seeing, and this something else that Jeff said in the talk, is that the effects here are somewhat specific on these tests of executive function. There are simpler tests -- reaction time. When you see something on the screen, you press a button. What we don't see there is a significant effect of the drug. It's only on these more complex tests where you really have to engage parts of your brain.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

So in your talk, you said the data you got from Huntington's was completely unexpected. I guess the question is what were you expecting to get?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

Well, we didn't know. I mean no one had ever -- so the question -- I used the term unexpected. Maybe I should have said pleasantly surprised. But I think it's fair to say this is a new mechanism. I think it's fair say no one's ever gotten this far with an NMDA-positive allosteric modulator, they're tricky drugs. So we really didn't know what to expect. And then you always have to ask the question when you go into a disease state. Is the brain going to be more responsive or less responsive? So what -- I think what we were gratified to see was that the effect that we saw in the 6-patient Huntington's look to be even greater numerically. Because remember, these aren't head-to-head data.

So we got to be clear, was even greater than what we saw in the normals, which suggested that some of our thinking about what NMDA hypo function and cognitive impairment, what that means and maybe we are on the right track of looking at deficits of 24S-hydroxycholesterol, what that biomarker data has given us. So when we -- so -- and frankly, we just didn't know. And I think of those of us who've worked in this area before, like we worked with Vyvanse, for example, there's a particular type of enhancement you see, performance enhancement. You see attention, rapid response time, but you don't see enhancement in processing, and you don't see enhancement in, basically, cognition with increasing cognitive burden. So that was what, to me, was the most surprising.

I think that it was a pretty unique effect. And that's why when we saw this, and we then we showed the data, and we haven't really made this data public before, we said, this is something we have to step back and be a little more prudent about because this may have broader potential than even an Alzheimer and then Huntington's. So we think ADHD, Alzheimer's, there are a number of areas, mild cognitive impairment, where this type of pharmacotherapeutic intervention might actually be meaningful for people. So that's how we're thinking about it. Jim, do you want to add anything else? I'm watching him. He's correct.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

(inaudible) if there's additional cohorts to look at a variety of other conditions. How many patients are you talking about adding when you get a figure on that?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

So the question is, what are we going to do next? And we initially thought that we would be doing a double-blind study of Huntington's. But one of the features that we saw is that we don't think we've reached the right dose. We can go higher, even with the effect we saw. The other is, the effect was pretty reproducible and profound. It's very much like the tremor effect. Most of the patients respond in some level. And when we saw that, we really had -- we stepped back and said, there are clearly other indications where enhancement of executive function might be therapeutically beneficial. And if you look at that -- those types of indications, they're quite broad.

So our idea is going to be there's a battery of different tests that one can apply. And we don't know if the effect in Huntington's is going to be the same effect that you might see in Alzheimer's or what you might see in MCI. We don't know. And so before we put all our chips on the table, we said, let's look at a number of these studies, open-label like we've always done, right? That's how we started with ZULRESSO, again, to tremor and depression, and let's see where we get the biggest effect, let's understand the pharmacodynamics, and only then will we commit to indications in larger studies. So that will all be done this year, probably 6 to 10 subjects, depending on the reproducibility of the finding.

One of the findings that you're seeing from the study in 718 is that you don't need to have a large cohort of patients just to get something. It looks like a very active molecule. So that, we believe, allows us to pursue the same strategy we've always pursued, which is human probe studies, small numbers, looking for a consistent effect size that allows us to design rather efficient Phase II programs.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

And then speaking of Phase II. Can you talk about the design and potential time lines for the essential tremor program?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

So the essential tremor program will begin -- should be beginning first quarter. We like this indication for a number of reasons. One is there's clearly -- it's an area of unmet medical need. You have people on primidone, on barbiturates and on benzos and Inderal LA and things of that nature. It's a very unsatisfied market. We like it for the other reason, which is you can measure tremor physically. You can wear a ring accelerometer or a wrist accelerometer, you can do provocative testing to actually measure this objectively. So -- and if -- after doing depression, it's really nice to have something that's measured. So it's a relief, I'll just say that. It's like you get actually granted. It's great stuff. So we like it for that reason.

And we like it because there's nothing that really -- it's a very -- it's a space of significant unmet medical need with very low competitive intensity. And the data have been very reliable. So we don't know the size of the study yet, it will probably be just a 2-arm study, because the drug has been very well tolerated. We'll probably go to a higher dose and to establish what the pharmacodynamics look like. So that's a study that we think is reasonably derisked at this point.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

I wanted to go back to 217, some of the other indications you talked about exploring. So TRD, Generalized Anxiety Disorder, thought process around dose, potential indications, post-MOUNTAIN, some of the work you're going to do in terms of exploring higher doses. Are those on pause at all (inaudible)?

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

Do you want to talk about that, Steve?

Stephen J. Kanes - *Sage Therapeutics, Inc. - Chief Medical Officer*

Sure. So the question is, there's a number of indications that we've talked about previously, both treatment-resistant depression, Generalized Anxiety Disorder, bipolar depression. The way that we think about this is, with patent protection, we have a composition of matter patent for 217 now through 2034. We begin to use the data in our clinical trials to identify what we want to do immediately and what we want to do over the long term. And that's almost the beginning of life cycle management. So we include endpoints or other exploratory analyses through the outcomes of our studies.

What's important to us right now, we're focusing on identifying the most efficient pathway to filing and to think about how to sequence additional work. So as we move forward, we'll continue to include endpoints that allow us to sort of work closely interrogate anxiety, think about other kinds of probe studies that might give us indications for other areas that are of interest. Right now, the focus for us is thinking through how our Phase III program leads to at least the filing, although those are areas that are absolutely essential to explore as well.

Michael Cloonan - *Sage Therapeutics, Inc. - Chief Business Officer*

Yes, maybe just to build on that, Cory. I mean we -- what Steve is saying, we always take a portfolio approach. We've been doing that for a while now, right? We have a whole breadth of opportunities across 217, across 324 and 718, as Jeff presented. But really, we have to make sure we're optimizing our resources and allocating them the right way. So we're constantly evaluating the portfolio with all the data that Steve mentioned, and that's how we're attacking the programs that we have now.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Okay. And then I guess Kimi bringing to pause.

Kimi E. Iguchi - *Sage Therapeutics, Inc. - CFO & Treasurer*

Thanks, Cory. I can always count on you, Cory.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Well, it is -- we get this question a lot too. I mean it's on the balance sheet. Capital requirements going forward, especially since you're not turning around. I mean maybe you really need to tell us in (inaudible) that will be nice. But what are the -- kind of where do you stand right now at the balance sheet?

Kimi E. Iguchi - *Sage Therapeutics, Inc. - CFO & Treasurer*

Yes, sure. So the question is on cash and burn. And so look, we've made a lot of progress this year. I think we're very fortunate for that. And we've done that with, I think, a pretty successful financial playbook. And one of the things from that is, if we look at our cash balance at the end of the year, the last financial guidance that we've provided was that we expected to have, at a minimum, of $950 million in cash at the end of the year. And in fact, we've ended the year with $1 billion in cash. So we're in a great financial position. We haven't, at this point, provided guidance for burn into 2020. It's early. We have our earnings call that will be coming up over the next month.

But the one thing I can say is that we'll continue to do things the way we've done it, which is to be very disciplined in how we think about our spend and our investments. We -- you heard Mike talk about how we think about resource allocation and we really prioritize and think about that. And so we'll continue to do that into 2020. And when we can provide more color on what that looks like, we'll certainly do that.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Will you guide on burn prior to getting FDA feedback?

Kimi E. Iguchi - *Sage Therapeutics, Inc. - CFO & Treasurer*

We're going to try to do what we can to help you think through the models. But at this point, I wouldn't commit to that. A couple of things I'll say is the FDA meeting will have a big impact on how we think about the investment throughout the portfolio, not just 217 but the other programs. I will also say that if you think about SG&A, we had a big year of build in SG&A with the launch and even getting the rest of the organization prepared to deal with the pipeline, the size that we have. So that's in a fairly stable place going into 2020. But again, we'll look to provide some more guidance as soon as we can.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

All right. I'm trying to see if you guys will give it before or after.

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

I know. It didn't work though. Nice try.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Thanks. And then I guess, Mike, before we run out here, just -- I know ZULRESSO is not like a big investor focus for you. (inaudible) kind of the key objectives for you on that front?

Michael Cloonan - *Sage Therapeutics, Inc. - Chief Business Officer*

Yes. So the question is about ZULRESSO, what are the key objectives. So it is a big priority for us, Cory, for sure, right? I mean the first launch of the company. And as Jeff said, we're on a journey with ZULRESSO. First product ever approved in postpartum depression. We're operationalizing that now. We feel very encouraged about the progress we've made. We've given metrics as of Q3, which I can repeat, but we're now 6 months into the launch, right? And we knew this was going to take some time to shift the paradigm, as Jeff described, you're operationalizing our REMS, you're asking moms to go into a health care setting for 60 hours.

But what we're probably most pleased with is that the real-world evidence that we've seen with ZULRESSO early in the launch has replicated what we saw in the clinical trials, right? So for the patients who have responded, we've often heard the phrase, "I finally feel like myself again." And so that's why when you think about some of the complexity that exists with ZULRESSO, why go through that. It's because of the output that moms and the families are seeing from ZULRESSO. So very encouraged by that.

Where our focus and our objectives are now is really the priorities are enabling the sites of care, and that's a big part for us, is how do we build up more sites of care that can actually infuse with ZULRESSO. As of the end of Q3, we had over 140 REMS-certified sites of care. So that's an indicator of success. We had 11 that we're treating at that point in time. But as I think we consistently said, it's going to take 6 to 9 months or more to get many of these sites up and running because there's many actions that they have to take to get through, including formulary approvals, reimbursements, REM certification and protocols. But we're pleased with the progress we're making.

And as Jeff said, one of the biggest things we continue to be focused on, which we're most encouraged by, is the payer coverage, right? That actually goes back to the early engagement we had with payers, months and months ago, to recognize the burden of PPD, and we're seeing that now with the 75% plus coverage. So we'll continue to work through those objectives. The patient experience is important. And we've also seen good demand. As Jeff said, over 200 patients with [STAR*D] forms in Q3 from 150 different HCPs. So well on our way, and we just want to keep pushing through those objectives in 2020.

Cory William Kasimov - *JP Morgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Great. Thanks, everyone.

Jeffrey M. Jonas - *Sage Therapeutics, Inc. - CEO, President & Director*

Thanks, everybody. All right. Thank you.

Kimi E. Iguchi - *Sage Therapeutics, Inc. - CFO & Treasurer*

Thank you.