Pasithea Therapeutics
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Presenters
Tiago Reis Marques
Matthew Lazarus
Larry Steinman

Tiago Reis Marques
Good morning. My name is Tiago Reis Marques and I´m the CEO of Pasithea Therapeutics. It is with great pleasure that I am here today with you to announce the acquisition of Alpha-5 Integrin, a preclinical biotech company. Joining me today is our Chairman Professor Steinman and our Chief Business Officer Mathew Lazarus.

Alpha-5 developed a collection of novel monoclonal antibodies with novel IP for the treatment of amyotrophic lateral sclerosis, known as ALS, and other neurological diseases such as Multiple Sclerosis. We are proud to make our investment in a therapeutic area with huge unmet need. This target is supported by extensive preclinical and human data providing a novel mechanism of action in the treatment of ALS.

We have reproducible data showing survival and motor function efficacy in the SOD mouse model, and we will hear more about the biological rational in the coming presentation. These antibodies also show a strong activity profile in animal models of Multiple Sclerosis, providing Pasithea the ability to expand these antibodies through multiple indications in CNS disorders.

Along with adding a new drug with a novel mechanism of action to our pipeline, the transaction will bring Pasithea a state-of-the-art lab and a group of experienced scientists, bringing R&D capability to Pasithea. The newly formed scientific team at Pasithea will also advance our tolerizing vaccine program targeting GlialCAM as well as our C4 complement program currently being advanced by Evotech. We are excited to have a talented team of individuals joining us to create value for our shareholders and advance these exciting programs into human.

Now, to provide more information about the transaction I will pass the word to Mathew Lazarus.

Mathew Lazarus
Thanks, Tiago. Hi everybody. I'm very happy to be with you today. In closing the transaction of Alpha-5 Integrin, LLC Pasithea acquired all of the outstanding equity interests of Alpha-5 Integrin, LLC at an enterprise value of $3.75 million dollars, payable in 3.26 million shares of Pasithea common stock, valued at $1.15 per share, an approximate 11% premium to the closing price on June 17th, plus one million five year warrants which strike at $1.80 per share.

Paul Manning, Chairman and CEO of PBM Capital, a healthcare focused investment firm and Alpha-5 Integrin LLC's largest shareholder will own approximately 10% of the outstanding shares of Pasithea at closing. We are excited to have a healthcare investor like Paul Manning joining our shareholder registry as Paul as well as his investment firm PBM Capital have a long track record of success including the notable sale of Dova Pharmaceuticals to SOBI Pharma for over $900 million dollars as well as the sale of Avexis to Novartis for over $8.7 billion dollars.

I would like to introduce and then turn the call over to Dr. Larry Steinman to discuss the biologic rationale of Alpha-5 beta-1 Integrin in treating ALS and Multiple Sclerosis. Dr. Steinman is a member of the National Academy of Sciences and the National Academy of Medicine, and a Professor of Neurology and Neurological Sciences, Pediatrics, and Genetics at Stanford University. In this institution he served as the Chair of the Interdepartmental Program in Immunology from 2003-2011.

Dr. Steinman's research focuses on what provokes relapses and remission in multiple sclerosis, the nature of the molecules that serve as a brake on the brain inflammation, and the quest for a tolerizing vaccine for autoimmune diseases like type one Diabetes and neuromyelitis optica. He has developed two antigen specific therapies using DNA vaccines for MS and type one Diabetes. He was senior author on the seminal 1992 Nature article that reported the key role of a particular integrin in brain inflammation. This research led to the development of the drug Tysabri, which is used to treat patients with MS as well as Crohn's disease.

Dr. Steinman received his BA from Dartmouth College and his MD from Harvard University. He was a post-doctoral fellow and chemical immunology fellow at the Weizmann Institute of Science in Israel. Dr. Steinman returned to Stanford University Hospital as a resident in pediatric and adult neurology and then joined the faculty at Stanford in 1980. Dr Steinman became the Chairman of Pasithea in 2021.

Dr. Steinman has received numerous honors and awards, including the John M. Dystel Prize from the Academy of Neurology and the National MS Society for his research on MS, as well as the Charcot Prize for Lifetime Achievement in MS research. He has twice been awarded the Senator Jacob Javits Neuroscience Investigator Award by the National Institute of Neurological Diseases and Stroke.

Dr Steinman, thank you for taking the time to walk investors through the biologic rationale of targeting Alpha-5 beta-1 Integrin in both ALS and MS.

Larry Steinman
Thank you, Matthew. And thank you Tiago for the kind words. I'd like to tell you today about the program that Pasithea has acquired to develop a transformative treatment for a terrible disease, amyotrophic lateral sclerosis. And I am very excited about this. As a clinical neurologist teaching at Stanford and seeing patients for the past 42 years, amyotrophic lateral sclerosis motor neuron

disease, also known as Lou Gehrig's disease, may be one of the most devastating of all the diseases of mankind that I see as a neurologist.

So let me give you some background on this. We have seen a unique expression and activity profile in both human ALS and in a mouse model of ALS. We see elevated expression of a molecule that I'll tell you about today called Alpha-5 Integrin. It's also technically known as CD49e and it's seen in ALS patients, but only in the motor areas and at the blood brain barrier.

We've been able to test an antibody to Alpha-5 Integrin in a very strong animal model of ALS where the human mutant gene that is sometimes associated with ALS is installed in a mouse, in a transgenic mouse. I'll describe to you the mechanism of action of how the antibody to Alpha5 Integrin works in regulating the leakiness at the blood brain barrier and its effect on the immune cells that infiltrate both the central nervous system in the motor areas and in the peripheral nervous system.

I'll also share with you the very strong activity profile in animal models of multiple sclerosis. Having been a participant in the earliest days of the development of Tysabri, I shall share with you data that shows that our results with anti-Alpha-5 Integrin in the same animal model are actually even stronger than what we saw in the model leading to the development of Tysabri. I'll share with you that we have developed at the company multiple novel antibodies that have IP filings supporting them.

We have an established safety profile with this target. The target has been addressed with antibodies in phase two clinical studies in oncology with a very good safety profile. And we expect to develop and start human clinical trials by the end of 2023.

So let me give you some further background about ALS. The average age of onset is in the mid-50s. Most of the time we don't know the cause, although in about five to 10% of the cases we know that there is a mutant gene involved and there is a familial penetration of the disease. And it can be caused by mutations in a gene called SOD -- that's the model that we tested it in in the mouse -- and two other genes are well known associated with the disease, one called C9orf, and one called TDP-43.

This is a disease that has a slightly higher ratio in males than females. The incidence is one to two and a half per 100,000, and the prevalence is five per 100,000. Featured in this slide is Steve Gleason who was a professional American football player with the New Orleans Saints. The clinical manifestations of the disease present with muscle weakness, cramps, fasciculations, spasticity. There's difficulty chewing and swallowing, sometimes difficulty in speaking. There's in some cases emotional lability and then there is a striking and very scary atrophy of the musculature.

So, this is the disease we face. And as I mentioned, it's one of the most severe diseases. At the end of the disease, while cognition remains intact one can only move the eyes and it resembles

something that we call in neurology a locked-in syndrome. There are currently only two treatments that are approved by the Food and Drug Administration for amyotrophic lateral sclerosis. These are riluzole and edaravone, also known as Rilutek and Radicava. There are a number of molecules in the clinic to test their performance in ALS and they're listed here on the slide to the right.

So Alpha-5 beta-1 Integrin is known as the fibronectin receptor. The integrins are a family of molecules that have two protein chains, one the Alpha chain, the other the beta chain, and there are essentially 28 different combinations. Alpha-5 beta-1 Integrin is expressed only on a limited number of cells: microglia, macrophages, the mast cell, and cells at the blood brain barrier that have the technical term perivascular glia. Integrins are validated targets and have been approved for three different indications. The drugs are Tysabri, Entyvio, and ReoPro.

As I mentioned I was involved in the development of Tysabri. I prescribe it as a neurologist. And I was also on the Board of Directors 30 years ago at Centocor when ReoPro was approved. Alpha-5 beta-1 Integrin is a well characterized target. As I mentioned, Alpha-5 beta-1 Integrin monoclonal antibodies have been developed for oncology and have been taken into the clinic by protein design labs in a partnership with Biogen and Pfizer. One of the molecules and one of our scientists had a hands-on experience in the clinical trials. This molecule called volociximab advanced into phase two and had an acceptable safety profile in oncology.

So we're dealing with molecules that have led to approved drugs that target the integrins that's well known and has really transformed a few fields. The experience after Tysabri continued in my lab. We've paid a lot of attention to the integrin molecules and to the idea that the immune system has to traffic into the brain in order to cause damage. So we used a technology that was developed down the handle at Stanford called single cell mass cytometry and published a paper in 2018 in a peer-reviewed highly prestigious journal called Nature Neuroscience where we tested various disease types to see which integrins played a major role.

Now the subject of the traffic of immune cells into the brain has been studied for a long time. The gentleman you see at the bottom won the Nobel Prize 100 years ago for discovering how the nervous system is wired together. He was a brilliant artist as well as a fantastic scientist, having received the Nobel Prize. And on the left is a sketch he drew of immune cells penetrating the blood brain barrier and going into the brain. We took those ideas and in the development of Tysabri the artists, sort of the journal where the history of the development of Tysabri was given, 20 years after the discovery the artist drew a very similar picture.

And this is the type of movement that we're impeding with the Alpha-5 beta-1 antibody. This traffic, if you will, from the blood into the brain or spinal cord. Now in this paper we showed some of the earliest data that Alpha-5 Integrin increases during the development of motor neuron disease. And the diagram that appeared in the paper is over on the right side of that slide. So as disease progresses there's a bigger and bigger burden of Alpha-5 Integrin. And I'm going to show you the cells that they're expressed on in humans and share with you some remarkable

neuropathology studies showing the specific areas where Alpha-5 is expressed. And it's rather dramatic because it's only in the diseased motor areas and it's not at all in the sensory areas.

So again, as we go deeper into this story the current therapies for ALS have really only a minimal impact on disease. So, there's a large unmet clinical need for this horrible disease. Alpha-5 Integrin expression is significantly increased as disease progresses, and we want to stop that. And we've learned that the anti-Alpha-5 Integrin targets four cell types: the microglia, the macrophages, the mast cells, and cells at the blood brain barrier. So on the right of the slide, you can see these various cell types and at the lower right you see the first picture of many I'm going to show you of cells at the blood brain barrier at the motor region, not the sensory region, of the spinal cord of an individual who died with ALS.

This collaboration was done with colleagues at the Mayo Clinic. The Mayo Clinic, of course, is famous for many things, one of which was that the baseball player Lou Gehrig, who the disease is named after in some quarters, went to see the Mayo brothers when he was diagnosed with motor neuron disease.

So, here is one of the most dramatic slides from the Mayo Clinic collection in our collaboration. In the motor neuron tracks, the wires that take the message to move a finger, a leg, toes, to have your diaphragm breathe, these are all in the motor neuron tracks. And in those areas, we see this brownish staining. That's a stain with an antibody that detects Alpha-5 Integrin. Right next to it there is a set of axons. If you want to look at it as electrical wiring, a set of cables that has nothing to do with the motor system, only the sensory system. That's not stained with Alpha-5.

In the middle is a diagram where the actual quantitation was done. And in MND, which is motor neuron disease, both in the gray matter and the white matter there is intense CD49e Alpha-5 Integrin. Whereas in non-motor neuron disease there is much less. It's essentially background. On the right you see another dramatic picture. There's a motor neuron that's in the spinal cord and next to it is an Alpha-5 beta-1 positive macrophage which is going to eat the motor neuron which is five times its size.

Now, a macrophage comes from two roots: macro meaning big, phage meaning eater. And these are really big eaters. Here this little guy, this cell, the macrophage is going to eat a motor neuron five times its diameter. Some other areas where Alpha-5 Integrin is expressed. On the left is a picture from the SOD mouse where that human mutant gene that causes rare cases of motor neuron disease is put into a mouse and they get severe motor neuron disease. As the disease progresses, now the stain is in orange in the mouse system. And you can see on the peripheral nerve -- this is equivalent to the sciatic nerve -- there is intense staining. Whereas on an animal that doesn't have that gene there's only background staining.

On the right is a dramatic picture that in the peripheral nerves as they come out of the spinal cord in the motor part of the peripheral nerve there's intense staining again with Alpha-5 and you can see that in the box outlined in red, whereas in the sensory nerve there's no Alpha-5

staining. And I make a repeated point about this because we're addressing a target that's only present at the site of disease. This is a very specific degeneration in the nervous system, and we want to stop that phenomena of the destruction of the motor neuron so that individuals with ALS can live longer and have more motor strength.

That macrophage that I showed you two slides ago ends up devouring the motor neuron. And here is a picture of where there used to be a motor neuron and all you see are chunks of the motor neuron stained with Alpha-5 Integrin that had been on the macrophage that ingested it. We call that empty cell bed -- looks like a forest that burned down if you want to use that metaphor. It's called neuronophagia. And on the right is another descriptive picture of an empty cell bed of an individual who died of ALS.

There's been a lot of work not only in our lab but in other labs that have looked at Alpha-5 Integrin, but the focus was not on this molecule, it was on other things. So, on the left is a picture from the paper we published in Nature Neuroscience of increased expression of the Alpha-5 Integrin as the disease progresses. A study from France by a collaborator involved in these studies showed that Alpha-5 Integrin increases from the pre-symptomatic stage up to the end stage. This is the paper by Shio(PH) published in 2020. Alpha-4 Integrin, the target of Tysabri, isn't expressed at all. That's shown in those little boxes on the left side of that.

At Harvard, Isaac Chiu and coworkers showed that Alpha-5 Integrin is increased in the same SOD model, so there's a lot of agreement across the world: Stanford, France, Harvard. And then a study in Italy showed that Alpha-5 Integrin is actually increased in spinal cord tissue in human ALS, confirming what we're seeing as well from our collaboration with the Mayo. A few more pictures. This is the fascinating role of Alpha-5 Integrin at the interface between the blood and brain. On the left is a picture of the spinal cord with ALS where we've stained a component of the water channel known as Aquaporin-4. It's a remarkable molecule for which a Nobel Prize was given, and it plays a role in the movement of lymphocytes out of that blood vessel -- we're looking at the left panel -- into the brain.

And then when you stain with Alpha-5 Integrin, CD49e, you can see the blood vessels that have intense staining with Alpha-5 but also this perimeter where the blue arrows are that's filled with Alpha-5. And I'm going to show you some pictures from our laboratory at Pasithea that has done some work on this. So at the blood brain barrier, a lot of Alpha-5 Integrin. And in ALS but not in other diseases like Alzheimer's at the limiting area of the blood brain barrier shown with these dotted red lines, there's staining with Alpha-5 Integrin. And this is a critical molecule in determining whether the blood brain barrier is sealed shut as it is in those of us who don't have any disease versus ALS where that blood brain barrier is leaky.

As I said, there's no role for this in Alzheimer's disease or another rare disease called PSP but it's prominent all over the motor areas in ALS. So at the laboratory that -- the wet laboratory that Pasithea is acquiring from Alpha-5 Integrin, we've done studies with some of the anti- Alpha-5 antibodies that we've raised against human Alpha-5, and these antibodies are able to block the

opening of the blood brain barrier that's instigated by an inflammatory molecule called PNF. You may have heard of TNF because it's the target of an antibody in the disease rheumatoid arthritis and inflammatory valve disease. So TNF opens the blood brain barrier, and these antibodies seal it up, these antibodies to Alpha-5 Integrin. And that's shown on the right in that bar graph with human blood brain barrier endothelial cells.

Few other things. The inflammation in ALS extends into the motor region. This is a stain with a particular type of immune cell called a T-cell that's seen in the ALS spinal cord but not in individuals with motor neuron disease. And this is quantitated by our collaborators at the Mayo Clinic on the right.

Now as I mentioned, we've done an experiment at Stanford that was repeated at a contract research organization by an independent group where we gave an antibody to Alpha-5 Integrin through the bloodstream at a dose of four milligrams per kilogram. And there was benefit at many levels. The graph shows increased survival. They did better on a beam walk. If you can think of our Olympians on the balance beam, the mice with this model of ALS performed with fewer slips and performed in faster times walking across the balance beam. That's the beam walk.

Vircelli's scores shows that there was a separation in favor of better motor performance after getting Alpha-5 antibody, and in these two experiments we were able to show a reduced amount of inflammation within the motor areas of the spinal cord. I wanted to share a movie with you of what's going on. This is an animal that got a control antibody, not Alpha-5. And you can see it can't groom itself, it's not moving very well. And go on to the next slide. This sleek looking animal with a well-groomed coat was given the anti-Alpha-5 antibody. So they both have the same motor neuron gene. You can see it's moving around very well. And we go to the next group, this is again mice that have the anti-Alpha-5 antibody. They're moving very well. They're nicely groomed, they're foraging for food. And here is a -- in the final little movie I'm going to show here a mouse with severe motor neuron disease that got the control antibody. You can see it can barely move, it can't pick its legs up, and it's really a night and day difference.

Eventually all the animals succumb, but for a long period there's really a dramatic difference between those given anti-Alpha-5 and those given the control antibody. And this slide simply recapitulates what I told you about the survival benefit. It's statistically significant. In the Stanford experiment we discontinued treatment when more than 50% of the animals were still alive and the animals that were given the control antibody were down to about 25 or 20% dead. After you stop giving the antibody the animals do succumb, and this is going to be an issue that there may need to be long doses of antibody perhaps for the rest of a person's life with giving anti-Alpha-5 in order to block the pathology. But those are the experiments that we'll find out as we go into human trials.

So at Pasithea we've characterized these antibodies. As I said, the Alpha-5 beta-1 is a binder of a molecule called fibronectin and we have antibodies that are good at interfering with the interaction between these and some are complete blockers. We've developed a group of human

antibodies, some are non-blocking, some partial blocking, some strong blocking. And these are the antibodies that we're continuing to characterize as we go to choose our lead candidate to take into the clinic at the end of this year, and then it will go through further testing toxicology and so before we actually start human trials.

So again, to summarize, there are only two treatments, Rilutek and Radicava, for amyotrophic lateral sclerosis approved by the FDA. They're not highly effective at all. And we hope we can have something that is more Tysabri like in the way it -- Tysabri had a transformative effect on MS. We want to do this with the Alpha-5 in ALS. That's our aspiration. Other indications include multiple sclerosis where, as I mentioned, and I'll show you again the data, our anti-Alpha-5 antibody actually performs better than Tysabri in the early tests.

And then there's some rare diseases. A form of encephalitis called Rasmussen's encephalitis where they have to take out half of the brain to stop seizures. And there's some indications that anti-Alpha-5 may provide a benefit there. And then there's another disease, Charcot-Marie-Tooth, affecting about 100,000 people where Alpha-5 Integrin may play a role, so we're going to investigate that.

As I mentioned, Alpha-5 antibody treatment in the animal model of multiple sclerosis was able to significantly knock down the severity of disease both in a prevention model and treatment of ongoing disease after the mice were paralyzed. That's shown in the panel on the right where the anti-Alpha-5 actually stopped the progression of multiple sclerosis after there was paralysis present. And that was published in our 2018 paper. This is just a artistic view of what we might be able to do in one of the autoimmune epilepsies, that Rasmussen's encephalitis, where they take out half the brain.

So to summarize, the current therapies for ALS have a large, unmet clinical need. Alpha-5 Integrin is significantly increased, blocking disease progression in mouse models and appearing only in the motor areas of human ALS. It's present on four cell types: microglia, macrophages, mast cells, and those cells right at the blood brain barrier. The anti-Alpha-5 Integrin tested so far performs well in a very harsh model of motor neuron disease and it has impressive activity in the model of ALS. So the road map is for us to select our lead candidate by the end of 2022, to complete toxicology studies by the second quarter of 2023, to have discussions with the regulatory authorities including orphan drug designation, and to file an IND in the fourth quarter of 2023, and to begin human trials somewhere near the end of 2023.

I thank you for your attention, and I'm going to turn it back to our CEO, Dr. Tiago Marques for some final words.

Tiago Reis Marques
Thank you, Larry, for showing this exciting biology. Pasithea is now the owner of exciting IP and a clear roadmap to be able to start our human clinical trials by the end of 2023. We will provide

further updates on our tolerizing vaccine program for MS as well as the complement program targeting C4 at future investor conference. And I must end. Thank you for attending our call.