**ASX ANNOUNCEMENT**

# Strategic Update Teleconference Transcript

**Sydney, 30 April 2021. Actinogen Medical ASX: ACW ('ACW' or 'the Company')** is pleased to provide an edited transcript from the most recent teleconference held at 9.00am (AEST) on Friday, 23 April 2021.

The teleconference covered the details of the investor presentation that was released on 21 April 2021 in the Strategic Update and Teleconference Call Notification announcement.

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**Operator:** Thank you for standing by and welcome to the Actinogen Strategic Update and Investor Presentation. All participants are in a listen-only mode. There will be a presentation followed by a question and answer session. If you wish to ask a question, you will need to press the star key followed by the number one on your telephone keypad. I would now like to hand the conference over to Dr. Geoff Brooke, Chairman. Please go ahead.

**Dr Geoff Brooke:** Well, good morning everybody, it's Geoff Brooke here, I'm the Chairman of Actinogen. I'm not going to say too much. It's really my role just to welcome you to the Actinogen Strategic Update and Investor Presentation, but more importantly, to introduce you to Steven Gourlay, who is our new CEO.

Steve is a physician with a PhD, and an MBA. After about 10 years in medical practise as a specialist physician, he went and worked for Genentech, one of the world's most successful biotech companies, where he primarily designed clinical trials. He then actually came and worked with me at GBS venture partners for a number of years, doing biotech start-ups and helping them design and run clinical trials.

After six or seven years together with me at GBS, he then went back to the US and became the Chief Medical Officer of a brand new start-up where he, from go to whoa inside six years, took small molecules from animals all the way through to phase 3, the last stage of clinical trials. And as I said, inside six years, the company was sold for 3.7 billion USD having been a start-up when Steve went there.

So, Steve has an incredibly relevant background for Actinogen and I'm absolutely thrilled that he decided to move back to Australia. He had more or less a year to recharge the batteries, and I contacted him toward the end of last year, got him to have a look at Actinogen and tell me what he thought of it and what he thought we could do to improve things. Cutting long story short, he, as he will explain, more or less fell in love with it, saw the great opportunity and between the two of us, he agreed to take over as full-time CEO, which the board's absolutely thrilled with and hopefully the market is as well as seen by the recent increase in share price.

With that introduction, I'd like to hand it over to Steve, who'll tell you a little bit of why he's interested and then run through the presentation. So, we look forward to the presentation, and then please, if you have any questions we'd love to hear them. Okay, Steve, over to you. Thank you.

**Dr Steven Gourlay:** Thanks Geoff for that warm introduction. I'm very pleased to be here as Geoff said. My job in this presentation is really to explain to you why Actinogen is such an interesting opportunity and a great fit for me, in my experience of early, mid-stage and late-stage drug development. Fundamentally there are three things; we know the drug works, we know the drug is safe, and we have full funding of $15 million in the bank, which will cover the three different clinical disease programs for the phase 2 studies we have planned. So that's the fundamental, and I'll come back to that a couple of times during the presentation.

As I became enamoured with the stage of development that Actinogen has with its small molecule, I also tipped over $300,000 of my own money into the company as part of a shortfall placement prior to my appointment. I also did this at Principia, my previous job, because I like to invest in the companies that I really believe in, where I have a role to play in management.

So fundamentally we now have multiple shots on goal, are planning a series of exciting upcoming trials, and we have a good team of folks to help progress that pipeline.

An overall snapshot for Actinogen; there's a number of important features and I'll just touch on a few of them. We have demonstrated rapid onset of clinical activity, in particular, improvement in memory, attention and cognition in human subjects within two weeks of onset. Our molecule is an 11β-HSD1 enzyme inhibitor that gets into the brain, unlike most small molecule enzymes and previous drugs that were targeting this enzyme. It is safe and well tolerated with more than 200 subjects treated to date, we've got extensive regulatory toxicology preclinical animal work generated already, and a number of very attractive indications that we can pursue in addition to Alzheimer's disease, which the company has been looking at before. I'll talk to you in some detail about Fragile X, and there is a third undisclosed indication that I'm very excited about, that we'll be able to talk about later in the year.

We have good patent protection and a strong cash balance of $15.2 million as of the 31st of March. The molecule itself is, as I said, a small molecule meaning it's a pill or a capsule. In this case, we have a capsule which is administered just once a day, which is ideal for commercial launch later in its development. It gets into the brain and is able to inhibit the production of the stress hormone, cortisol, as it is transformed from inert cortisone to cortisol. Elevated levels of cortisol in the blood and the brain have been associated with poor cognition and a number of different diseases, including Alzheimer's disease, Fragile X, Schizophrenia, to a certain extent Diabetes, and quite a few other diseases. So, dysregulation of cortisol, the stress hormone, is a really interesting target. People have not been able to go after this adequately before because molecules have not had good brain penetration, but our molecule does.

As well as having demonstrated cognitive activity in humans, so we know that it works in the brain, we've also been able to measure the pharmacodynamic activity of the drug by measuring different hormone levels in the blood. We know that even at a modest 10 milligram dose, which we are using for future clinical trials, we see full pharmacodynamic activity. As well, we have seen cognitive activity before with the 20 milligram dose.
We have a manufacturing process that is relatively straightforward and is being scaled up. The FDA recently granted us a valuable, Rare Paediatric Disease Designation for Fragile X syndrome, and I'll explain what that is and how valuable that is a little bit later in the presentation. We have that $15 million of capital, and we have a comprehensive dataset of human clinical data as well as scientific literature on this enzyme target. So, we're well-placed to commence multiple phase 2 trials in the near term.

Our pipeline slide shows three separate rows. The XanaMIA study, which is commencing in a few months' time, is different from what was originally envisaged because it now has what we call a "dose-ranging" Part A, or front end, to explore 5 and 10 milligram doses versus placebo. It is very similar to a study called XanaHES that the Company performed previously, where cognitive improvement was showing at a 20 milligrams dose as early as two weeks after therapy commenced. Essentially, we're adding 5 and 10 milligram groups into that dataset so we can confirm the minimum effective dose for this drug in cognition. Based on our pharmacodynamic work, including human PET data, which I will show you, we believe the 10mg and possibly the 5mg are fully pharmacodynamically and clinically active doses.

The second part of this study will be in patients who have documentation of Alzheimer's disease with modern biomarkers measurable in blood. This is a new ability of ours to be able to measure that in the last couple of years, as the field of Alzheimer's has developed. These patients will be early Alzheimer's patients who are not yet having any functional difficulties but are having some difficulties of memory and have a positive biomarker.

The first part of this study will read out in the first half of 2022, so it's a fairly quick study, and the second part will read out a year or so later in 2023.

The second program is our Fragile X program. Fragile X is a disease with no approved drugs and it's the commonest genetic cause of Autism and mental retardation. We are in the middle of preparation for discussion with the FDA, and soon after towards the end of the year we'll be commencing what we're calling the XanaFX study, which is a phase 2 study in adolescent males aged 12 to 18. This study will report out in the first part of 2023.Thirdly, we have an additional indication which we are finalising. There's a short list of possible targets, which include schizophrenia and diabetes - where patients do have cognitive impairment, but there are other diseases that we're interested in as well and we will disclose more about that at a later date. However, for the target indication we have in mind, the phase 2 trial for that is covered by the amount of capital we have.

In the next few slides I'm going to talk a little bit about Alzheimer's disease and the background data to our molecule in patients and related studies. So, the XanaMIA study will do its first part in healthy elderly folks. When I say elderly, I mean 50 years and above like me, and this is the same population that we studied in XanaHES. In Part B, we're using Alzheimer's disease patients with very early stages of the disease - this is what we call mild cognitive impairment. The market for Alzheimer's disease through the spectrum is very, very large; some would put it at $14 billion in the coming years, it's probably even greater than that. We are using in our program, the most modern and up-to-date assessment of biomarkers and endpoints, which makes finding and proving cognition in patients much more likely to succeed than in studies that were designed 5 or 10 years ago, where the biology and the endpoints were relatively poorly understood.

The XanaHES study achieved breakthrough results by demonstrating cognitive improvement on working memory, visual attention and psychomotor function with what we call a Cogstate Neuro Test Battery. This is a modern computerised test done on an iPad, which is much more sensitive than the traditional old fashioned Alzheimer's disease measures to look at cognition, and it's something that is improved within two weeks of taking the Xanamem drug. This was done in 30 patients who were taking the drug versus 12 patients with placebo. In the new study, we'll be doing something with a similar number of patients. We have recently drawn towards the end of our human PET nuclear brain scan study, and in this study, a special tracer is used to show blockage of the target enzyme in the brain, proving that our drug is working in the brain and the extent to which it's inhibiting the function of that enzyme. At baseline, when you look at these scans, you see a glowing picture of enzyme activity, which is completely suppressed by doses of 10 and 20 milligrams of Xanamem and nearly completely by 5 milligrams of Xanamem.

These data are very strong indicators that the minimally effective dose is likely to be 5 or 10 milligrams and not higher and this is consistent with all the data we've generated throughout the programme with other measures such as hormones measured in the blood.

So the redesigned XanaMIA study is now going to study a modest sized number of patients who are healthy, but may be taking normal medications for older subjects, and will be aged 50 years and above. We'll be using the sensitive Cogstate Neuro Test Battery as we did before and adding to it an endpoint called the Digit Symbol Substitution Test (iDSST), which is a very old fashioned, nearly a hundred year-old paper test that's been computerised to be used with Cogstate, and it has been used by the FDA to approve the cognitive enhancement claim of an anti-depressant called vortioxetine. So, we'll be including that and doing the doses of 5, 10 and placebo.

Subsequently, we'll be taking those patients with early Alzheimer's disease, and these patients won't have functional impairment due to their disease. They will have had a blood test to confirm that they've got Alzheimer's, for example, amyloid measured in the blood. We'll be using those same modern and sensitive cognition tests called Cogstate and the iDSST from Part A and introducing other cognitive measures that are

acceptable to regulators and probably going to be used in later studies.

So essentially, we're doing the minimally effective dose in the first part and the efficacy in the second part and at the end of that study, we will be able to say, without question, that Xanamem improves cognition in patients with Alzheimer's.

The next section I'd like to talk about is Fragile X syndrome, which is the commonest genetic cause of developmental problems including Autism and mental retardation, and is a significant unmet medical need. Should we be successful in our phase 2 study in this disease, there would be a huge global groundswell of support from patient organisations as well as physicians involved in this field because of the lack of any approved medications. Currently these children, if they have issues with anxiety or behavioural problems, take a fairly heavy duty medication designed to suppress individual symptoms, which is not ideal.

Currently, while there are no approved drugs to treat Fragile X, there are a very small number of companies around the world trying to develop drugs. Most of those have been unsuccessful in showing changes in endpoints. As an example, one drug, which is a CBD cannabinol extract, had an effect on one domain of testing, but the barrier to continuing to develop these drugs is relatively low because there are no approved drugs - so we believe that company is going forward to continue their work with the FDA.

We have been awarded a Rare Paediatric Disease Designation and we're eligible for Orphan Drug Designation as well. This is a very attractive designation because it gives you priority review, meaning it speeds up the FDA's review when you apply for marketing approval. It also gives you a priority review voucher, which you can trade for example, to any big pharma, and these have been sold in recent times for 100 to 125 million USD, so it's a very valuable designation should we get Fragile X approved as our first indication. Fragile X basically represents our "fast-to-market" strategy.

The data we generate in Fragile X, assuming positive results can be leveraged in other related indications, for example Autism Spectrum disorder. Even just Fragile X alone has a substantial global market size in the order of $250 million plus. A little bit about why we think this is going to work in Fragile X; Fragile X children do have raised levels of cortisol compared to other normal children, however, the strongest direct evidence comes from a knockout mouse model where you can actually create a mouse with Fragile X. Those mice have considerably elevated levels of anxiety, which are normalised completely by inhibition of the 11β-HSD1 enzyme. So, this is very strong evidence that our drug might have a dramatic effect on anxiety, but in addition, the hope is that we'll also positively improve cognition and learning to a certain extent, perhaps speech and language, behaviour problems and possibly even sleep. All of those endpoints will be explored in our phase 2 clinical trial.

So that trial will be, as all our clinical trials planned in the near term are, done in Australia, taking advantage of the Australian tax credit and also the very high quality and suitability for submission to the FDA and the European Medicines Association for clinical trial data generated in Australia. The Fragile X trial will be around 30 or 40 adolescent males, double-blind, placebo controlled, quite rigorous, and we will be evaluating all of those different dimensions I mentioned just before. So the upcoming milestones are; that we'll get feedback from our interaction with the FDA in the middle of the year and we'll be commencing the XanaFX trial in the second half of the year with top-line data expected from most likely early 2023.

Overall, our outlook is that we're in a phase of accelerating clinical development in three different indications. Those data will be used to generate the protocols to take those indications further, assuming they're positive, but of course also to engage with big pharma partners, as we always do. We've been engaging with some granting bodies as well, but we're not really counting those granting bodies in our P&L or forecast. And of course, when we consider other company valuations in the US who are working in the Alzheimer's field, our current valuation is extremely modest compared to valuations for some companies, such as a company called

Athira, and various others with valuations north of 350 million USD and beyond the billion dollars. So, I consider this position that Actinogen finds itself in, with a molecule that works and multiple indications with very strong rationale, to be a remarkable opportunity - one that I'm super excited to help with over the coming years.

The next steps or catalysts are: we will read out the Part A data in early 2022, the XanaFX data in early 2023, and the XanaMIA Alzheimer's disease patients sometime in 2023. We'll be pursuing, as we always do, strong partners from partnership discussions, academic collaborations, and the appropriate grants, and expanding the team to help us meet these timelines. We're always pursuing publications and suitable scientific presentations on the drug and the target.

I will just, again, conclude that we are in a remarkable position to start phase 2 in multiple indications with a drug that works, is safe, and we have the funding to cover all of those phase 2 clinical trials I discussed today. And with that, I'll give it back to the moderator to ask for questions.

**Operator:** Thank you. If you wish to ask a question, please press star one on your telephone and wait for your name to be announced. If you wish to cancel your request, please press star two. If you are on a speaker phone, please pick up the handset to ask your question. Your first question comes from Alan Sauran, a retail investor. Please go ahead.

**Alan Sauran:** Hello, I'm a retail investor, I've asked this question two years ago - Dr. Brooke may recall it. It's about dosing frequency, and I was given one answer at that time, but I suspect the answer may be different today and I'd like to understand why. So, the dosing frequency in 2016, the University of Edinburgh published a paper on UE 2343 which is Xanamem, and they said that the terminal plasma half-life was 10 to 14 hours. So, 12 hours on average, which means that after 24 hours you're left with only one quarter of the concentration. Can you please explain why it is suddenly appropriate now to have once daily dosing? Thank you.

**Steven Gourlay:** Sure, my pleasure. Thank you for the question. So, while it's true with a half-life of 10 to 14 hours with a single dose, most of the drug will be gone - about a quarter will be left after 24 hours. When you take the drug every day after about five half-lives, or 50-70 hours, you're then at steady state. So when you take a drug once a day with a half-life of 10 to 14 hours, it's pretty much always given as a once a day because the steady state levels are quite high, and so you just see a modest variation between the peak and the trough between doses, and furthermore, the new data that I was lucky enough to inherit is that we have looked at differences in timing of dosing in our PET study, which confirms that you see good enzyme inhibition with once a day dosing. So, we do have verification of that with this measure of enzyme inhibition in the brain. So, it's a great question, but I think I feel very comfortable that once a day is absolutely the right approach.

**Alan Sauran:** My supplementary question. If you do some simple graphing, you will find out there is no steady state with a half-life of 12 hours, it'll be going up and down and the maximum over the 24-hour cycle is very different from the minimum, and the answer I was given two years ago is either slow-release formulation or twice daily dosing and I was given that by both the CEO and Chairman. So, simple mathematics will show that your answer is wrong, and I am totally confused about the entire company direction, simple mathematics is correct.

**Steven Gourlay:** Well, I mean, with all due respect, I appreciate your point of view. I'm trained in clinical pharmacology, and if you were to ask the clinical pharmacologists in all of the pharma companies across the world what they would normally do with a half-life of 14 hours, it would be once a day therapy - I can assure you. And furthermore, as I mentioned, we have confirmed that it's working exactly the way we want by actually directly measuring it in the brains of humans. So, your assumption about that variation between peak and

trough at steady state - it's not of concern to me, and I don't think it should be of concern to anybody else, given that we've verified the action of the drug in the body so completely.

**Operator:** Thank you. Once again, if you wish to ask a question, please press star one on your telephone and wait for your name to be announced. We'll wait for more questions to enter the queue. Thank you.

Your next question comes from Tony Ciro, a private investor. Please go ahead.

**Tony Ciro:** Hi, thank you for taking my call. Just a very simple question here. I mean, I appreciate that the molecule is being used to fight serious illnesses like Alzheimer's and other related diseases, but what I don't seem to fully comprehend - if the molecule has been proved effective to reduce cortisol levels, which is related to stress and anxiety, why wouldn't that be a sufficient unmet medical need? There's a lot of people that suffer stress and anxiety without having to develop Alzheimer's and other major mental illnesses. Why couldn't we just do a study to prove that we've got a drug here that reduces the cortisol levels, it reduces stress and anxiety, and that's a huge medical problem in Australia and overseas.

**Steven Gourlay:** Look, that is a great question and the principal answer is that regulators like the TGA and the FDA will not be keen on approving a drug for general use in what they consider to be a healthy non-diseased population, without hundreds of thousands of patients' worth of safety data, because it's not a disease per se. So, from a drug development point of view, one needs to approach recognised diseases that the FDA and other regulators will agree with. However, in the future of development of these types of drugs, you could imagine maybe that you would be able to use that in much milder or non-diseased patient population. Perhaps in the future, but it's not something that we have on our regulatory radar from a pragmatic point of view.

And then I would just say one other thing: high doses of this molecule have been shown to reduce levels of cortisol in the blood, but the doses we are taking forward as our fully pharmacodynamic dose of 10 milligrams or less, those doses don't actually change levels in cortisol. And the reason that's good is that there's lots of regulation in the body to keep it very even, because it's an essential part of cell function and really what we're doing is inhibiting stress-related levels in the brain, which of course we can't measure directly. Did I answer your question sufficiently there?

**Tony Ciro:** Yeah, look, I think you have. I mean, we're always told by medical practitioners that stress is a significant problem - mental and emotional stress, which really there aren't many drugs there to use. And look, you've explained it and I think now I understand why that's the case. Unfortunately, I think Actinogen has an incredible opportunity in reducing stress, which is really associated with so many illnesses. So, if we're successful with Alzheimer's, I think the breadth of illnesses that we could probably treat are so many.

**Steven Gourlay:** Well, thank you for that comment, I think that is absolutely true. That's part of the reason I'm here. I'm very excited to be able to do three different diseases at once. That's what I love to do.

**Tony Ciro:** Thank you.

**Operator:** Thank you. That's all the time we have for questions now. I'll hand back to Dr Gourlay for closing remarks.

**Steven Gourlay:** Thank you all for joining us today. It's a pleasure to meet some of you and I'd just like to reiterate why I personally invested, and why I'm excited to have taken the role to join Geoff and the rest of the team at Actinogen. I am convinced, based on the data we have in hand today, that we have a drug that works to improve cognition. We understand the dose, we understand clinical safety with a large safety database, and we are poised to rapidly enrol these three phase 2 studies with the money we have in the bank

currently. So, I'm very focused on operations and execution of those trials, and very much looking forward to the future.

**ENDS**


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***Announcement authorised by the Board of Directors of Actinogen Medical***

**About Actinogen Medical**
Actinogen Medical (ASX:ACW) is an ASX-listed biotechnology company developing novel therapies for neurological diseases associated with dysregulated brain cortisol. The company is currently developing its lead compound, Xanamem™, as a promising new therapy for Alzheimer's Disease, Fragile X syndrome, and other potential neurological diseases. The cognitive dysfunction, behavioural abnormalities, and neuropsychological burden associated with these conditions is significantly debilitating for patients, and there is a substantial unmet medical need for new and improved treatments.

**About Xanamem™**
Xanamem's novel mechanism of action works by blocking the production of intracellular cortisol – the stress hormone – through the inhibition of the 11β-HSD1 enzyme in the brain. There is a strong association between persistent stress and the production of excess cortisol that leads to detrimental changes in the brain, affecting memory, cognitive function and behaviour and neuropsychological symptoms.

The Company has studied 11β-HSD1 inhibition by Xanamem in more than 200 volunteers and patients, finding a statistically significant improvement in cognition over placebo in healthy, older volunteers. A series of Phase II studies in multiple indications will be conducted to further confirm and characterise Xanamem's efficacy and safety.

Xanamem is an investigational product and is not approved for use outside of a clinical trial by the FDA or by any global regulatory authority. Xanamem™ is a trademark of Actinogen Medical.

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