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**Voice-over:** The *BioWorld Insider Podcast*.

**Lynn Yoffee:** This is the *BioWorld Insider Podcast*. I'm Lynn Yoffee, BioWorld's publisher.

Amyotrophic Lateral Sclerosis. Incurable, and with no clear cause in most cases, ALS is a progressive, fatal neurodegenerative disease. It attacks neurones that control voluntary movement. As those neurones die, people with ALS experience a gradual loss of muscle movement, speech, swallowing, and eventually the ability to breathe without mechanical ventilation.

Also known as Lou Gehrig's disease and motor neurone disease, ALS affects a little more than four people out of every 100,000, or about 343,600 globally. It's diagnosed most often in older white men, but it also affects women, younger people, and people of all races. Each year, there are an estimated 105,000 new cases.

So far there are just two drugs that have gained broad regulatory approvals to slow the progression of the disease. Riluzole, a medicine first approved in the US in 1995 and now sold by several drug makers as a generic, and Mitsubishi Tanabe Pharma's Radicava, a medicine first approved in Japan in 2015 and then approved in the US in 2017. Just one additional therapy has won approval globally, the autologous bone marrow-derived mesenchymal stem cell therapy, NeuroNata-R in South Korea.

Still, most people with ALS live just three to five years beyond the first signs of the disease.

On the precipice of joining those medicines perhaps is AMX0035, a candidate from Amylyx Pharmaceuticals now under review at the FDA with a June 29th PDUFA date. However, the company will have to overcome the March vote of an FDA Advisory Committee that, while split, ultimately voted that the company's Phase 2 study called CENTAUR did not demonstrate substantial evidence of effectiveness to support approval.

We're pleased to have Amylyx's Co-CEOs and Co-Founders, Josh Cohen and Justin Klee joining us today to talk about what's next for the programme.

Not far behind Amylyx is Clene Nanomedicine with its gold nanocrystal suspension, CNM-Au8. It's an experimental therapy in phase 3 testing as part of Massachusetts General Hospital's HEALEY ALS Platform Trial. Results for those experiments are expected in the second half of 2022.

Dr. Zachary Simmons, a professor and vice chair for research in Penn State's Department of Neurology, is an investigator in the HEALEY ALS Trial. He joins us today, along with the president and CEO of Clene, Rob Etherington. They'll be speaking with BioWorld managing editor, Michael Fitzhugh. Michael?

**Michael Fitzhugh:** Thanks, Lynn. Thanks to all our guests for joining us. I'm expecting we're going to cover a lot of ground in this episode. I just want to outline a little bit about what's ahead. We're going to start with a big picture view of what it's like for ALS patients post-diagnosis in developed markets right now.

After that, we'll move on to talking about a major platform trial underway at the Sean Healey & AMG Centre for ALS at Mass General, and the Clene's gold nanocrystal suspension, one of the potential therapies in testing in the trial.

Finally, we'll dive into the timely story of Amylyx's AMX0035, a fixed-dose combination of sodium phenylbutyrate and taurursodiol.

Dr. Simmons, let's start with you. Your workaround ALS has covered a lot of ground from the founding of an ALS Clinic at Penn State nearly 30 years ago to evaluate a newly referred patients with possible ALS. What's it like for ALS patients today? What's the standard of care?

**Dr. Zachary Simmons:** Thank you very much for asking me to be here today. The biggest change that I've seen over the past 30 years is the increasingly widespread availability of the multidisciplinary clinic as the standard of care. The term multidisciplinary clinic means that individuals with ALS and their caregivers are seen at each visit not solely by their physician, but by a team of healthcare professionals--a nurse, physical and occupational therapist, speech therapist, dietician, social worker, mental health professional, a respiratory therapist, and in our clinic and some others, a pastoral care counsellor.

The goal is to try to address the many needs of these individuals, while at the same time, reducing the burden associated with multiple different visits scheduled at different times. We know that multidisciplinary care extends survival and improves quality of life, which is why it has become the standard of care.

Other aspects of standard of care involve the user of non-invasive ventilatory devices for those individuals whose breathing capacity is below a certain level, the provision of equipment and supplies to improve safety, and increase mobility and independence, and the prescription of FDA-approved medications for slowing the progression of ALS itself, and for helping the many symptoms our patients develop, such as depression, anxiety, problems with secretions, and muscle cramps.

**Michael:** That multidisciplinary care is much more immersive approach than I realised. Why do we need new medicines? What will new medicines bring to the table in that bigger wraparound picture for patients?

**Dr. Simmons:** That's a very important question. If you think about it historically, as was said in the introduction, the first drug that was approved by the FDA for ALS, riluzole was approved nearly 30 years ago. What riluzole has been shown to do is to modestly prolong survival. The second was edaravone (Radicava), which was approved for intravenous administration a few years ago, but the IV form is somewhat burdensome to patients because of its frequent administration. It usually requires the placement of a catheter or a port. . The FDA has just recently approved an oral form of the drug. Edaravone slows ALS progression in some patients and can be given along with riluzole.

There are currently no other FDA-approved drugs for altering the natural history of ALS, although as was mentioned earlier, AMX0035 is now being considered for approval by the FDA. Despite these advances in treatment, the average lifespan for someone with ALS, from the time of onset of symptoms until death, is still less than three years. There are definitely some whose illness progresses slowly and who survived 5, 10, or even 20 or more years, but these still constitute the minority of individuals with ALS. New medications are needed to improve this outlook by extending survival, or better yet, stopping ALS progression together, and putting people into remission the same way that cancer drugs do.

**Michael:** I knew that there's some incremental efforts going on. I think Radicava is being developed as oral therapy. I think that there's an oral form of Radicava being developed, but what improvements overall can we expect from a new generation of ALS medicines? Is it primarily incremental life extension, or as you suggest, maybe is there a possibility that we might see in medicine that actually stops the progression of the disease altogether?

**Dr. Simmons:** My hope and the hope of most of those I talk to in the ALS community of course is for a cure. I still hold that out as the ultimate goal. My hope for the next generation of medications for ALS is really focused on prolonging survival by dramatically slowing progression and ultimately stopping progression of ALS altogether, which of course would lead to better function and a higher quality of life for a longer period of time.

Our current trials, including those in the HEALEY trial, are based on the goal of slowing progression. I foresee a time in the not too distant future when individuals with ALS will be treated most likely with a combination of several medications, a cocktail, if you will, that each address a different mechanism by which ALS damages motor neurones. My hope is that by combining these medications, the goal would be to address many different pathways that malfunction in ALS and result in the loss of motor neurones. I think that's the next realistic goal.

This is why the current trials are investigating medications that act on so many different biological pathways in the nervous system. Aside from these, of course, there's also considerable research into stem cell treatments and genetically-based treatments. Although these have not yet shown success, I'm hopeful about those as well.

**Michael:** You mentioned the HEALEY ALS Platform Trial, can you just tell us a little bit about how platform trial maybe differs from the more common randomised controlled trial of the type that I bet our listeners are pretty familiar with.

**Dr. Simmons:** Yes. The HEALEY trial is an exciting development in the way that we evaluate drugs for ALS. The goal is to permit the more rapid development of new treatments by requiring fewer individuals to assess each new drug. The leaders in this have been the group in MGH.

The methodology of the trial is that several drugs are tested once, or they're tested in rapid succession using a protocol that's very similar for all the drugs tested so that the startup for each new drug is simpler and shorter, and then individuals who qualify for the trial are randomly assigned to a drug or placebo group, but the ratio is 3 to 1, meaning that three people in the trial receive the study drug for every one who receives placebo, because the placebo group is shared by all of the trial arms.

The HEALEY trial began with three drugs, all of which have completed their double-blind phase and for which results should be available later this year. Since then, a fourth drug has been added to the regimen and has completed enrollment. Fifth drug is now open for enrollment, and a sixth is being planned.

The placebo-controlled phase during which the study participants and their physicians do not know whether they're receiving drug or placebo lasts 24 weeks and is followed by an open-label phase during which individuals are permitted to continue in the trial with the assurance that they'll receive the active drug, or they can choose to be randomised back into the trial again if they still qualify in order to be in a different arm. This study of so many new drugs in such a short period of time has really been a game changer for ALS treatment.

**Michael:** That's amazing. It's such a complex and intricate design, but it sounds so efficient and obviously so needed right now. As you mentioned, we're going to be seeing results from that trial later this year. I think that there's going to be readouts perhaps if I understand the trial correctly from UCB's zilucoplan, Biohaven's verdiperstat, Prilenia Therapeutics' pridopidine, and Seelos Therapeutics' trehalose, which, oh my goodness, probably murdering the pronunciation of that, as so often [laughs] I do with these drug names.

The one that I really want to talk about next is Clene's CNM-Au8. *BioWorld Insider* listeners may recall that Clene's Chief Medical Officer, Rob Glanzman, joined us in Episode 14, Aduhelm's Hard Lessons and What It Means for Other Alzheimer's Drugs. Now, we're pleased to have Clene's President and CEO, Robert Etherington, joining us. Welcome, Rob.

**Robert Etherington:** Thank you, Michael, for the introduction. Thank you for inviting me.

**Michael:** So glad to have you here. Tell us a little bit about CNM-Au8. What is it? How's it meant to work?

**Robert:** CNM-Au8 is a catalytically active nanocrystal. What that means by catalyst is if we hearken back to high school chemistry, a catalyst lowers an activation energy to achieve another energy. Our acid is a drug that patients drink every morning, orally, and there are a number of clinical studies currently underway, and, of course, ALS as we've been discussing but also other neurodegenerative diseases.

As a nanocrystal suspension, patients are actually drinking clean surface, which is to say no synthetic chemistry, highly faceted crystal of gold. Yes, it sounds very different than a classical approach. At the atomic scale we're talking, so that's 13 nanometres in size, which is to say so small that crystal of just atoms of gold can go inside the mitochondria.

Why that matters is because we see brain-blood penetration. We see that our drug is going straight inside the brain and driving an energetic response. What that means basically is that you and I, and the entire human family, we slow down as we get older, but in ALS, there's this massive disease insult that causes all of these neurological functional deficits of which Dr. Simmons just spoke of.

Our asset is giving the neurone--the basic essential component of how our bodies move and walk and talk and eat and chew and breathe, the neurone is getting the energy it requires to help against this assault and take care of its own housekeeping.

**Michael:** Wow, that sounds amazing. I have to say that the idea of drinking gold sounds really cool, just on the face of it. Now, back in November 2021, BioWorld reported about a phase 2 trial in which CNM-Au8 didn't meet the primary and/or secondary endpoints of the study that was called RESCUE-ALS. At the time, in the face of that, you were really excited about the data and other ALS experts around the time were as well. Can you tell us what you saw in that data that's really encouraged and fueled further clinical work in the programme?

**Robert:** Sure, so just a little bit of background. That was a small study in ALS, a phase 2 proof of concept as we call it in drug clinical development. Yes, we missed the primary endpoint that was using MUNIX, which stands for motor unit index. The motor unit is the way that our brains talk to our muscles. In this case, we were looking specifically at the connection to the muscle of the hand and the arm and the leg.

Though we had a very solid trend towards changing muscle function, we did not meet the endpoint with statistical significance. However, we saw a lot of different things that we weren't expecting to see. The basic thesis here is, as I said earlier, if we can target energy metabolism, the way our body effectively uses energy, then CNM-Au8 may be able to protect motor neurones and restore function.

We saw a statistically significant quality of life. We saw statistically significant disease progression changes. That is, patients on CNM-Au8 had less chance of needing a tracheostomy to breathe. They had less chance of needing a gastrostomy tube to get all of their food and water. They had less of a chance to require full-time BiPap, which is basically how we breathe.

We also saw a continuing developing impact on long-term survival which is most important. We literally just presented data this morning in fact that suggests that against placebo, we have an evolving and emerging improvement in survival. That data was presented this morning at the ENCALS meeting, and we just placed it on our website.

What we've learned is that we were looking at this MUNIX, which is an important biomarker, but it wasn't the whole story. Now we are awaiting the ALS HEALEY study as Dr. Simmons just referenced, because our asset was one of the drugs chosen for that, is already completed all of its patient enrollment, and that data will be coming in a number of months in the second half of this year.

**Michael:** I should have said it earlier, but Dr. Simmons is the primary investigator for that arm of the trial testing CNM-Au8. Am I getting that right, Dr. Simmons?

**Dr. Simmons:** The primary investigator at our site and down of the overall study.

**Michael:** Got it. Sorry about that. Great.

**Dr. Simmons:** That's okay.

**Michael:** Thank you.

**Dr. Simmons:** It's okay.

**Michael:** Dr. Simmons outlined real advantages of a platform trial from a clinical standpoint. I was wondering from an operational standpoint, as the head of a company leading this drug programme, from the company side, what are the advantages of participating in that type of trial versus another?

**Robert:** We were thrilled that we were selected. There was a number of companies that applied, and they only were able to select a relative few. As Dr. Simmons mentioned, just three to begin, of which Clene was one of those first three, patients love such a study because when they come into the study, they have a less risk of going on placebo.

The company, in this case, Clene, we love the study because it enables us to actually share the pooled placebo from the other arms. There's two advantages. For the patient, they're more likely to get on active drug. For the company, we can share the data from the placebo from the other regimens. The consequence of this is we could increase our powering.

Also, I should note, the HEALEY study does not look at MUNIX, this biomarker that I referenced in RESCUE. On the contrary, it looks that ALSFRS, which is a functional measure of ALS, and Dr. Simmons might wish to comment further, but in my simple mind, it's just basically how you move and walk and talk and eat and chew and breathe. That's what we are studying in our case. The HEALEY study also looks at survival. How patients survive and live, and unfortunately, pass away through the course of the study.

**Michael:** If the phase 3 readout from HEALEY ALS turns out positive, then what's next for the programme?

**Robert:** The agency has already said to Harvard, who is the sponsor of, and effectively "owns" this investigational new drug application for this programme, that this is potentially a registration study. For those companies or company, in other words, a number of the programmes of the study. A number of the regimens could potentially apply for the agency for clinical approval.

Clene is quite excited because taken on top of the emerging data that we weren't expecting to see in our exploratory endpoints from RESCUE, which were positive. If we see those same results occur in this much larger, it's six to eight times larger, I should note. The HEALEY study is six to eight times larger than RESCUE. If we see those same study results in HEALEY, then we could take the drug to the agency and ask them in a new drug application for clinical and commercial approval.

**Michael:** Is that something that would potentially happen early next year?

**Robert:** Yes, I think it could happen within the first half of next year indeed.

**Michael:** Excellent. Thank you, Rob, for telling us about all that.

I want to move on to talking about another drug that is not part of the HEALEY trial, but it's been very much in the spotlight recently, Amylyx's AMX0035, or 0035, I should say. Here to tell us about that are Amylyx's co-CEOs and co-founders, Josh Cohen and Justin Klee. Welcome, guys.

**Justin Klee:** Thanks so much for having us.

**Josh Cohen:** Absolutely, thank you.

**Michael:** Glad you're here. I think the Amylyx story really speaks to the urgency of the need that the ALS community appears to feel very understandably around gaining access to new therapies. Can you tell us a little bit about the March 30th Ad Com meeting that gave voice to that?

**Josh:** Absolutely. Maybe first to give a little bit of background. AMX0035 is a drug that targets some of the key underlying pathways of cellular death. The drug was studied in a large randomised placebo controlled study across many sites in the United States. Those results were published in *The New England Journal of Medicine*, and more recently in two additional publications, in *Muscle & Nerve* and *JNNP*. Broadly, what we saw was that people randomised to AMX0035 retain function longer. We've published a survival benefit as well in *Muscle & Nerve* and in other journals and publications.

At the Ad Com, I think it was primarily a biostatistical debate about different ways to model disease progression and model ALS clinical trials. We had designed all of our biostatistics and modeling with the team at Mass General, and it's all a lot of advice and guidance from the ALS community as we built and designed the trial. We felt that we really had designed this in the state of the art, best possible way. I think we were pretty pleased too when the biostatistician on the panel also voted in favor of the drug, and in his comments also stated that he thought the the biostatistics were handled really well.

I think overall, we're pretty thrilled about our data. We're really excited to be able to publish it in a place like *The New England Journal of Medicine*. This is the scientific process. I think the FDA's job and the job of an advisory committee is to poke and prod, and pressure test every little aspect, the data and otherwise, but I think exactly as you said and as was highlighted in the open public hearing, this is not a disease where we need to be too nitpicky or really-- You hear from people with ALS and what they're thinking about is potentially a death that basically involves suffocation, or not being able to speak or eat their favorite food or hug a loved one. I think for them, every day, every hour matters. This is a fast disease, and median survival about two years. I think there really is a lot of urgency.

Hearing from from all the patients and caregivers and advocacy groups and doctors during the public hearing just really highlighted what we're fighting against. I think we had Amylyx really shared commitment that we're going to keep fighting until this disease is done, and that's what we're here to do.

**Michael:** I know that that fight obviously can take many forms, whether through advocacy or through working with patient groups. Obviously, there's the clinical aspects. I think that I recall correctly running a phase 3 trial. Even as we're recording, you're presenting some new data, a new post-hoc analysis of data from the phase 2 trial that Ad Com looked at. Can you tell us a little bit about the work that's been underway since the outcome, and this presentation today at ENCALS?

**Justin:** Yes, I'd be happy to. Thanks so much, Michael. This is Justin. As you said, we're continuing to generate data on AMX0035 through our Phase 3 PHOENIX trial. That's both here in the US, as well as in Europe. It's a collaboration through the NEALS organisation, which is the largest ALS hospital consortium in the US, ENCALS/TRICALS in Europe, which is the largest European consortium.

For us, we always tried to bring all the different stakeholders together and an opportunity to have the leaders of the field working with us on this phase 3 trial is tremendously exciting. Enrollment is ongoing as we speak. We do not expect top line results though until probably early 2024. I think while we're tremendously excited about the trial and the data that will generate from it, I think the unfortunate reality that we're facing is that by the time the PHOENIX trial readsout, many people living with ALS today won't be here anymore to see those results. I think it just constantly reminds us how precious time is for people with ALS.

To the point on additional analyses, including what we're presenting at ENCALS, I think that Josh highlighted quite a bit of it. We had the first two foundational publications, first in *The New England Journal*, and then in *Muscle & Nerve* looking at the 24-week primary endpoint that was the ALS functional rating scale, and then the longer term survival benefit.

Now we've looked at two additional sets of things. First, our pre-specified analysis on key study events. That's looking at things like time to hospitalisation, time to tracheostomy, things that are really, really important for people with ALS and people who care for people with ALS. Then we've published another follow-up publication to our first one, in *Muscle & Nerve.* Again, in *Muscle & Nerve,* looking at the long-term survival analysis, both an update to the survival analysis, as well as leveraging methods that have been used in oncology to look at.

We, after 24 weeks, allowed, all participants have gone to active treatment, which is a wonderful thing to do. Of course, if people on placebo are getting active treatment, it may impact the treatment benefit that you're able to see. Groups in oncology have worked out methodology to try to account for this. What we've seen is that when we use these different methods, the survival benefit from AMX0035 in the study ranges from a benefit of about 10.5 months to as much as 18 months compared with the 6.9 months we saw originally. We're really excited about that additional data, both that will be generating from the phase 3 trial, as well as the new analysis that we've published and are presenting right now.

**Michael:** With the PDUFA on June 29th, what are you expecting in very near horizon? Do you anticipate receiving a complete response letter, and moving ahead with the phase 3 trial? Where do you think things are going to go?

**Josh:** Yes, we're still under review. There's probably not much we can comment on at this point regarding the outcome of that review. I think we have some really, really strong data and science behind the programme, and the phase 3 is ongoing regardless. I don't think that the PDUFA outcome really affects the phase 3 all that much. I think maybe just to add too, the drug is also under review, not just in the US, but also in Canada, and in Europe. We're continuing to evaluate other areas, territories, et cetera, where that might be appropriate to look to as well.

I think at the end of the day, our goal and our decision-making is pretty simple. We're trying to do whatever can help people with ALS and whatever we can do to improve their lives as quickly as we possibly can, acting with urgency. We've always tried to take a very collaborative approach with the different health authorities, so we're going to continue doing that and making our best scientific cases and moving forward.

**Justin:** Michael, just to add one other thing too, just to react to something that Dr. Simmons who brought up earlier, who's a world expert. I think the point on, we so often focused on new treatments, which I think is of course critical, but the points Dr. Simmons was raising on multidisciplinary care, I just think, are wonderful and often maybe overlooked by folks like us who focus mostly on the industry.

I think it just highlights in ALS, we really need a community effort. It's a really tough disease, and I think the way that we're really going to solve it is both through treatment approaches, cocktail approaches as Dr. Simmons said, as well as the multidisciplinary care. I think as we go forward in all of this, our goal is also to try to be a good partner in the community, and continue to advance on all fronts including the treatment side.

**Michael:** Excellent. I think that it's clear to me that there's so much energy and effort, and just seriousness of purpose behind both of these programmes that we've talked about today, and the clinical side with Dr. Simmons is so instrumental. Really can't thank you all enough for joining us today.

It's been very interesting to hear about where things are with the development of new therapies in ALS, and a great learning opportunity for me, so thank you for that. I wish you all luck as your programmes proceed and trials unfold, and thank you for joining us today.

**Josh:** Thank you so much, Michael.

**Dr. Simmons:** Thank you very much.

**Michael:** Thank you.

**Lynn:** Justin, Josh, Rob, and Dr. Simmons, thanks for joining us today. As always, BioWorld will continue to keep you informed of all the most important scientific, clinical, and business updates. That's our show for today. If you need to track the development of drugs, turn to bioworld.com, follow us on Twitter, or email us at newsdesk@bioworld.com.

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**Voice-over:** BioWorld, published by Clarivate, is a subscription-based news service, but all of our COVID-19 content, more than 7,000 articles and data entries since the start of the pandemic, are freely accessible.

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