Clene Inc.

CNM-Au8 ALS Program Update

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PRESENTATION

Operator

Good day, ladies and gentlemen, and welcome to Clene's ALS Program Update Conference Call. All participants are in a listen-only mode. Later we will conduct a question-and-answer session and instructions will follow at that time. If anyone should require Operator assistance, please press star, then zero on your touch-tone phone. As a reminder, this call may be recorded.

I would now like to introduce your host for today's conference, Rob Etherington. You may begin.

Rob Etherington

Thank you for joining us on today's conference call. We hope that you had a great Thanksgiving last week with your family and friends.

I am Rob Etherington, CEO of Clene Nanomedicine. Joining me on this call are Dr. Benjamin Greenberg, the Head of Medical for Clene, Vice Chair of Clinical and Translational Research at his university; Dr. Jinsy Andrews, the Director of the ALS Center in the Department of Neurology at NYU Grossman School of Medicine and the principal investigator of our NIH sponsored EAP trial of which we are about to speak to; Michael Hotchkin, the Chief Development Officer, and Morgan Brown, our Chief Financial Officer.

During today's presentation we will make several forward-looking statements. We'll have no obligation to update these statements, but we encourage everybody to refer to our Form 10-K and Form 10-Qs that we filed this morning.

We are thrilled to stand before you today to present a very important key piece of data that we have needed for this entire year to support our accelerated New Drug Application submission for CNM-Au8 in the treatment of ALS. We have been working on this program now for 12 years and have been treating patients both in the randomized double-blind clinical trials as well as multiple—three and counting for ALS—expanded access protocols that enable participants' compassionate use of CNM-Au8, including critically, this one that we're about to speak to sponsored by the NIH.

We have previously demonstrated a meaningful survival benefit in ALS patients and significant decreases in the biomarker neurofilament light in our HEALEY ALS Platform Trial. The FDA wanted additional confirmation of our data sets, so let's turn now to Slide 3 in our deck and we'll speak to these.

The FDA told us in a September 30 meeting, the final meeting minutes of which we received a few weeks ago in November, the following statement: If you are able to provide substantiation of the effects on neurofilament light, we would be willing to consider the 24-week data from HEALEY and the post-hoc analyses on long-term survival if they are capable of providing the evidence that the change in neurofilament is reasonably likely to predict clinical benefit and potentially serve as a confirmatory evidence.

This statement, the latter piece of which is taken precisely from the accelerated approval statute, is where we're going to focus today.

We will tackle first, substantial neurofilament decline and substantiating biomarkers generally in the following slides, then we will talk about how neurofilament change is indeed associated with risk of death, and then we will review extensive evidence of the clinical benefit that we intend to submit as the confirmatory evidence, showing long-term survival from CNM-Au8.

We are profoundly grateful for the close collaboration and support from the entire ALS community, which includes patients, their families, caregivers, treating physicians, scientific researchers and all the many

people that work to support ALS patient associations, not only in the U.S. but around the world. I want to also thank the dedicated Clene employees who have got us here.

So now, Slide 2 represents the evidence that has come, or rather the statements that have come from the agency that have enabled the evidence that we are proceeding piece by piece. These are excerpted statements from the FDA letters to Clene that FDA said that we could look at an analysis of change from baseline for neurofilament at 6 months and longer in the EAP, an analysis of biomarker change for neurofilament in the open-label extension of HEALEY—that is those individuals that were on placebo and then converted, or that we could look at supportive biomarkers that are ALS disease-specific to also buttress or support the neurofilament seen in HEALEY. So, Clene has decided to tackle all three of these areas.

Let us turn to Slide 5 and have Dr. Greenberg explain what ALS disease relevant biomarkers are all about.

Dr. Benjamin Greenberg

Great. Thank you, Rob. Good morning everyone.

As was mentioned, there is an intense interest in looking at the proteins that can be released from different cells within the central nervous system as quantifiable markers of disease activity, both from a prognostic perspective and relative to a response to therapy. There are two that have gained national and international attention over the last decade in the setting of ALS.

The first, which is the more widely well-known marker neurofilament light chain, or NfL, is a normal structural protein within neurons. It's basically the scaffolding within the axon of the neuron, and as neurons are damaged by degenerative processes, the amount of neurofilament light chain that is released into the spinal fluid and ultimately the blood goes up over time. As we'll see in a moment, the level of NfL at the time of a patient's diagnosis with ALS can be prognostic for their disease course.

A second, lesser well-known protein but recognized by regulatory authorities and experts in the field is glial fibrillary acidic protein or GFAP, sometimes called G-FAP. This is a protein that lives in a glial cell within the brain, so while NfL is within neurons, GFAP is within astrocytes and it is well documented within ALS that as degeneration occurs, the astrocytes become reactive, they produce more GFAP and this gets released into the spinal fluid and ultimately into the blood, and it is a marker of that reactive astrogliosis, that astrocytic activity that is a hallmark of the pathogenesis of ALS.

If we go to Slide 6, what is important here is the clinical relevance of these protein markers. On the left, based on peer-reviewed literature over the years, is a predictive model based on an individual's baseline NfL level. This followed patients over time and documented the higher your NfL level at baseline, the more rapid your progression of the disease and the higher likelihood of mortality earlier in the course of your disease. So baseline neurofilament light chain was felt to be very clinically relevant to our ALS patients for predicting the future.

Likewise, GFAP shows a similar predictive capability. The higher the level representing more activated astrocytes, presumably because there's more degeneration going on, the faster a person will progress relative to their ALS diagnosis.

So from background literature, it is well-established that these protein markers can be predictive in patients. And interestingly, patients can have different combinations. They can be high on both markers, one or the other, or neither. So it was important for us and for our colleagues and regulatory authorities to look at these markers relative to the ALS populations we have studied.

It's with this as a background that I'm thrilled to turn things over to my colleague, Dr. Andrews from NYU, to talk about NfL and what's been discovered through the NIH-Expanded Access Protocol that she leads.

We'll turn to Slide 7, and I'll turn things over.

Dr. Jinsy Andrews

Thank you so much. I'm Dr. Jinsy Andrews and I'm the ALS Center Director at NYU, as well as the Clinical Trial Director. I'm also the Principal Investigator for the NIH-Expanded Access Program using CNM-Au8 in ALS participants. I just wanted to disclose that I'm not compensated for participation in this conference and I'm not a consultant for Clene Nanoscience.

I'm excited to kind of share some of the data from the NIH-Expanded Access Program. It provides a really large, real-world type of biomarker data set. What we were able to do with the NIH-funded program was to take participants and match them to a natural history cohort from a data set called ANSWER-ALS, which is a very robust biological and clinical repository. It provided us what we call, and what we will refer to as a Full Analysis Set of a total of 291 participants.

If you go to the next slide, this is a slide looking at the participant flow of both the NIH Expanded Access participants from EAP-04 and ANSWER-ALS, and how we were able to derive in a valuable set, and really what was the most important part of this was trying to make sure that we had participants with a baseline neurofilament and post-baseline neurofilament for an evaluable set, so we had about 114 participants that matched to the ANSWER-ALS cohort, and 177 from ANSWER-ALS that matched to our NIH-EAP for a total Full Analysis Set of 291 participants.

If you go to the next slide, this is the slide that shows significant neurofilament AUC differences across all matched participants. It's a comparison of—it's within the Full Analysis Set, and the slide shows comparison to the ANSWER-ALS match controls at Week 36.

So across, as we look at this, we see NfL values on the left-hand graph at 12 weeks, 24 weeks, and 36 weeks, and then the right-hand graph shows us the AUC changes versus matched controls.

Across the full matched data set, CNM-Au8 produced a significant reduction in the neurofilament AUC for all patients, so the totality, both non-bulbar and bulbar patients compared to matched ANSWER-ALS controls. The primary analysis, just to kind of level-set us, was designed for nine months with a secondary set at six months to kind of match the HEALEY Platform Trial data set, which was also set at six months. We also had a one-year data point, which is at 48 weeks, which was also included in the statistical analysis plan for sensitivity. That significant neurofilament difference, or that effect, holds after adjusting for all pre-specified covariates for each time point. This data is particularly remarkable as this Expanded Access population was really different from previous clinical ALS trials. The ALS trials really look at earlier onset ALS participants, whereas the Expanded Access, they've had disease for longer, and they're sicker with a wider array of clinical variability.

If you go to the next slide, this slide here is the significant neurofilament AUC differences across all matched participants. This is looking at bulbar onset. We broke it down. The bulbar onset patients who typically declined faster showed a stronger and statistically significant neurofilament reduction. This is clinically meaningful because bulbar patients are typically faster progressing and they're sicker. It's also relevant because in clinical trials, especially the HEALEY Platform Trial, bulbar patients, there was a bias against evaluating bulbar patients because participants had to be able to swallow pills or swallow liquids to be screened into the HEALEY-ALS Platform Trial.

If you go to the next slide, this, in contrast, is the primary efficacy analysis for neurofilament analysis in the non-bulbar population. So in the non-bulbar population, the neurofilament reduction has a trend favoring CNM-Au8, but doesn't reach significance. This is consistent with the greater biomarker volatility in the limb onset populations. Also, I think what's the bigger picture here is that when you take all matched participants, you still see that significant effect across the population that favors CNM-Au8.

If you go to the next slide, this is a slide that's looking at all the prespecified subgroups. When you look at these prespecified subgroups, it's important to note that the younger participants and the people that were

on Riluzole seem to have a similarly statistically significant neurofilament reduction. So we had all matched participants have a significant reduction. Of course, the bulbar onset, which we saw previously in the previous slides, and then the younger participants and the ones that are on Riluzole.

If you go to the next slide, which is Slide 13, we'll talk a little bit more about neurofilament and GFAP. As you heard before, neurofilament reflects neuronal injury. GFAP is a reflection of astrocytic injury. Essentially, regulatory bodies around the world really look for, especially in ALS clinical development programs, any biomarkers that can be linked to clinical benefit, so we explored these in the Expanded Access Program.

So if you go to the next slide, we've already reviewed neurofilament, light chain, and GFAP as ALS disease relevant biomarkers. Neurofilament obviously has a precedent of having significance and basis for an accelerated approval in ALS. GFAP helps us fill the story a little bit more about astrocytic injury.

If you go to the next slide, this is a slide—yes, go ahead.

Rob Etherington

Just one second. This is Rob Etherington. I'm just giving a heads up to those listening. We're having multiple people tell us that the webinar slide aspect of this is not working. We apologize. This is a different service than the dial-in. This is a web company that we have engaged to present these slides, so forgive us if you can't see them. The team is working on why this internet site is not working for some of you. We have a number on this site, so we're grateful for your attention, but we also have a number still attempting to come in.

Just heads up that we will be posting all of these slides on our website and through an 8-K right after this meeting.

Thank you, Jinsy.

Dr. Jinsy Andrews

Oh, thank you so much. I think that's important. I'll try to be more descriptive on the slides as we're looking at them, but also to try to provide the big picture story where the Expanded Access Program that's NIH-funded has helped to provide supportive data in the biomarker arena to help with understanding CNM-Au8's effect on the disease itself in terms of biomarker and also its potential clinical effect on more sick patients.

We were approximately at Slide 15 where we're looking at a slide that shows the neurofilament change and GFAP change in the CNM-Au8 versus placebo. This is the HEALEY neurofilament and the GFAP biomarker effects.

As earlier shown and previously shown in the double-blind placebo-controlled HEALEY Platform Trial, the CNM-Au8 showed consistent reductions and statistically significant data at the prespecified six-month point duration or Week 24 in HEALEY.

Now, Clene's regimen was Regimen C of that HEALEY trial and was the only of eight now completed HEALEY regimens to have a neurofilament achieve a prespecified significant reduction in neurofilament. I think that's an important point in the HEALEY-ALS Platform Trial setting with regards to CNM-Au8.

Now, in this new analysis of the HEALEY samples, we also looked at GFAP, and GFAP has also been evaluated in a new analysis through Week 24. And of note, both the p-value and the GMR reductions are nearly identical between the two different biomarkers from the same data set, from the HEALEY ALS trial double-blind placebo-controlled period. So it is remarkable to see that both neurofilament and GFAP have convergent signals across two independent biomarkers.

Also of note, the area under the curve, the AUC data are strongly statistically significant for both. This kind of strengthens our perception of CNM-Au8 having an effect in ALS in terms of a potential clinically meaningful benefit.

Now, if you go to the next slide, this is data from the NIH-Expanded Access Program. What we see is that the pattern of neurofilament and GFAP reductions in the NIH-Expanded Access Program are concordant with what we see in the HEALEY-ALS Platform Trial with strong evidence of significance. The neurofilament and GFAP levels are declining concordantly at each time point. We have Week 24 time point, Week 36 time point, and Week 48 time point in this particular slide.

Now, if you go to the next slide, this is the plasma NfL and GFAP change which are closely correlated in the placebo participants in the HEALEY-ALS Platform Trial. This slide essentially helps show us that it strengthens the neurofilament GFAP correlation. Placebo participants were also evaluated in the HEALEY-ALS program and we saw very strong correlation. P-value is 0.0012 and a p-value of 0.0018 in NfL and GFAP changes. So showing these biomarkers track together in ALS helps us kind of strengthen our evaluation of what we see when participants are treated with CNM-Au8 and the changes that we see with neurofilament and GFAP.

Now, if you go to the next slide, this is the slide where—Slide 18—where we see similar neurofilament and GFAP reduction in ex-placebo to CNM-Au8 population. So when I say that, I mean people who were initially randomized to placebo and then transitioned to CNM-Au8 in the HEALEY-ALS Platform Trial.

So even when evaluating a relatively small data set—so this is only 31 participants in the HEALEY placebo participants set for Regimen C. After starting on placebo for the first 24 weeks and then choosing to transition to CNM-Au8, we see similar directional reductions in the neurofilament and GFAP. The data set of only 31 participants was very underpowered for this analysis, so we did not see a statistical significance. However, the GMR decline effect was consistent and comparable to the effect originally seen in the statistically significant double-blind period. That kind of is consistent with what we're seeing with previous evaluations for neurofilament and GFAP.

Now, if you go to the next slide, Slide 19, we can see that across the treated population the distribution of the neurofilament and GFAP declines further—declines and further supports a treatment-linked biological effect. Now, we saw a marked AUC decline by treatment group with responders clearly clustering distinctly lower in combined biomarker response of neurofilament and GFAP relative to controls.

Now, if you go to the next slide—this is Slide 20. This is NfL and GFAP AUC—I'm describing the title slide in case you can't see the slide. Neurofilament and GFAP AUC decline distribution—I'm sorry, improved with survival. This is NfL and GFAP AUC decline associated with improved survival. What we're seeing is that patients who showed a marked biomarker improvement in both neurofilament and GFAP demonstrated the strongest improvement in survival. This helps us understand the mechanistic plausibility that biomarker changes translate to clinical benefit.

Essentially, the 25th and 33rd percentile responders who declined in both neurofilament and GFAP had very clinically meaningful survival observed, and so the p-value there was 0.02 and 0.01. When applying neurofilament GFAP AUC responder threshold, CNM-Au8 responders experienced better survival outcomes, so this helps to link the biomarker to clinical impacts such as survival.

If you go to the next slide, Slide 21, we're going to talk a little bit about increased neurofilament associated with the risk of death in ALS.

I think there is a lot of data growing. If you look at the next slide, there is a lot of literature out there in ALS to support neurofilament and its relationship to survival, and there's a growing body of literature for this. But this slide in particular shows that neurofilament change significantly impacts ALS survival. So a joint model shows that each one unit increase in the log neurofilament raises mortality risk by about 41%, and this is

powerful, and it's a quantitative link between biomarker change and the risk of death. So the survival hazard associated with neurofilament change is substantial and consistent with the ALS biology.

If you go to the next slide, we'll talk a little bit about survival. Both the original CNM-Au8 assigned participants and the ex-placebo participants—and I want to show you this in the next few slides—show a clear long-term survival benefit.

If you go to the next slide, this data is data from the HEALEY-ALS Platform Trial. This is survival analysis. This is Slide 24.

Analyses are anchored to clinically relevant time points, prespecified at 12 months, and the median treatment discontinuation was approximately 16 months on this slide. If you look at the two groups of the participants that were evaluated, the Full Analysis Set was all randomized participants, and the CRS was a filter for comparable baseline risk severity using baseline neurofilament scores and baseline TRICALS risk scores. These are things that are commonly used in clinical trials to look at risk and try to get cohorts that are matching or similar.

This CRS set is using baseline neurofilament and baseline TRICALS risk scores so that the Regimen C and Regimen A populations were comparable, and the risk set adjustments ensure comparability between CNM-Au8 and controls. It's a little tricky, but that CRS, when I say that, it's the Comparable Risk Set. The FAS is the Full Analysis Set.

If you go to the next slide, this is Slide 25. This is looking at CNM-Au8 30-milligram survival versus RGA controls or Regimen A controls from the HEALEY-ALS Platform Trial. At 12 months, CNM-Au8 showed a prespecified significant 73% reduction for the Full Analysis Set and a significant 77% reduction in the mortality risk for the Comparable Risk Set, both at p less than 0.01.

If you go to the next slide, so this actually is the slide that I was referring to in terms of the CNM-Au8 prespecified significance on the reduction on the Full Analysis Set and the 77% reduction in the mortality risk.

If you go to the next slide here, this is Slide 27. This is the results for improved long-term survival versus Regimen A and CNM-Au8 30-milligram versus Regimen A concurrent controls. In this slide, by Month 16, there's a risk reduction of death that continues with a 52% reduction in mortality risk for the Full Analysis Set and about a 64% reduction for the Comparable Risk Set, showing that the signal is durable and consistent. Both are significant at p equals 0.008.

If you go to the next slide, and I think what really helps us here, this is Slide 28, which looks at the improved long-term survival in ex-placebo to CNM-Au8 participants from the HEALEY-ALS trial. This is yet another example from the HEALEY placebo participants as the enduring power of CNM-Au8 to provide a significant benefit in ALS. Here, the HEALEY placebo participants who transitioned to active drug after their placebo-controlled participation at Week 24, or six months, were evaluated for survival. And of these, though a relatively small data set of about 31 participants that switched from placebo to active treatment, participants who switched to CNM-Au8 showed a 51% reduction in mortality risk at 12 months after beginning active treatment with a p-value of 0.0025. This is real-world evidence and evidence to help support that CNM-Au8 may have benefit across a wider cohort of participants, not just clinical trial-eligible participants. Again, the data here is showing a consistent benefit of CNM-Au8 treatment to affect survival during the open-label extension of the HEALEY-ALS Platform Trial.

I think overall, that was a lot of data that I tried to squeeze in in a short amount of time, but the NIH-Expanded Access Program has helped to provide us with additional biomarker data that relates to neurofilament, which has a relationship to axonal injury, and GFAP, which has a relationship to astrocytic injury. These are independent biomarkers, but that helps us understand that there's an enduring effect of CNM-Au8 across a broader population. We see concordance with data that's derived from other data sets. So the NIH-Expanded Access Program has provided additional data that's concordant with previous data

collected from placebo-controlled trials to help support and help us understand the effect of CNM-Au8 in survival for ALS.

With that, I'll turn it over to Rob maybe for Slide 29, which is the FDA guidance for accelerated approval. So I'll turn it over to Rob.

Rob Etherington

Thank you, Jinsy.

Clene has met with the FDA face-to-face—either face-to-face in White Oak in their Maryland facility or face-to-face virtually on a Zoom—four times, four times in the previous 12 months and one week. So that is actually a lot of dialogue. We are super grateful for the agency working with us in many ways.

The slide you're looking at is from the FDA website, is a summary of their guidance for accelerated approval. Accelerated approval is all based around the thesis of the surrogate. In this case, by surrogate, we are talking about a biomarker.

Item one and three on this list are obviously an easy check mark. ALS is definitively a serious condition and most evidently given its uniform fatality and unmet medical need.

Item three on this list is a requirement of a post-approval confirmatory trial. Clene has already organized the Phase 3 clinical study that we are planning with an endpoint of survival with three different turns of protocol discussions with the FDA and with approval thereof, and approval also in Australia, the country of Australia where we're prepared to commence this study in 2026.

What's left is number two in the slide you see—a meaningful benefit over the available therapy on a surrogate endpoint, which means a biomarker. In this case, means neurofilament or GFAP—or as we've just demonstrated through Jinsy's excellent presentation, both—that is reasonably likely to predict clinical benefit.

Before we get to the questions, let's go to Slide 30. Clene has already submitted in the last few days, a Type C Meeting request to the agency to discuss all of this data, to immediately start the clock, preparatory for a face-to-face meeting to have the agency consider the overall totality, the overall comprehensive view of what you've just seen, plus what we've earlier presented in previous press releases and in previous data, the biomarker and long-term survival evidence. We expect this meeting to be with the FDA during the first quarter of 2026 and we are currently readying a new drug application inclusive of all of this data for submission.

So let us now turn to some questions and answers. Again, apologies. We are certainly grateful that the dial-in is working. This is a separate company, just to be clear. We contracted with a classically hosted company for this webinar that does investor webinars all the time and we are trying to figure out in real-time what's going on. The company's working on it. As I've stated, we will post these slides on our website so you can see them subsequently. We'll also be filing them with the SEC as is normal.

So let us turn now to the operator for opening up the Q&A.

Operator

Thank you. We will now be conducting a question-and-answer session. If you would like to ask a question, please press star, one on your telephone keypad. A confirmation tone will indicate the line is in the question queue. You may press star, two to remove yourself from the queue. For participants using speaker equipment, it may be necessary to pick up the handset before pressing the star keys.

One moment, please, while we poll for questions.

Our first question comes from the line of Naz Rahman with Maxim Group. Please proceed with your question.

Naz Rahman

Congrats on the progress and congrats on the data. It looks fantastic. Thanks for taking my questions. I just have a few.

You mentioned that the patients in the NIH-Expanded Access Programs were more advanced. I was curious; were any of these patients previously treated with any other unapproved or experimental ALS therapies? Were they in any other studies and did that anyhow confound the data?

Hello, can you hear me?

Dr. Jinsy Andrews

Yes. Can you hear me? It's Dr. Andrews.

Naz Rahman

Yes, I can hear you.

Dr. Jinsy Andrews

I will say that, yes, they are on standard of care background therapy like Riluzole and they can be on edaravone.

The data specifically, essentially the participants that have enrolled in the NIH-Expanded Access Program were not at the time of enrollment on it, on any experimental therapy, only for the nature for the fact that they're advanced. But we didn't collect specifically if they had any exposure to any other experimental therapies previous to that. So, should they earlier in their disease, had they had an opportunity to participate or not. What I will say though is that half of the participants are remotely enrolled and many of them did not even have access to an ALS research center. So many of them never had an opportunity to participate.

Naz Rahman

Got it, that was very helpful. If I could add a follow-up? These are, once again, advanced patients. Could you potentially characterize and contextualize how advanced they are, whether it's in terms of ALSFRS or whether it's in terms of disease onset or any other metric you may use?

Dr. Jinsy Andrews

Yes. The inclusion/exclusion criteria essentially stated, but did not specify like very detailed specifics about their inclusion criteria. But they typically had disease longer than three years and they could have respiratory decline where they are using non-invasive ventilators. There was no—there was a presentation actually. I don't know if we have this in the appendix on what they looked like because we have some baseline demographics. I'll try to pull that up. But essentially they're breathing.

Typically the one of the eligibility criteria is that they cannot be clinical trial eligible and so that means that some of these participants may have had disease longer than three years or their breathing is around 50%. So it's a lot different than participants for clinical trials that are eligible now for some of the recruiting clinical trials.

Naz Rahman

Got it, that was very helpful. Once again, congrats on all the data and progress.

Dr. Jinsy Andrews

Thank you.

Operator

Thank you. Our next question comes from the line of Justin Walsh with JonesTrading. Please proceed with your question.

Justin Walsh

Hi, thanks for taking the questions. Assuming a favorable Type C Meeting with the FDA, do you have thoughts on key topics that could come up during a potential advisory committee meeting?

Rob Etherington

Jinsy, why don't you speak to that first and I'll jump in.

Dr. Jinsy Andrews

Essentially you're asking what kind of topics would be, what could come up in a potential advisory meeting?

Justin Walsh

Yes. Where do you think the KOLs and ALS experts would try to poke holes or what do you think they would focus on?

Dr. Jinsy Andrews

Yes, that's a good question.

I think honestly, I think some of the questions were already asked by the FDA. They wanted to see some of the preliminary data that was pulled from the HEALEY-ALS Platform Trial. That was a six-month study with an open-label extension and there were some preliminary signals there. The questions I think KOLs had about CNM-Au8 were really aligned with the questions that FDA asked for more data to support what Clene was seeing in terms of neurofilament and survival benefits. That's why I think the data from the NIH-Expanded Access Program is pretty important in terms of biomarkers and clinical benefit in terms of survival analyses.

I think that if there are other questions, they may ask potentially the relationship or the mechanism of astrocyte injury and axonal injury or nerve injury and how that relates to CNM-Au8. I think there is some plausible scientific rationale for the effect of CNM-Au8 on preserving motor neurons, so with the bioenergetics and helping with inflammation in the cell. It can indirectly impact the reactivity of the astrocytes. So I think that the biomarkers themselves, there is some scientific rationale that could kind of answer some of the questions that might come up about the relationship of CNM-Au8 and the relationship to neurofilament and GFAP.

Rob Etherington

Then, Justin, I'll just add, this is a key series of dialogues that the Company has had. They really wanted to make sure that from one study, HEALEY, there was a neurofilament data that could be substantiated elsewhere. That's the reason the Company has decided to approach this with all three legs of the stool, the

leg being a new biomarker, GFAP. And we saw, as we just saw in the slides—and the slides are now up, by the way, thank you. The Internet has been fixed.

But in any event, the GFAP and the neurofilament were nearly identical geometrical mean ratio changes, identical p-values. Then we wanted to also to use the EAP in a completely different patient population that was varied in their disease state, varied in their diagnosis, varied in their treatment patterns to see if we can actually see the neurofilament consistent with what we saw in the full data set against HEALEY. And indeed, we just did that.

Justin Walsh

Great, thanks. One follow-up, I'm wondering if you can provide any additional color on the expected Phase 3 RESTORE-ALS trial design. And based on the data we've seen so far, how much confidence should we have that the Phase 3 trial will be successful?

Rob Etherington

Michael, let's turn to you to discuss the Phase 3 design you've been discussing with the agency.

Michael Hotchkin

Certainly. Thanks, Rob. All of our modeling using data from both the HEALEY-ALS Platform Trial as well as our prior Australian study, RESCUE-ALS, all point to the same conclusion. Both indicate that the enrollment criteria we designed for RESTORE should identify individuals most likely to show a treatment effect from our CNM-Au8 30-milligram dose. Those concordant findings, I think, increase the probability of success.

Of course, that's why we do Phase 3 rigorous controlled studies. But if I were handicapping this, I'd definitely vote in our favor.

Justin Walsh

Great. Thanks for taking the questions.

Operator

Thank you. Our next question comes from the line of Joe Pantginis with HC Wainwright. Please proceed with your question.

Lander Egaña-Gorroño

Hi, team. This is Lander on for Joe. Congrats on the data and thanks for taking our questions.

So maybe first, can you provide some color as to the comfort around using matched controls in the EAP analysis?

Dr. Jinsy Andrews

I'll go first. I think this is always a discussion of trying to figure out how best to do a comparison when you treat all your participants. I think that there is a lot of strength in the propensity matched controls and actually some of the matching was very critical in this particular cohort because there isn't a lot of data sets out there for more advanced ALS participants and there's a lot of confounding variables that can affect survival.

When you're matching, it's important to make sure you match in an independent data set—that was ANSWER-ALS—and also to match for baseline characteristics so that they're best matched to the

participants that you actually treated and can serve as a proper control without confounding variables biasing the evaluation or the analysis of effect in any direction.

So for that, I think that especially from the KOL community, this probably is the most ideal way to look at efficacy in a expanded access program per se where all the participants are treated.

Lander Egaña-Gorroño

Great, that's very helpful. Maybe one more follow-up? We think that the bulbar-onset benefit is quite interesting. Do you think that this would drive maybe label inclusion initially?

Dr. Jinsy Andrews

I think one of the benefits here—that's always a risk, but I think what reduces that risk is that, remember, we parsed out the bulbar and the non-bulbar participants and that becomes a smaller sample size. But if you take the Full Analysis Set of all the matched participants and group them, in totality you see the effect across all participants that are treated. So regardless of bulbar or non-bulbar, when you group everybody together, you see the effect and its significance and it favors CNM-Au8.

Lander Egaña-Gorroño

Awesome, that's very helpful. Congrats again. Thank you.

Operator

Thank you. Our next question comes from the line of Sumant Kulkarni with Canaccord Genuity. Please proceed with your question.

Sumant Kulkarni

Good morning. Thanks for all your work on behalf of patients and for taking our questions. I have a two-parter for Dr. Andrews first and then a question for the company.

For Dr. Andrews, if you were to present these results to the FDA at a Type C Meeting, what would you point to as the most striking results here that might support a case for accelerated approval in ALS?

And if this product were to gain accelerated approval, would the differences in biomarker results seen in bulbar versus limb onset have any bearing on doctors recommending the real-world use of this product in ALS regardless of the onset type?

Dr. Jinsy Andrews

I think the first is the biomarker. I think that one of the most striking things about—so I'll be honest and transparent. I've shared this with the company. In Expanded Access, I thought the participants would be more advanced and it would be more difficult to salvage motor neurons or to see an effect in a more advanced population. So for me, the most striking thing is that there was movement of neurofilament in this cohort. Often when a drug product is evaluated in clinical trials in ALS, there's always this lingering question of, “Okay, yes, we treat people earlier in the disease, but does the drug have continued effect as the disease progresses?” And I think that's been the debate with things like edaravone on the market already. I think the movement of neurofilament in this cohort, pre- and post-treatment, was impressive.

But I think with neurofilament, when regulatory authorities, especially in the United States, when they look at neurofilament in the setting of ALS, from my perspective, in my opinion, they really want to see the totality of the data and see if there's any other data that can be concordant with neurofilament, and so they always

will review that. I think the fact that we have GFAP moving in concordance with the neurofilament is very striking.

GFAP itself alone is not great for disease progression in ALS, or tracking disease progression, and there's a lot of back and forth in the literature. But this is one of the few times we're looking where we can see GFAP and neurofilament tracking with each other in a more advanced population.

Then the relationship of these biomarkers to survival—not disease progression, but survival—is pretty significant as that is the gold standard for evaluation from the regulatory perspective. So in that way, I think the biomarker data is pretty striking.

The second question you asked me is about clinical perception of who to give this type of potential therapy to. Honestly, whether—and I'm speaking based on experience—I see patients every day. Also, we have edaravone that's on the market and although that was approved for participants who are early and rapidly declining with ALS, it's broadly prescribed and I'll tell you why. There's a high unmet need in ALS and if there's more of a response in a bulbar onset versus limb, if there's a benefit in all, clinicians will prescribe it for all and add it to the standard of care that's already available in the United States.

Sumant Kulkarni

Thanks for that perspective.

For the company, given the primary analysis population was non-bulbar onset participants here, what would be your best way forward at the upcoming Type C Meeting? Especially given all the uncertainty at the agency?

Rob Etherington

Certainly, there's uncertainty at the agency. Let's answer this in two parts. Michael, I'll have you comment first on your approach, and then I'll comment secondly.

Michael Hotchkin

Certainly. We designed this app respectively based on the results we observed in the HEALEY-ALS Platform Trial. Now, many fewer participants for bulbar onset in HEALEY, and I think we had single digits on placebo and maybe 10 on active, thereabouts. I'd have to go back and confirm the exact counts. We didn't see a signal there. Here we see a much more robust signal. And I think it speaks to the broader pathophysiology of ALS that the lack of response in HEALEY was driven by a small sample. Here we're seeing individual patients with really substantial declines, and those seem to be focused in the bulbar onset population.

So I think the dialogue with the agency will likely revolve around the Full Analysis Set and to what extent FDA accepts that.

Rob Etherington

I was going to say the same thing, Sumant. Thank you, Michael. That the agency really is wanting to see what we saw in HEALEY, which was a full analysis set, and now we see that confirmed.

We have this very interesting bulbar signal that is a p-value of 0.00 number. So remarkably significant in bulbar too, which as Jinsy just has stated was unexpected. So we're actually very thrilled, in fact, to go in and take this data and have a conversation with the agency about it.

Sumant Kulkarni

Thank you.

Operator

Thank you. Our next question comes from the line of Elemer Piros with Lucid Capital Markets. Please proceed with your question.

Elemer Piros

Yes, I have a simple one. The proposed Phase 3 trial will have a survival endpoint, primary endpoint. How settled that line of thinking versus ALSFRS as a primary endpoint?

Michael Hotchkin

I'll take that one, Rob. I still think in the context of ALS, the strongest and most robust benefit for patients, and we've done research in the patient community, people living with ALS. We've done research with key opinion leaders and obviously regulatory standards. I still lean toward time to death or death equivalent as a primary outcome that has the most rigor and least possibility of bias.

Elemer Piros

Thank you.

Rob Etherington

We're adding—Elemer, I was going to say ALSFRS will be a secondary exploratory endpoint. So we're adding this beyond the primary. But to the point, we think that survival in ALS is indeed what is the most important endpoint to pursue, especially for a drug like CNM-Au8 that has so much extensive survival data.

Please continue with your next question.

Elemer Piros

Yes, thank you. So when you didn't see an impact on NfL change or if it went in the wrong direction, have you looked at that population and looked at their survival?

Rob Etherington

I'm not sure when we didn't see an impact in what, which case, which example do you mean?

Elemer Piros

In the NfL change. If the NfL change was going in the wrong direction, have you looked at that population and look at their survival as compared to NfL responders?

Dr. Jinsy Andrews

So you're asking did we see any participants that had a rise in NfL, and in that cohort, did we look at survival?

Elemer Piros

Yes, thank you.

Dr. Jinsy Andrews

Because that would be the wrong direction, yes, okay.

Michael, did we see that?

Michael Hotchkin

Yes, those numbers are small, but there's still a difference in favor of CNM-Au8.

I think overall, we see a treatment benefit for CNM-Au8 Those are the Full Analysis Set analyses and the Comparable Risk Set analyses that Dr. Andrews presented. For those really tiny subgroups, we see the best overall survival benefit in the individuals within the HEALEY data set that had both an NfL and a GFAP decline, but there's still a survival benefit in individuals that have NfL increases, although I'd have to go back and look at the p-value there. We're talking about smaller and smaller cuts of the data.

Elemer Piros

Yes. Thank you very much, Michael.

Operator

Thank you. Our next question comes from the line of Bruce Jackson with The Benchmark Company. Please proceed with your question.

Bruce Jackson

Hi, good morning. Thanks for taking my question and congratulations on the results and on moving the science forward. It's really remarkable.

The question I've got is actually about your MS program. Can you maybe speculate a little bit about what this could mean for your MS program and what are the applicability of the results here and how might that affect your trial design for MS? Thank you.

Rob Etherington

Let's tackle that in two parts. I'll start first and Michael can chime in.

We met with the FDA face-to-face to discuss the end of our Phase 2 data in August. We've already announced this meeting publicly. What we've done there is we think reversed 30 years of precedence for EDSS, which is the Expanded Disability Status Scale, long used over three decades as the primary endpoint, and persuaded the agency that we need a cognition endpoint for a drug like CNM-Au8. The final particulars of that cognition endpoint, the agency still wants to have a number of dialogues with Clene and we are planning to meet with them also in the first quarter to discuss this.

This is actually groundbreaking, however, because a drug like CNM-Au8 that has the effect that it has, and we're seeing that on the neurofilament and the GFAP example in this case, does need to be approached in a different way in multiple sclerosis.

Michael, do you want to comment further on how these results might translate?

Michael Hotchkin

Oops, I just noticed I was muted.

I was just saying, I think broadly, the concordance of biomarker effects for both GFAP and NfL have impact in diseases like MS and other neurodegenerative disorders. I think as a thesis for how CNM-Au8 impacts the brain, it may be broadly supportive of additional clinical (inaudible) trials in diseases like MS and others.

Rob Etherington

Operator, can you hear us?

Operator

Yes. Thank you. Our next question comes from the line of Jonathan Aschoff with ROTH Capital. Please proceed with your question.

Jonathan Aschoff

Thanks. Hey guys, I was wondering, your NfL and the GFAP analysis, was it done? You've already had several meetings with the FDA; I can't imagine they didn't give you a really explicit statistical analysis plan to follow. Are the data you're showing today the results of applying that exact statistical analysis plan or has it not been conveyed to you as exactly as I'm assuming it must have been?

Michael Hotchkin

Yes, the statistical analysis plan was discussed and agreed upon with FDA. There are a couple of small, minor plan deviations. But yes, we followed a prespecified SAP with FDA.

Jonathan Aschoff

So why need another meeting if it's already sort of looking the way you want it to as assessed the way they want it to?

Rob Etherington

We'll answer that in two parts.

At the September 30 meeting, we actually asked them if they wanted to see this data in context and come back and have us present it and the agency replied in the affirmative that indeed they did. And so we're doing this meeting, actually, Jonathan, to take into context, not only the biomarker results, but the entirety of the clinical benefit as seen in the survival documents. And the agency did tell us in the November meeting responses that they wanted us to return to discuss everything in context.

We've also found, to your point with our multiple meetings, that every meeting we have with the agency moves the bar forward. But that is entirely why we also are preparing this NDA with this new data in parallel.

Jonathan Aschoff

Thank you very much, guys.

Operator

Thank you. Our next question comes from Naz Rahman with Maxim Group. Please proceed with your question.

Naz Rahman

Hi, everyone. Thanks for taking a follow-up. Assuming you file an NDA in 1Q, you're obviously going to have an outcome. Let's say, hypothetically, the outcome (phon) is in, like, late spring or summer. At that point, how much survival data do you think you'll have with Au8? Like, could you contextualize how many patients will have been on therapy for how long? Also, are you going to continue doing NfL collections or data analysis going into an outcome, or have you stopped that process? Thanks.

Rob Etherington

Michael, do you want to take that first and I'll follow up?

Michael Hotchkin

Go ahead, Rob.

Rob Etherington

All told, we have more than 500 individuals in the EAP. We have 45 that we've treated and followed in RESCUE; 160 that we've treated and followed in the Phase 2 HEALEY program and we continue to follow these individuals as we've updated in today's deck in survival. So there's quite a wide bolus, as we spoke last night, Naz, with that data. Yes, we will continue to update and follow them as we also launch our Phase 3.

Now, that was the first part of your question. What was the second part?

Naz Rahman

In terms of the survival data, I guess how much survival data will you have going into, let's say, a potential outcome into spring, summer? Like, how many patients would have been on therapy for, I guess, like, how long? Or I guess how many patients would have survived for how long? If you can sort of contextualize that.

Rob Etherington

Our first patients were actually put into our clinical study—in the EAP, rather, in the fall of 2019, and we actually know of individuals that are still on the drug, that we are still treating since that period. So there will be people by summer of '26 that would have been on drug for six-plus years.

Naz Rahman

Got it, thank you. Once again, congrats on the progress.

Rob Etherington

Thank you.

Operator

Thank you. We have reached the end of the question-and-answer session. Therefore, I would like to turn the floor back to Rob Etherington for closing remarks.

Rob Etherington

Thank you everybody for staying with us on the call and in the questions. We, again, are very grateful for Dr. Jinsy Andrews for joining us and for everybody that participated in today's call. Thank you for taking an hour of your morning time with us.

We are grateful for all of the patients that have helped us in all of these clinical studies and all the people that support Clene. We will now let you proceed with your morning. Thank you very much.

Operator

Thank you. This concludes today's conference and you may disconnect your lines at this time. Thank you for your participation.