Slide 1

Slide 2

Good morning and thank you all for your time today. My name is Justin Klee, and I am the Co-CEO and Co-Founder of Amylyx Pharmaceuticals. With me is my fellow Co-CEO and Co-Founder Joshua Cohen. It is an honor to present to this esteemed group.

Before we start, we want to acknowledge the thousands of people who have been integral to this program, without whom we would not be here today. Sadly, many of those people are no longer with us. And we can think of no greater honor to their memory than pursuing a treatment for ALS.

We also want to thank the FDA, also without whom we would not be here today. In the summer of 2021 we were working on study initiation for our second study in people with ALS. The agency emailed our head of regulatory affairs, requesting that we submit for a pre-NDA meeting on July 15th, and submit them a briefing book in just 8 days' time. During and after the meeting they asked that we move with similar haste to submit an NDA as fast as we could, given the urgency and unmet need in ALS.

Slide 3

While rare, I'm sure Amyotrophic Lateral Sclerosis, or ALS, is no stranger to anyone on this panel. It's a progressively devastating and universally fatal disease with limited treatment options.

ALS causes the degeneration and death of motor neurons, which leads to a rapid loss of even basic functions, and death within just a few years.

Despite many wonderful efforts, ALS today remains largely the same disease as when Lou Gehrig brought the nation to tears with his "Luckiest Man Alive" speech…. And since that speech, an estimated 500,000 Americans have died from ALS.

Slide 4

Josh and I founded Amylyx to try to help change that fate. We thought that if we took a different approach – focusing on the endoplasmic reticulum and mitochondrial stress pathways that lead to degeneration and death of neurons…

…we might find a treatment that could help people with ALS. We knew the odds were long, but we firmly believed that if we stuck to rigorous science and analysis, were able to partner with the best doctors and researchers in the field and stayed focused on helping the people we were trying to serve, we would find the right path forward.

Slide 5

AMX35 is a combination of sodium phenylbutyrate (PB) and taurursodiol (TURSO) and is indicated for the treatment of ALS.

The recommended starting dose of AMX35 is 1 sachet once daily for 21 days with a subsequent maintenance dose of 1 sachet twice daily, 1 in the morning and 1 in the evening.

Let me provide a brief background on the clinical development and regulatory history of AXM35.

Slide 6

Data supporting the efficacy and safety of AMX35 comes from the CENTAUR study, which started in June of 2017, and encompassed a randomized controlled phase and an open label phase.

We were very proud to publish with our colleagues the results of the 24-week randomized trial in the New England Journal of Medicine in September of 2020 and subsequently the overall survival benefit in Muscle and Nerve in October of 2020.

The CENTAUR open label phase ended in March of 2021.

And in October of 2021, the first participant was dosed in the Phoenix trial, a second large placebo-controlled study in people with ALS.

On June 10th of 2021, Amylyx was notified that FDA had scheduled a pre-NDA meeting for July 15th. During and after the pre-NDA meeting, the Division asked Amylyx to submit the NDA as quickly as possible.

The NDA was submitted on October 29th. The NDA was accepted and filed on December 23rd under Priority Review and an advisory committee was scheduled for March 30th 2022.

I'll now turn to my fellow co-CEO and co-founder Josh…

Slide 7

Thanks Justin.

The CENTAUR trial and data you are reviewing today was conducted with leaders in the field of ALS research and care, at top ALS centers of excellence across the United States. The co-PIs of the study were Dr. Sabrina Paganoni who you will hear from today, and Dr. Merit Cudkowicz, Chief of Neurology of the Massachusetts General Hospital and widely regarded as one of the top ALS researchers in the world. The mixed effects model used for the clinical outcomes – including for the primary analysis – was developed by Dr. David Schoenfeld, Professor Emeritus at Harvard Medical School and the most cited and highly regarded statistician in the field of ALS clinical trials. Dr. Schoenfeld is also the co-inventor of the Finkelstein-Schoenfeld joint rank method frequently cited by FDA, and as early as 2016 strongly encouraged both us and the FDA that a shared baseline mixed effects model would be the most appropriate method for this trial.

To that end, the trial met its prespecified primary endpoint - slowing the progression of functional decline – using the most widely used clinical scale in ALS, the ALSFRS-R.

Importantly, AMX35 showed a statistically significant benefit in Overall Survival, extending the lives of those receiving AMX35.

This is the first time a treatment has shown a benefit on both function and survival in ALS, the two key measures in a relentlessly progressive, fatal disease.

And AMX35 showed a good safety profile, with numerically fewer serious adverse events in the treatment arm as compared with placebo.

Slide 8

The FDA has commented on aspects of the CENTAUR study and pointed out statistical considerations between our methodologies and theirs. We will address

each of these points and provide a detailed explanation of what was done and why.

There are many different models and analyses that can be used on clinical data. We will present many of these today assessing the robustness of the primary endpoint and survival.

However, what is most important is that our prespecified models show a beneficial effect on both function and survival for people living with ALS, a progressive, fatal disease with very limited treatment options.

Slide 9

And these results only further our resolve to continue learning about AMX35. So, while this is under review, and as strongly encouraged by FDA, we are also running another large placebo-controlled study in people with ALS which is already recruiting participants, with sites selected primarily outside of the US. We expect this study to read out in 2024.

We have also initiated a large expanded access program for people living with ALS in the US who don't qualify for the ongoing trial.

Slide 10

Today our presentation will focus on the science – the statistics, the outcomes, the sensitivities, the safety, and the benefits of AMX0035, as well as the high unmet need. And importantly, we'll focus on what these results may mean for people living with this devastating diagnosis.

Dr. Sabrina Paganoni, one of the top ALS clinical trialists in the world will share more about the unmet need in ALS and her clinical perspective on the data. Dr. Jeremy Shefner, director of outcomes and clinical monitoring for the largest ALS clinical trial consortium in the United States, will share his perspectives on outcomes and methodology in ALS trials. And, Dr. Timmons from Amylyx will share an overview of the clinical trial data.

Slide 11

We have additional experts with us as well today to help answer your questions.

All outside experts have been compensated for their time preparing for today's meeting.

Thank you very much for your time and for the opportunity to introduce ourselves. We would now like to turn the presentation to Dr. Sabrina Paganoni.

Slide 12

My name is Sabrina Paganoni, and I am the Co-Director of the Neurological Clinical Research Institute at Mass General.

I'm also a physician scientist at the Healey and AMG Center for ALS and an Associate Professor at Harvard Medical School.

I served as the Principal Investigator of the AMX35 CENTAUR trial.

I'd like to share why ALS became so personal to me to the point that I decided to dedicate my scientific and clinical work to this disease.

In 2008, when I was just starting my residency, I was taken under the wing of a fabulous mentor, Dr. Lisa Krivickas, a specialist in ALS. Unbeknownst to me at the time, Lisa had JUST been diagnosed with ALS herself. Even as her disease progressed, her mentorship continued - She soon started using a cane, then a scooter, but she never stopped mentoring me. 2 years after I met Lisa, she died from ALS – she was 45.

Since then, it's been my honor to continue Lisa's work. And that is why I am so happy to be here today – to share more about ALS and the impact it has on my patients, their families and communities and all of us who work to treat, and someday cure, this disease.

Slide 13

While ALS meets the definition for a rare disease, it has a large impact and affects a broad range of people. In the US alone, up to 30,000 people are currently living with ALS.

And perhaps more surprising, is the lifetime risk of getting ALS.

As a woman, my lifetime risk is approximately 1 in 440. For men, the risk is even higher: 1 out of every 350 men WILL develop ALS in their lifetime. This means that

as many as one million people who are alive today in the US will be diagnosed with ALS over the course of their lifetime.

In my clinic, I see patients as young as 25 and as old as 85, men and women, people of every color and socioeconomic status- all facing the same relentless illness.

Slide 14

ALS begins with upper and lower motor neuron degeneration and death, resulting in bulbar, fine motor, gross motor, and respiratory muscle weakness.

This muscle weakness translates to loss of function – the loss of the ability to talk, eat, dress oneself, write/type, walk, and eventually breathe.

Slide 15

In ALS clinics and in clinical trials, we can measure a variety of outcomes related to the disease process, including muscle strength, respiratory capacity, and time to requiring tracheostomy and respiratory support.

Because function is so closely tied to muscle weakness, and so important for people with ALS, our key measure is the ALS Functional Rating Scale or ALSFRS-R.

The ALSFRS-R is the most widely used ALS rating scale in clinical practice AND clinical trials.

There are 4 domains in the scale – bulbar, fine motor, gross motor, and respiratory function.

Slide 16

The ALSFRS-R measures independence in performing 12 important daily functions that fall under the 4 categories just outlined.

The range of the scale goes from 0 to 48, with a higher number representing better function. The total score is calculated by adding up the answers to 12 questions, each rated on a scale of 0 to 4.

On this slide, I am showing an example question under the bulbar category for swallowing. In this example, a score of 4 represents complete function, or normal

ability to swallow, and a score of 0 represents complete LOSS of function, such as requiring a feeding tube

Slide 17

The advantages of the ALSFRS-R are that the categories are relevant to ALS, it's a sensitive and reliable tool for assessing activities of daily living, and is quickly administered.

The ALSFRS-R can be administered in person or by phone. And the equivalency of phone versus in-person testing has been established.

It has high inter-rater reliability and test-retest reliability

In ALS participants, changes in ALSFRS-R scores predict survival and correlate with quality of life measures

Let me provide more details on the clinical meaningfulness of the ALSFRS-R.

Slide 18

In terms of survival, data from an ALS clinic in New York City showed that the ALSFRS-R TOTAL score at baseline was a strong predictor of death or tracheostomy, and for each one-point decrease in the total score, there was a 7% increase in the risk of death or tracheostomy.

Slide 19

Other studies have shown a correlation of the ALSFRS-R with quality of life measures.

And finally, it's helpful to know what a meaningful change is on this scale.

Slide 20

A survey of 65 ALS experts in the US found that MOST would consider a 20% change in the rate of decline of the ALSFRS-R total score as clinically significant.

This aligns with how I interpret the scale as well.

Slide 21

I have learned from my patients that when you have ALS you do not live on a standard clock.

The ALS clock is very short

– it's already shortened by how long it takes most people to get diagnosed – for many, 12 months or even more.

As you can see from this data from an ALS clinic in the US, median SURVIVAL is only around 2 years after diagnosis, making time the most precious commodity.

For this reason, survival is generally included as an endpoint in ALS clinical trials.

Slide 22

Clinically meaningful overall survival benefit is demonstrated by median overall survival, or OS, and hazard ratios, or HR.

In oncology, physicians often communicate survival benefits to patients in terms of months with median survival as an understandable data point. We can look to oncology guidelines for how to assess the clinical meaningfulness of survival outcomes - ASCO guidelines specify a 2.5 to 6 months improvement in median overall survival as clinically meaningful.

Another important assessment is the hazard ratio or HR.

Oncology guidelines recommend HR as an informative outcome in combination with median OS - an HR of less than 0.8 is generally considered a clinically meaningful benefit.

Unfortunately, achieving these goals in ALS is quite difficult, and we don't have guidelines of our own.

Slide 23

I mentioned earlier that ALS begins with upper and lower motor neuron loss, but what causes the motor neurons to die?

While we don't fully understand it yet, we have made significant strides in understanding the various mechanisms that lead to their death. And it's a multi-pathway problem

ALS is a complex disease – and as we have seen with other complex diseases, such as cancer or HIV, the first treatments that were developed worked as part of a cocktail of drugs

The more we learn about ALS, the more apparent it becomes that effective treatments will likely require a cocktail targeting multiple pathways at once to tackle the many different mechanisms that are at play.

Slide 24

The care we provide in ALS clinics includes key interventions such as physical and occupational therapy, nutrition support that often includes a feeding tube, respiratory support that eventually includes a ventilator, as well as speech and assistive technology, such as voice banking, to support communication when the ability to speak is lost.

ALS is universally fatal, so my care also includes talking to my patients about palliative medicine and hospice.

Slide 25

Of course, multidisciplinary care also includes the use of approved medications. And today, there are only two approved products in the US for treating ALS, riluzole and edaravone.

Riluzole was approved by the FDA in 1995. It blocks glutamatergic neurotransmission in the central nervous system. The original trials showed a survival benefit of 2 to 3 months and no effect on function.

I generally start Riluzole soon after the diagnosis of ALS.

Edaravone was approved more recently in 2017

The approval of edaravone was welcome news for the ALS community who had been waiting for a new drug for 25 years.

Edaravone works as an antioxidant. And in the trial that led to its approval, edaravone was shown to slow functional decline with no effect on survival.

Edaravone's administration is complex, requiring frequent intravenous infusions and for this reason it is typically used less frequently.

Slide 26

As you can see, we need more treatments for people living with ALS.

By the time people are diagnosed, the ALS clock has already been ticking for months

We need a treatment that will retain physical function AND prolong survival.

ALS is all about time….and right now, there is not enough of it for the people I see in my clinic -but I have hope that that will change

Thank you , and I will now turn the presentation over to Dr. Shefner.

Slide 27

Good morning. My name is Jeremy Shefner. I'm the Chair of Neurology at the Barrow Neurologic Institute and I'm a trained neurologist and neuromuscular specialist.

Slide 28

I've been involved in ALS research for many years.

In 1996, I cofounded the Northeast ALS Clinical Trials Consortium, which has grown into the largest consortium of academic centers performing ALS trials in the world.

I've also served either on the executive committee or as overall PI of multiple/ multi-center ALS clinical trials. My research interests focus on the development and validation of functional outcomes for ALS.

In 2014, I received the Sheila Essey Award for ALS research, which is given annually by the American Academy of Neurology and the ALS Association.

As you've heard from Dr. Paganoni, the ALS functional rating scale is the most commonly used outcome measure as a primary outcome in late-stage ALS trials.

I'm here to provide my perspective on the extent to which the decline of ALSFRS-R in clinical trials is linear and also to discuss the use of the joint rank in the analysis of ALSFRS-R data in ALS clinical trials.

Slide 29

The slide presented here shows the behavior of the ALSFRS-R in three trials each of 12 months duration. From a visual assessment, the decline is exceedingly

linear. The range of the ALSFRS-R spanned in these three studies is quite broad, going from 43-26.

If you compare these data to those under discussion here, you can see that just as in these prior studies, the data are quite linear in their appearance. The values here go from approximately 36 at baseline to 28 at 24 weeks, well within the boundaries of previous ALS studies including those represented on this slide.

I want to stress that non-linearity in ALSFRS decline is certainly possible; for that reason, all SAPs for recent ALS trials involve sensitivity analyses testing the linearity hypothesis. This was performed for the study under consideration here, and there was no evidence that the data violated the assumption of linearity.

I also want to talk about how the ALSFRS-R was assessed in the AMX35 Centaur trial.

Slide 30

Generally, in clinical trials the goal of statistical modeling is to maximize sensitivity to detect true treatment effects—whether positive or negative—and to provide clinically meaningful information to physicians and patients.

For the CENTAUR trial, Dr. David Schoenfeld, an experience ALS statistician who developed the joint rank test, recommended the shared baseline, linear, mixed effects model of the ALSFRS-R as the most appropriate primary analysis for several reasons.

A mixed effect regression model provides a sensitive estimate of a treatment effect, effectively handles missing data, allows inclusion of important prognostic covariates, and is a clinically meaningful endpoint used in many ALS trials.

The joint rank test, whose use has been recommended by the FDA, has several limitations that I'd like address.

This method was developed to account for missing data from a functional assessment due to mortality. However, studies have shown that when the number of deaths is low, the joint rank test is less sensitive than many other methods. In particular, a study from 2018 performed multiple simulations on clinical trial data and showed increased sensitivity of the shared baseline model compared to the joint rank test.

As the Centaur trial was expected to have few deaths in the initial 24-week randomized phase, a joint-rank test is not the most sensitive way to assess efficacy.

Additionally, the joint rank model is not designed to adjust for covariates, which we know are very important in predicting outcomes in ALS. A final statistical point is that, while the joint rank was developed to account for missing data due to death, it does not have robust methods to account for data that is missing for other reasons.

Finally, the Joint-rank model's output is a non-parametric ranking statistic which has no intuitive clinical meaning. Because of this, explaining the importance of a statistically significant effect on the statistic is challenging to patients and their caregivers.

Slide 31

So, in summary, the two things I would stress are that the ALSFRS-R decline over time is linear in past ALS trials and appears to be linear in this case. Sensitivity analyses to test this assumption have not shown significant deviation.

Secondly, the prespecified shared baseline, linear, mixed effects model chosen for the primary outcome in the Centaur trial was appropriate.

As expected, there were few deaths over 24 weeks, therefore limiting the utility of the joint rank analysis in this study.

Thank you, and I will now hand the presentation over to Dr. Timmons.

Slide 32

Thank you, Dr. Shefner. My name is Jamie Timmons and I'm the head of Scientific Communications at Amylyx. I'm pleased to be here today to share our clinical efficacy results and to highlight the positive benefit / risk of AMX35.

Today I will highlight results that show that AMX35 is the first product to demonstrate a statistically significant benefit on function and longer survival, while being generally safe and well-tolerated.

The results show that AMX35 would give those living with ALS and their families more valuable time.

Slide 33

The CENTAUR study was conducted in 25 centers around the United States and consisted of two phases – a randomized controlled phase and an open label phase.

In the randomized controlled phase, participants were randomized in a 2:1 fashion to receive AMX35 plus standard of care or placebo plus standard of care.

Eligible participants were 18 years of age to under 80 years of age with a confirmed diagnosis of sporadic or familial ALS.

This trial included participants with clinically definite ALS, meaning participants had ALS symptoms in at least 3 of 4 body regions. Eligible participants also had a symptom onset of less than or equal to 18 months, and a slow vital capacity of greater than 60% of their predicted standardized value at their Screening Visit.

All participants were allowed to remain on or receive either or both of the existing approved therapies for ALS, riluzole and edaravone.

Participants who completed the randomized controlled phase on study drug were allowed to enter the open label phase of the study.

In the open label phase, participants originally randomized to receive AMX35 were allowed to continue, and those originally randomized to placebo were allowed to start AMX35.

Investigators and participants were blinded to study treatment throughout CENTAUR.

I'll now describe the endpoints used throughout the study.

Slide 34

The 2 phases of CENTAUR allowed the capture of important endpoints at key points in time.

During the 24-week randomized controlled phase, the primary endpoint was function.

The analysis of function was extended out to 48 weeks during the open-label phase.

Key secondary clinical endpoints included muscle strength and respiratory function. These were also measured during both phases of the study.

The final key outcome was time to events, which was measured from the start of randomization through March 1, 2021, which was up to 42 months after initial randomization.

Slide 35

All endpoints used validated tools to measure changes related to ALS disease progression.

As Drs. Paganoni and Shefner explained, the Amyotrophic Lateral Sclerosis Functional Rating Scale or ALSFRS-R is the standard scale to evaluate function in people living with ALS and was the primary endpoint in the study. All ALSFRS-R evaluators were NEALS certified and, whenever possible, the same ALSFRS-R evaluator was used to retain consistency within sites. Most ALSFRS-R assessments were administered in clinic, but there were some measurements by phone. As Dr. Paganoni reviewed earlier, the equivalency of phone versus in-person ALSFRS-R capture has been established.

In terms of key secondary endpoints, the Accurate Test of Limb Isometric Strength, or ATLIS, objectively assesses strength in 12 muscles over 4 limbs. CENTAUR was one of the first studies in ALS to employ this device.

And Slow Vital Capacity, or SVC, evaluates the total volume of air a person can expire during a slow exhalation. SVC has been shown to decline in people with ALS and correlates with deterioration in other respiratory measures, time to tracheostomy, and death.

Finally, time to event assessments included composite and individual measures of time to death (overall survival), time to first hospitalization, and time to death or death equivalent which includes tracheostomy or permanent assisted ventilation. Placement of a tracheostomy or permanent assisted ventilation can prolong life by many years, but does not alter the underlying disease pathophysiology of ALS. Analyses with and without tracheostomies or permanent assisted ventilation are, therefore, important to support the robustness of survival results.

Throughout this presentation, I will address comments raised by the FDA in terms of our study design and conduct and analysis methods with the goal to provide clarity around key points and rationale for our approach to aid in your deliberations.

Slide 36

To start, at the beginning of CENTAUR, a randomization implementation problem was identified and addressed by the unblinded statistician. Let's walk through the details.

In CENTAUR, kits were shipped one by one after successful screening visits.

While preparing for the first Data Safety Monitoring Board meeting in November 2017, the unblinded statistician found that the initial 18 study kits shipped were all active. This was due to an error at the distribution center. They proceeded to instruct the distribution center to balance these 18 kits by shipping a block of 9 placebo kits to maintain randomization.

After correction, the 2:1 active:placebo ratio was maintained.

The unblinded statistician notified Amylyx of this issue in January 2020, two months after study unblinding in November 2019. Participants, investigators, and study staff were never unblinded due to this error.

Upon notification, Amylyx initiated a thorough investigation of the root cause, in consultation with the unblinded statistician and the distribution center. Amylyx also consulted with external statisticians to determine the best approach to assess the impact. The statisticians recommended a sensitivity analysis to exclude the participants affected by the error.

Later in this presentation, I will share this analysis, which shows no impact on the primary outcome.

Slide 37

The FDA commented on the potential for unblinding due to adverse events and study drug taste, which is certainly an important risk to assess.

AMX35 does have a bitter taste; placebo was carefully taste-matched in the study and included a bittering agent. AMX35 can also cause GI adverse events. While

there are some differences in the incidence of types of GI adverse events between groups, the differences were small, events were generally mild, and the overall incidence of GI adverse events was similar between the AMX35 and placebo groups, 66% and 63%, respectively.

Based on an exit questionnaire performed at the end of the randomized phase that asked investigators and participants what treatment arm they were assigned to, neither study investigators nor participants were able to guess treatment assignment at a rate any better than chance.

Slide 38

One additional point related to study blinding. As stated earlier, investigators and participants were blinded to original study treatment throughout the entirety of both the randomized and open label phases of CENTAUR. The FDA has rightly noted that this is not specifically stated in the protocol, however all sites and investigators can attest that unblinded treatment information was not provided until the end of the open label phase and this is stated in the overall survival publication in Muscle and Nerve, of which all site PIs are co-authors.

Sites were emailed this information on October 15, 2021. As a reminder, the last participant, last visit of the open label phase was March 1, 2021.

Slide 39

The prespecified hierarchy for the randomized controlled phase is shown on the left and open-label phase on the right. The decision to use two prespecified hierarchies was based on interpretation of the 2019 FDA Guidance for Industry in ALS.

In today's presentation, I will review the bolded clinical endpoints.

Slide 40

Both prespecified statistical analysis plans were finalized prior to database lock and study unblinding in 2019.

An additional supplemental statistical analysis plan was submitted after study unblinding due to the importance of analyzing overall survival in the ITT population in addition to the prespecified mITT population. This statistical analysis

plan stated that it was supplemental to the open label phase statistical analysis plan, but would not replace it.

Slide 41

Next, let's review some background on the sample size calculation. A shared-baseline, mixed-effects analysis performed on data from ALS clinical trial databases in participants who met 2 key criteria from CENTAUR (definite ALS and ≤ 18 months from symptom onset) with a 2:1 participant randomization between treatment and placebo indicated that approximately 131 participants followed over 6 months would provide 80% power to detect a 30% treatment effect when tested at a one-sided alpha of 0.05.

This sample size calculation is conservative for a few reasons, namely that powering was conducted on a dataset which had less frequent ALSFRS-R visits and a less homogenous group than CENTAUR and it also did not calculate for the increased precision from the use of covariates.

Slide 42

The prespecified efficacy analysis population was the modified intent to treat or mITT, population. This group was defined as all participants who received at least one dose of study drug and had at least one post-baseline ALSFRS-R measurement.

The prespecified mITT population definition was recommended by the FDA.

The safety population is the same as the ITT population, which included all participants who were randomized and received at least 1 dose of study drug.

Slide 43

The study disposition for the randomized controlled phase is as follows. 137 participants were randomized 2:1 to active treatment or placebo. Two participants in the AMX35 group dropped out of the study before the Week 3 visit and did not have a follow-up ALSFRS-R measurement. They are therefore, by the prespecified analysis plan, not included in the mITT population. One of these participants died due to respiratory arrest secondary to aspiration pneumonia before the Week 3 visit. The other participant took less than 3 days' worth of AMX35 and died 27 days after treatment discontinuation following surgery for

perforated diverticulitis. Both of these deaths were considered not related to study drug.

Overall, 23% of participants prematurely discontinued from the study, which is consistent with the historical dropout rate observed in other ALS clinical trials, as noted in the briefing book. As you can see, a similar proportion of participants completed the study in each group.

The most common reason for study discontinuation in both groups was participant decision. This included various reasons such as adverse events, disease progression, perceived lack of efficacy, taste complaints, travel difficulties, and enrolling in another study.

Slide 44

92% of eligible participants who completed the randomized phase on study drug enrolled in the open-label phase, 56 participants originally randomized to AMX35 and 34 participants originally randomized to placebo.

All participants received AMX0035 in the open label phase.

At week 48 (the cut-off for ALSFRS-R, ATLIS, and SVC open label phase outcomes), 42 participants originally randomized to AMX35 and 19 participants originally randomized to placebo remained in the open-label phase.

The most common reason for open-label phase discontinuation in both groups was participant decision.

On March 1, 2021, Amylyx terminated the open label phase as there were few remaining participants, keeping the infrastructure of a multicenter trial ongoing was not practical, and ongoing evaluations were burdensome for participants. Remaining participants were able to move into an extended use protocol to continue AMX35 and safety monitoring. These participants are noted as discontinuations by study sponsor in the diagram.

Slide 45

Demographics were well-balanced between the two groups.

Participants had a mean age of 58. Age, sex, race and BMI all were balanced, and

All participants were enrolled in the United States.

Slide 46

Baseline disease characteristics for the Randomized Controlled Phase were generally similar between the two groups and were consistent with the disease population.

On average, participants were enrolled about 6 months post-diagnosis and about 13.5 months after the first onset of ALS symptoms.

Baseline scores for efficacy endpoints measured in the study were also similar between the two groups, with an average ALSFRS-R Total Score of 36.0 out of a total of 48, an average ATLIS score of 56 percent of predicted normal, and an average slow vital capacity score of 84 percent of predicted normal value at baseline.

The pre-baseline ALSFRS-R slope, or DEL-FS, was defined as the rate of decline in total score from symptom onset to study baseline and was also well-balanced between groups.

Slide 47

Most participants were taking either of the two medications approved for ALS, riluzole or edaravone, at or prior to beginning the study. A higher percentage of participants in the placebo group were taking one or both of these medications at baseline.

Next, let's review our rationale for the choice of primary endpoint model used to help address the FDA's concerns around these measures.

Slide 48

The continuous primary and secondary efficacy measures (ALSFRS-R, ATLIS, and SVC) used the same statistical model – a random-slope, shared baseline, linear mixed effects model. Participants who dropped out had all available baseline and post-baseline data included in the analysis; missing values were handled using a missing at random assumption

The model assumes a shared baseline - that all participants had the same baseline ALSFRS-R total score. The model also assumes linearity, which the FDA has raised as a concern.

As Dr. Shefner explained earlier, the ALSFRS-R has shown linear progression over time in many studies. To analyze potential nonlinearity in ALSFRS-R progression in CENTAUR, the statistical analysis plan included testing a model that included quadratic terms for time and for key covariates.

In the analysis plan, if the quadratic term for time in the mixed model was found to have significance (defined as $P<0.10$), then a quadratic model would be used instead of the linear model. However, the quadratic terms for time per the pre-specified SAP were not significant ($P>0.10$) for the primary outcome; therefore, only linear terms were retained for the final analysis.

Slide 49

In addition to the discussion around linearity, the FDA also raises concerns that a joint rank analysis was not used as the primary endpoint to address missing functional data due to deaths.

Dr. Shefner nicely reviewed the rationale for the primary endpoint choice in CENTAUR and the table shown here briefly recaps those points.

For all the reasons that study statistician Dr. Schoenfeld recommended the shared baseline, linear, mixed effects model of the ALSFRS-R as an appropriate primary analysis, including that it would provide a sensitive estimate of a treatment effect, effectively handles missing data not due to death, allows the inclusion of important prognostic covariates, and provides a clinically meaningful result, there are almost the exact opposite reasons for why the joint rank analysis was not an appropriate primary endpoint for the CENTAUR trial. Most notably, the joint-rank analysis only provides an abstract rank statistic which cannot be translated into a treatment effect of slowing of disease nor compared between trials.

Turning now to the primary endpoint results.

Slide 50

The prespecified primary endpoint was met in the randomized controlled phase of the trial.

Participants treated with AMX35 showed a statistically significant slowing of functional decline compared to placebo.

The groups separated at a rate of 0.42 points per month, which represents a 25% slower decline in function for the AMX35 group compared to placebo.

Importantly, this separation began as early as week 6 and was sustained through Week 24. This effect was seen on top of standard of care use of approved ALS medications, riluzole and edaravone.

Slide 51

At the end of the randomized controlled phase, this slowing of functional decline in the group treated with AMX35 resulted in a 2.32 point benefit on the ALSFRS-R scale.

Slide 52

As discussed earlier, the primary model assumes that both the AMX35 and placebo arms start from the same baseline score and progress linearly over time. Analyses were performed to determine whether either the shared-baseline or linearity assumptions were critical to detect a treatment effect.

A post hoc analysis was conducted in which each individual participant's change from baseline was evaluated instead of assuming a shared baseline across the study. Under this statistical model shown in the top row, AMX35 treatment had a 2.9 point mean difference in the ALSFRS-R total score after 24 weeks.

An additional analysis was also performed that did not use a linear model and instead utilized separate means by visit, a so-called traditional mixed model for repeated measures. This model, in the second row, shows similar results. We do note that our means-by-visit results do not exactly match the Division's—we attempted to run a traditional MMRM and have not seen the statistical methodology by the Division so it is hard to know what the differences may be. Regardless, the outcomes are generally similar.

These results demonstrate that the shared baseline assumption and the linearity assumption are not required to observe benefit.

Slide 53

To provide a visual, the graph of the separate means by visit data are shown here. As Dr. Shefner pointed out earlier, even without the linear assumption, the

progression of the ALSFRS-R is linear over the course of the randomized control phase and the results remain consistent when linearity is not assumed.

Slide 54

Shifting gears, here I am showing results from the sensitivity analysis conducted as a result of the randomization error discussed earlier.

This sensitivity analysis excludes participants who were affected by this error at the start of the study. As shown, the results were not different from the prespecified primary analysis shown at the top. This suggests that the randomization error did not select for different participants or bias the primary result.

Slide 55

As noted, most participants in the study were taking riluzole or edaravone at baseline. In uncommon cases, participants did initiate these drugs during the study. The FDA has commented on an imbalance in the number of participants in each arm initiating edaravone or riluzole post-baseline, and potential risks for confounding due to this imbalance.

Sensitivity analyses were performed to address both baseline use and post-baseline initiation of these concomitant medications. The effect of these medications on the primary outcome was analyzed both with a time-dependent covariate based on total post-baseline use during the randomized controlled phase of the study and with a categorical covariate based on baseline use of riluzole and edaravone.

Results shown here are from the analysis using the time-dependent covariate and show that the beneficial effect of AMX35 on ALSFRS-R was consistent after adjusting for time on each medication during the randomized controlled phase.

Slide 56

Results from the analysis adjusting for baseline use of edaravone and riluzole were also consistent with the primary outcome as seen here. The data shown are points change per month with the primary outcome at the top and then the adjustment for edaravone and riluzole below. As you can see, results were

consistent with the primary outcome when adjusting for the use or non-use of edaravone and riluzole.

These two concomitant medication analyses addresses the FDA's concern about potential confounding from these medications.

Slide 57

As shown earlier, 23% of participants discontinued the study, so it was important to analyze the impact of missing data on the primary outcome.

A linear mixed model for repeated measures using multiple imputation from the placebo arm to impute assessments missing after discontinuation of study drug was performed as a prespecified sensitivity analysis.

The analysis assumed participants who discontinued from the AMX35 group were the same as matching participants who never took active treatment. This represents a common imputation method to provide a conservative estimate of he effects of missing data.

The treatment effect sizes and p-values remained similar to the primary analysis, suggesting that the primary endpoint results are robust even under conservative assumptions regarding missing data and dropouts.

Slide 58

While the joint rank analysis was not an appropriate primary endpoint for the study, post hoc sensitivity analyses were undertaken to account for the impact of deaths on the primary outcomes. As reviewed earlier, the joint rank analysis is expected to have less power to detect treatment differences in this trial.

The top row is a joint rank analysis that utilized last available data for deriving rank.

To help address the FDA's comments around the handling a missing data and exclusion of participants in the mITT population, a second analysis was performed that instead utilized multiple imputation on the ALSFRS-R outcomes in the ITT population, shown in the second row.

Finally, given that the initiation of permanent assisted ventilation is considered a death equivalent event, truly that a participant would die without ventilatory

support, it is also informative to include both death and permanent assisted ventilation events in the joint rank analysis, as shown at the bottom.

We note that our results are slightly different than the FDA's. We do not have adequate information on the FDA's model to determine differences but it is possible this is due to different multiple imputation algorithms. Regardless, the results are very similar.

Despite being less powered, these post hoc analyses were consistent with the results of the pre-specified primary efficacy analysis.

Slide 59

An alternative analysis to account for death in assessing the primary outcome is to assign a worst case value for the ALSFRS-R.

This slide shows a few different approaches for this worst case analysis. A pre-specified left censored analysis that adjusts the ALSFRS-R towards a worse outcome for participants who died, and then post hoc analyses that use a worst-case imputation of an ALSFRS-R score of 7 (the lowest observed value in the study) and 0 (the lowest possible ALSFRS-R score)

The results of these models are consistent with the primary outcome and provide confirmation that when death is incorporated into the primary outcome, the results remain consistent.

Overall, both the joint-rank and additional continuous models to account for death confirmed that the primary outcomes results are unlikely to be confounded by death.

Slide 60

Since CENTAUR was a large, multicenter trial with 25 centers spread across the US, it's important to analyze the contribution of each site to the overall result.

A sensitivity analysis which removed each site one at a time and evaluated the ALSFRS-R change from baseline result. This analysis used the change from baseline model as the shared-baseline model would miss baseline differences at sites which could be important.

Each line represents a site – the number of participants at each site are listed along the right of the slide. This analysis showed that no single site was disproportionately responsible for the difference in ALSFRS-R between AMX35 and placebo; the effect size remained consistent and statistically significant across all sites.

Slide 61

Finally, it can be helpful to look at the primary outcome data from the individual response perspective. While there is no clear definition for what constitutes a "responder" in ALS clinical trials as all participants continue to progress, one simple approach is to compare rate of disease progression before and after initiation of treatment with study drug. In this post hoc analysis, participants whose actual rate of change from baseline in the ALSFRS-R at week 18 was ≤ their own pre-baseline progression rate (del-FS) were defined as having a response in slowing ALS progression. Participants who dropped out before week 18 were automatically considered "non-responders." This is expected to be a conservative analysis as the del-FS has consistently been found to underestimate post-baseline ALSFRS-R decline in clinical trials.

Using this conservative definition, individual response was observed in a greater proportion of participants receiving AMX35 (41%) vs placebo (19%, P=0.008).

This concludes the review of ALSFRS-R data from the 24-week randomized controlled phase, let's now shift to the longer-term ALSFRS-R results through Week 48.

Slide 62

As a reminder, all participants who completed the 24-week randomized controlled phase on study drug were eligible to continue on treatment or cross-over from placebo.

Here are the results of the ALSFRS-R evaluated using the same shared-baseline, mixed-effects model as the randomized controlled phase now out to 48 weeks. This compares the difference in slope from the randomized controlled phase baseline through Week 48 between the 2 original treatment groups.

Comparing the slope difference between the two groups at 48 weeks, a statistically significant, 4.2 point difference on the ALSFRS-R for the group originally randomized to AMX35 is seen.

This model assumes a single slope over the 48-week period and is, therefore, assessing if the treatment effect is sustained, but not if there is a crossover effect.

Slide 63

To assess if the group originally randomized to placebo received benefit from AMX35 after cross-over, the estimated rates of progression in the ALSFRS-R during each phase of the study (randomized controlled and open label) can be compared using the primary model as shown on this slide.

It's important to caveat that crossover analyses are inherently challenging due to missing data and as people are at different stages of disease in the initial 24-weeks as compared to the following 24-weeks.

However, as seen in the placebo + SOC row, results suggest that the originally randomized placebo group had numerically slower progression once they crossed over to AMX35.

Slide 64

Let's pause briefly to review the ALSFRS-R results presented thus far.

Participants treated with AMX35 showed a statistically significant slowing of functional decline compared to placebo at the end of 24 weeks.

This finding was robust across a number of sensitivity analyses evaluating for the impact of missing data, participant death, concomitant medication use, model linearity assumptions, and individual site impact. Notably, results on the less-sensitive joint-rank analysis suggested by the FDA are consistent.

Furthermore, participants originally randomized to AMX35 showed sustained benefit of treatment on the ALSFRS-R at 48 weeks and there was some evidence for a benefit when the placebo group crossed over to AMX35.

Slide 65

I'll now show the data from key clinical secondary endpoints.

Slide 66

Here are the secondary clinical endpoint results from the randomized controlled phase, the first 24 weeks. Again, shown at the top is the primary endpoint. While the study was only powered to detect differences on the primary outcome, all clinical secondary endpoints shown favor AMX35, further supporting the primary endpoint findings.

The first secondary outcome was Total ATLIS; because ATLIS did not reach statistical significance, all subsequent secondary outcome p values presented are nominal.

As a reminder, the ATLIS measures muscle strength. Results for both upper and lower limb strength favor AMX35 over placebo.

The upper limb score was nominally significant, while the lower and total scores did not reach significance.

Another key secondary outcome was pulmonary function, as measured by the slow vital capacity, or SVC.

At the end of the 24-week randomized controlled phase participants on placebo were observed to have 61% of normal breathing capacity while participants on AMX35 had 66% of normal breathing capacity, a clinically meaningful difference of 5% of normal breathing capacity at the end of 24 weeks.

Slide 67

We saw similar benefits on these same measures at 48 weeks. Same as the Week 48 ALSFRS-R data I reviewed earlier, the analyses shown here are comparing the difference in slope from the randomized controlled phase baseline through Week 48 between the 2 original treatment groups.

The ATLIS and Slow Vital Capacity secondary endpoints all were in favor of AMX35 treatment.

Now turning to time to event outcomes, including overall survival.

Slide 68

The progressive loss of function in ALS eventually results in hospitalizations, the need for tracheostomy and permanent assisted ventilation, and eventually death.

The final set of data I will review today assessed these pre-specified time to event endpoints from study baseline out to 42 months (or 3.5 years) after the initial randomization.

Slide 69

Note that while I presented the Week 48 ATLIS and SVC results after ALSFRS-R to share the continuous efficacy outcomes together, the composite time to event endpoint was pre-specified as the second efficacy outcome after ALSFRS-R in the long-term follow-up statistical analysis plan.

Slide 70

The time to event endpoints use a cut-off date of March 2021, which corresponds to last participant last visit in the Open Label Phase.

A key point when reviewing this data is that the groups compared are those originally randomized to AMX35 and originally randomized to placebo. Recall that the majority of participants in the original placebo group crossed over to AMX35 after the 24-week randomized controlled phase. Therefore, the delayed use of AMX35 in the majority of the original placebo group is likely to attenuate treatment differences.

The time to death or overall survival endpoint has minimal missing data – in fact, the survival status of 136 out of 137 participants is captured as of March 2021; the one participant not captured as of the cut-off date is censored as of their last clinic contact. Survival status was confirmed even on those participants who dropped out of the study through an evaluation of public records including the social security death index and state and city records.

While death events were able to be collected even for participants who dropped out of the study, hospitalizations and death equivalent events may not have been collected after dropout. As such, there is some risk of missing data when hospitalizations and tracheostomies and permanent assisted ventilation are included in the composite analysis.

Finally, I would like to highlight that we have noted FDA comments around what was pre-specified in the statistical analysis plan and have ensured that all values

presented today align with the plan. Specifically, we have addressed the comments on the likelihood ratio and baseline covariates.

Now, to review the pre-specified mITT composite time to event results.

Slide 71

The pre-specified time to event outcome was met. As of the March 1, 2021 cut-off date, 112 events were captured – that's 82% of randomized participants with an event. There was a statistically significant median 4.8 month difference in time to death, first hospitalization, or tracheostomy/permanent assisted ventilation in the group originally randomized to AMX35 compared to the group originally randomized to placebo. The hazard ratio was 0.62 and p-value was 0.023.

Slide 72

In addition to the composite pre-specified mITT time to event endpoint, the individual outcomes of time to first hospitalization, death, and death or death equivalent (tracheostomy or permanent assisted ventilation) all show a consistent benefit for early and continuous treatment with AMX35 in the mITT population.

Slide 73

While the statistical analysis plan prespecified the mITT population for efficacy outcomes, the ITT population is often considered the most robust population to use for survival outcomes. As such, we performed an ITT overall survival analysis at the same March 2021 cut-off on all participants randomized in CENTAUR to capture the most robust survival outcome possible. At the time of March 1, 2021 data cutoff, 94 deaths had occurred representing nearly 70% of randomized participants.

Recall that this overall survival analysis has essentially no missing data. In this comprehensive analysis, we see a statistically significant median survival difference of 4.8 months between those participants originally randomized to AMX35 compared to those originally randomized to placebo and a 36% reduction in the risk of death on top of standard of care.

It is expected this analysis underestimates the treatment benefit, given that the majority of original placebo participants do receive delayed AMX35 treatment

after 24 weeks. However, this analytical method preserves the randomization and is the most rigorous method of analyzing overall survival.

It's easy to get distracted by the nuance of the placebo group cross-over and how much the treatment effect may be underestimated because of that, but it bears repeating that treatment with AMX35 results in an ITT overall survival benefit of 4.8 months and a 36% reduction in the risk of death on top of standard of care in a rapidly progressing and universally fatal disease.

Slide 74

Similar to the mITT composite and its individual outcomes, the ITT composite and individual time to event outcomes of time to first hospitalization and death equivalent showed consistent benefit in increasing median time to event in the group originally randomized to AMX35.

Slide 75

Composite and individual overall survival outcomes were assessed at 3 timepoints over long-term follow-up: February 2020, July 2020, and March 2021. Let's walk through the rationale for each of these cut-offs.

February 2020 corresponds to the initial longer-term survival evaluation after the randomized controlled phase. This was performed in relation to a March 2020 Type C meeting with the FDA.

In, July 2020 the longest follow-up was 3-years post-randomization and ~50% of participants had reached median survival. This cut-off was published in Muscle and Nerve.

March 2021 corresponds to the last participant last visit in the open-label phase and was requested by the FDA as the key timepoint for analysis for benefit / risk. The long-term follow-up statistical analysis plan also specifies that survival would be assessed at the end of the study, so we have chosen to present this as the main analysis.

Regardless of cut-off date, the survival benefit for AMX35 was consistent, showing a hazard ratio between 0.57 to 0.64.

Slide 76

Before summarizing the data, I'd like to summarize key comments raised by the FDA and how we have addressed each of them.

Regarding the potential for unblinding, it is unlikely that taste or GI adverse events led to unblinding and exit questionnaire results support that investigators and participants were not unblinded.

In terms of linearity, the pre-specified sensitivity analyses supported the use of linear terms. The FDA also notes that the linearity assumption was not violated per the prespecified SAP.

Regarding the decision not to use joint rank, trial statistician and co-inventor of the Finkelstein-Schoenfeld joint rank strongly encouraged against its use as the primary outcome in this study due to the expectation that there would be a low frequency of deaths in the 24-week randomized period. Joint rank analyses were performed as post hoc sensitivity analyses and results were consistent with the pre-specified primary analysis despite less power with this method.

In terms of survival methodology, the data presented are fully aligned with the pre-specified statistical analysis plan and highlight that, while 3 different survival analysis cut-off dates were used, they all showed a consistent survival benefit with a hazard ration between 0.57 to 0.64.

Finally, as reviewed throughout the presentation, additional analyses were performed to address and align with comments from the FDA and those analyses all support the robustness of the data.

Slide 77

Now that we've spent some time on clarifying statistical differences, let's get back to the pre-specified efficacy results.

To summarize the efficacy data, AMX35 demonstrated a statistically significant and clinically meaningful benefit on both function and survival.

The prespecified primary outcome was met, AMX35 treatment resulted in a significant slowing of disease progression as measured by the gold-standard ALSFRS-R. This result remained robust across multiple sensitivity analyses and was on top of standard of care

Secondary outcomes measuring clinical decline supported the primary outcome and were numerically in favor of AMX35.

The prespecified mITT composite time to event outcome was met and,

most importantly, there was an ITT overall survival benefit that showed a 36% reduction in the risk of death over the time of follow-up in a universally fatal disease

Let me now briefly summarize the safety data…

Slide 78

Adverse events and deaths were balanced between the treatment and placebo arms.

While GI events with AMX35 occurred more frequently in the first 3 weeks of treatment, they generally tapered off to the same level as placebo throughout the rest of the study.

There were fewer SAEs with AMX35 and most were related to ALS progression.

More adverse events that led to drug withdrawal in the AMX0035 group were related to gastrointestinal symptoms.

Overall, AMX35 was well-tolerated, with a favorable safety profile.

Slide 79

To close, the totality of the evidence supports a positive benefit-risk for AMX35. There is substantial evidence of efficacy on critical endpoints of function and survival in a rare and rapidly fatal disease with high unmet need and AMX35 was generally safe and well-tolerated in the Centaur study.

I'll now turn to Dr. Paganoni to present her clinical perspective.

Slide 80

Thank you, Dr. Timmons.

I'd like to close the presentation by sharing my clinical perspective on the data you have seen today and what they mean for my patients and for physicians like me who treat them everyday.

Slide 81

What my patients keep reminding me is how precious time is and how little time they have. We all know that we have limited time in life, but when you have ALS, it is more urgent -every month, every week, every day counts. In this fast-progressing, universally fatal disease, more time to spend with your loved ones is a gift.

As a reminder, by the time someone is diagnosed, their symptoms have already started to take over their bodies, and they quickly lose independence – whether it's walking, feeding, dressing, or eventually breathing.

Patients tell us that they want to retain function for as long as possible.

The two currently approved treatments for ALS show either a benefit for survival or a slowing in functional decline, but neither has demonstrated both in the trials that led to their approval.

Slide 82

This importance of both function and survival is why AMX35 would make such a difference in the lives of people with ALS.

AMX35 leads to a sustained slowing in functional decline which means that access to this drug could allow people living with ALS to maintain their independence for longer. This 25% slowing of disease progression is statistically significant and exceeds the 20% threshold of being clinically meaningful according to experts.

In addition to longer functional retention, access to AMX35 also means longer survival. Importantly, people treated earlier and longer experienced the greatest benefit to survival. As a reminder, earlier I showed you that a median overall survival benefit of 2.5 to 6 months and a Hazard Ratio of less than 0.8 are considered clinically meaningful in oncology. Here, we see a median survival benefit of 4.8 months and an Hazard Ratio of 0.64 with AMX35, which are results we have not seen in any ALS clinical trials to date.

Slide 83

Of importance to all of us who are practicing clinicians, AMX35 has a favorable clinical profile.

It is easy to administer by mouth or feeding tube and is well-tolerated.

In the trial, gastrointestinal side effects such as nausea, diarrhea, or abdominal pain were seen. But they were generally MILD or moderate and manageable and occurred most frequently during the first 3 weeks.

As I mentioned earlier, the multi-pathway nature of ALS necessitates targeting different mechanisms at once with a cocktail approach. Based on the results of CENTAUR, AMX35 can be safely combined with riluzole, edaravone, or both, which makes it easy to add to standard of care.

Slide 84

The discussions we are having today are important for this trial and the ALS community at large.

As a lead investigator in numerous clinical trials, including the ongoing Phase 3 trial for AMX35, I understand the importance of substantial evidence. I recognize that the study was small, however, this is a rapidly progressing and fatal disease and it's important that we look at these results in this context.

At this time, we have evidence from a clinical trial that DEMONSTRATES the efficacy and safety of AMX35. The study met its prespecified primary outcome and the study showed a clinically meaningful benefit on both function and survival. In addition, AMX35 demonstrated a good safety profile. These are the outcomes that matter to patients.

For these reasons, if approved, I would immediately add AMX35 to my STANDARD OF CARE FOR ALS to ensure that my patients prolong THEIR FUNCTION AND THEIR LIVES for as long as possible.

Thank you for your attention.

Slide 85