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Center for Biologics Evaluation and Research (CBER)

75th Meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC)

Zoom Video Conference

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Chair (Acting)	Tabassum (Taby) Ahsan, Ph.D.	Vice-President, Cell Therapy Operations, City of Hope	Duarte, CA
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Guest Speaker			
Guest Speaker	Evan Y. Snyder, M.D., Ph.D., F.A.A.P.	Director, Center for Stem Cells and Regenerative Medicine Professor, Human Genetics Program Sanford Burnham Prebys Medical Discovery Institute	La Jolla, CA
Applicant Presenters			
	Stacy Lindborg, Ph.D.	Co-Chief Executive Officer, BrainStorm Cell Therapeutics	
	Anthony J. Windebank, M.D.	Judith and Jean Pape Adams Professor; Faculty Development Chair, Department of Neurology, Mayo Clinic	
	Lee-Jen Wei, Ph.D.	Professor of Biostatistics, Harvard University	
	Nathan Staff, M.D., Ph.D.	Professor of Neurology; Research Chair, Department of Neurology, Mayo Clinic	
	Robert Bowser, Ph.D.	Chief Scientific Officer; Chair, Department of Translational Neuroscience, Barrow Neurological Institute	
	Kirk Taylor, M.D.	Executive Vice President, Chief Medical Officer, BrainStorm Cell Therapeutics	
Open Public Hearing Speakers			

Mandi Bailey	
Andrea Goodman, M.S.W., M.P.H.	CEO of "I Am ALS"
Philip Green	
Robert Hebron	
Mitze Klingenberg, B.S.N., R.N.	
Joe Morris	
Ajay Sampat, M.D.	Associate Clinical Professor of Neurology, University of California Davis
Kandy Simons	
Josh and Paula Smith	
Amanda Stevens	
Michael Abrams, M.P.H., Ph.D.	Senior Health Researcher from the Public Citizen Health Research Group
Jeffrey A. Cohen, M.D.	Director of Experimental Therapeutics at the Cleveland Clinic Mellen MS Center
Brooke Eby	
Ron Hoffman	Founder and Executive Director, Compassionate Care ALS
Professor Dimitrios Karussis, M.D., Ph.D.	Director of the Neuroimmunology and Cell Therapies Unit at Hadassah University Hospital; Jerusalem, Israel
Brian Wallach	
Dr. Diana Zuckerman	President of the National Center for Health Research

Contents

Dr. Ahsan: Great. Thank you very much. In order to keep things moving so that all thoughts can be presented, Dr. Tuszynski, would you like to present on the topic of biomarker data and how it contributes to our understanding of product effectiveness?

Dr. Tuszynski: Okay, and by biomarker, I take it you mean the neurotrophic factors, yeah?

Dr. Ahsan: Yes.

Dr. Tuszynski: Okay.

Dr. Ahsan: Yes, thank you.

Dr. Tuszynski: So, the neurotrophic factors that were the subject of emphasis were BDNF, VEGF, hepatocyte growth factor, and LIF, Leukemia Inhibitory Factor. And in the literature, there is evidence to support an effect of BDNF and LIF on motor neuron survival, and there's also evidence to support their effects on upper motor neuron survival in the motor cortex. I'm not familiar with evidence that suggests that VEGF itself directly affects motor neuron survival in the spinal cord or the brain, but there might be a study I'm not familiar with. Then, with regard to hepatocyte growth factor, it's considered a trophic factor for several spinal cord populations though. Again, I'm not exactly aware whether it's been shown to have a specific effect on motor neurons. So, of these, the data from the Phase III clinical trial really showed no difference that was substantive or sustained in any of these. In the case of vascular endothelial growth factor, there was this rise that was shown at two weeks after injection and as was pointed out, we didn't have another two weeks sampling after the subsequent injection. So, we don't know if there might have been a boost. All we know is that there was this boost in VEGF, and it would have been informative to hear more from the sponsor why they think this boost in VEGF might have been useful for motor neuron degeneration. Did they think it was going to induce vascularization,

or did they think it was a direct trophic factor induced effect on the cells? And if the latter, again, I'm not familiar with such literature, but maybe it exists.

The amount of the various growth factors that was sampled in the spinal fluid, other than VEGF at the two-week time point, however, represented very little departure from the placebo data. And the point that I was making with regard to mechanism of action about half an hour ago was that in growth-factor trials, if one doesn't attain very substantial boosts and growth factor levels, even with substantial boosts in growth factor levels in the spinal fluid, there's very little evidence that those growth factors penetrate the spinal cord parenchyma. So, with the kind of very modest changes, if any, that we're seeing here, I'm not convinced that there's evidence that these biomarkers could be penetrating the parenchyma of the spinal cord to provide a beneficial effect. I haven't seen data that is compelling to indicate that these could be biologically meaningful elevations that are represented in the tissue itself. And I did explore that question with the sponsor in the question period initially, and I believe the answer was the growth factor levels were not measured there because it's difficult to do so. And it can be done, and I don't think that the data exist. Those are my comments.

Dr. Ahsan: Thank you very much. That's very helpful. I think in general, some questions about the selection of the subset of markers, the levels at which they're expressed, all of that is quite important. Are there any comments from the committee, particularly on this aspect of the biomarkers? We've had quite a bit of conversation on the biomarkers throughout. Are there any more additional comments that need to be made at this point? Great, thank you, Dr. Tuszynski. So now, if we could move to Dr. Alexander to start us off on the discussion on the topic of clinical data in support of effectiveness.

Dr. Alexander: Yeah, sure. Great discussion by the way. Thus far, I think the clinical data are helpful. They're just disappointing. And frankly, they're hard to reconcile with the compelling anecdotal evidence of effectiveness that we heard from the public speakers. We have a single trial at the dose and formulation that's proposed. Although the Phase II study didn't suggest efficacy. And frankly, both safety and efficacy in the Phase II study are hard to interpret because it was a different dose schedule and route of delivery. I did ask why they gave people 19 muscular injections or something if this doesn't cross the blood-brain barrier, but I didn't really understand the response. But that's a little bit neither here nor there.

Unfortunately, we have a single study, the Phase III study at the dose and formulation that's been proposed, and it unfortunately didn't achieve evidence of efficacy for either the primary or the secondary endpoints. I think we heard, and I certainly agree as an epidemiologist with the FDA's assertion, that post hoc analyses are subject to strong and untestable assumptions. And guidance may allow for the approval of a product based on a single pivotal trial plus confirmatory evidence, but not no clinical trial plus confirmatory evidence. Not a trial that's not successful in demonstration of efficacy. And frankly, although there are some, I think, unfortunate examples, I would argue, I think if you look at the majority of cases where FDA has used a single trial it's been with very strong evidence to support the approvals. The floor effect is possible with any bounded rating scale. I thought it was interesting to hear that, but then also I did appreciate hearing from one of the sponsor’s speakers that's addressed one question which I had, which is if it's present with any bounded scale, wouldn't why would It wasn't this anticipated, before the trial was done? But I think this addressed that a bit and spoke to the fact that it wasn't, it generally hasn't been seen. The effect hasn't been seen as strongly in ALS scales previously, and so on. Maybe it wasn't expected that people would be with a severe disease as

they were, but with all of that said, the analyses of the floor effect, I didn't find terribly convincing. And frankly, I think the FDA's analyses of that demonstrate why post hoc analyses, while they can be helpful and supportive, aren't sufficient in weight to overturn a negative top line result. And I guess the final two comments that I'll say one is that the rap or progressor or language is nearly identical to other committees I've served on, including Aducanumab in the case of Alzheimer's disease and at a person in the case of Duchenne's. And this sort of language is, I think, an understandable way to try to understand and make sense of disappointing topline results, but there will always be rapid progressors, right? There will always be people that respond more and less to a treatment. And of course, if you remove those who respond less, you end up with those who respond more.

So, I'm very interested in the sponsor's response to the same question I asked the FDA, which is, if you were to design a new trial, how would you do it differently? But it sounds like we'll have a chance to advise the sponsor on that shortly. And so, I'll conclude my comments with that. Thank you.

Dr. Ahsan: Thank you very much. And exactly right. We are meant to give some guidance on that, aspect. Dr. London.

Dr. London: Yes, just to follow-up on the floor effect. I think that if you believe there's a floor effect that actually is evidence to me that, unfortunately, this is not an appropriate endpoint to try and measure benefit of the treatment effect. So, if you believe the floor effect, I think it just leads us to the fact that we need to do better on a better primary endpoint. And unfortunately, I understand that this has been a standardized instrument used in ALS for many years, and we're not going to come up with a new instrument overnight. But hopefully there is something better and we can talk about that in the clinical trials proposal time slot.

Dr. Ahsan: Thank you, Dr. London. Dr. Johnson.

Dr. Johnson: Yes, thank you. I think I also agree that I found the clinical data not compelling enough to support efficacy and I wanted to particularly call out the imbalance in mortality, which has been brought up a couple of times and for me at least raises some safety concerns. I know people talked about the other potential side effects, but that type of imbalance would need to be addressed in future trial designs as it says beyond the primary endpoints that there may be a mortality issue.

Dr. Ahsan: Thank you, Dr. Wolfe.

Dr. Wolfe: Yeah, I'll just add on to what Dr. Johnson just said. We've talked about the survival data. When I was looking at the data, the actively treated arm, this was in the largest collection of adverse events, life-threatening adverse events. Bulbar and respiratory adverse events were higher in the actively treated arm. Again, I will bring up the point that the randomization, the burden of bulbar disease actually seemed to be less in the actively treated arms. So, there's something there that is not jelling. And when you add that on to the survival data it creates concern, at least for me.

Dr. Ahsan: Thank you. So, anyone else who would make like to make a comment? Not only on the clinical data, but the biomarker data, the mechanism of action, anything related to question one. Great, I think we had a good, robust, dynamic conversation. Let me try to pull it together a little bit and apologies if it's not so well-organized, and then if I miss something. Of course, potentially committee members can add on to what I say. So, I think, in general, the thought is the mechanism of action is not clear. And the sponsor did not necessarily put forth a clear hypothesis related to the mechanism of action in terms of the MSC roles and the NTFs.

It is understandable that at this point, it's early so that the hypothesis related to the trophic mechanism might be unclear, but there was still a lack of preclinical data that was presented. And in general, there was a lack of data that was presented that was unfortunate and makes it such that the committee has to make decisions based on what was presented. There was also some discussion that there are multiple NTFs and the thought was that they together have a function. However, the dosing of those and the target engagement of that was not clearly proposed forth in terms of the levels of elevation, potentially a weighted equation of the different ones that would help create a pattern that we saw in each individual patient cell types as they got overexpressed in this product of the MSC-NTF. It was also unclear how it would get delivered into what tissues. The thought is that's unclear, even when you have high concentrations, but with the low concentrations of some of the markers that were selected, that becomes further confounding as to how you would expect what tissues they would be in and how long that they would persist. The lack of data of showing even their persistence and expression in vitro makes it even more challenging to interpret how the in vivo environment might modulate that. So, in thinking about the biomarkers further, what governed the selection of those markers? How were they justified? How we expected those to function in those low levels, we usually expect a substantial boost in the trophic factors that we're hoping to have some role and mechanism of action. And it wasn't clear that was anything that was happening with this product. Again, we have no way to track the concentrations that were happening in vivo, nor how long they persisted but there was a lack of preclinical data that was presented to even give us some sense of that.

In terms of the neurofilament data that was confounding because the response was maybe the exact opposite of what we would expect if we thought that there was any correlation in the data that was presented by the FDA. And we saw such a clean correlation in the Tofersen data.

So, it leaves us with questions of what might be working there. In general, with the clinical effectiveness, the data was there for one clinical trial. I think Dr. Alexander made the comment that it's unusual to go with just one trial. If you do, you hope that the data is compelling. It wasn't so compelling in this case. And in fact, there was a concern about mortality and the bulbar responses and how those results were looking, all of this was further stratified. The statistics was stratified in this floor effect concept. There seems to be a very disparate interpretation by the FDA and the sponsor in that regard. The FDA taking the position that such stratification was in essence an overanalysis and leads to potentially false interpretation. The sponsor trying to make the case that floor effect really does separate out subpopulations that are clinically meaningful.

However, when we looked at that data that we looked at the floor effect and it was separated out for placebo versus treatment. The placebo floor effect was not distinguishable and that makes it challenging because we don't understand the baseline progression of the disease to really understand how the floor might play a role in that. I think that is the essence of the conversation on multiple different fronts without recapitulating exactly everything that was said. I don't think that at this point, we will be taking comments from the sponsor related to this, but is there anyone from the committee that would like to add nuance to what I said? Or something I may have misrepresented in the chaos of trying to summarize or maybe misunderstood? Any comments from the committee? Dr. Fischbeck, please.

Dr. Fischbeck: I don't want to hog the mic here, but I just wanted to reiterate or voice my support for the comments by Dr. Gold and Dr. Lee in response to the comment by Kathleen O'Sullivan-Fortin about individual experience with the drug versus the experience in an organized study like this. And I think we, the FDA, and by extension, the members of this committee are charged with trying to give patients and prescribing physicians information about the safety and efficacy of a

product. And if we don't have it, then it's good to say that or, if the risk-benefit isn't quite what the sponsor would like it to be, we're supposed to say that also. And it's dangerous, heartfelt as these testimonies are, and I can really feel the pain having taken care of a number of ALS patients over the years, and I think that it really is a disease that needs a safe and effective treatment. And I think there are a lot of other prospects out there that we have encourage and approving one like this would get in the way of that.

Dr. Ahsan: Great. Thank you, Dr. Fischbeck and to remind me to actually summarize that part, even though it wasn't part of the discussion question, we heard some anecdotal stories that are an important perspective to hear. But we also did hear from Dr. Lee about being very thoughtful and not overly optimistic interpreting data, because that also comes at a cost. So, there's a lot to consider the opportunity costs, but then also potentially the cost of going down the wrong direction. Both of those are things to think about. Whether we move forward or whether we not. Dr. Shah.

Dr. Shah: Yeah, I'll just comment. I'm a cancer physician. And I think one of the comments that somebody made was that incremental change in ALS, maybe you should follow where the field is with cancer and just cancer in general, what we've learned over the years. I think what I am really struggling with is that I don't know that the underlying pathophysiology of ALS is understood well enough. And so, we're trying to come up and understand the mechanism of mesenchymal cells and this endotrophic factor, but there's just so many components that are unknown. And so, despite the preponderance of data, all of the biomarkers, I feel like we're left with a lot of uncertainties when you don't really know what it is that you're trying to do. And so, the functional outcomes to me, even if it is in a few patients, how do you weigh that? And so, I think that's something I will say that I am very much struggling with.

Dr. Ahsan: Thank you. That's a great point. These cell therapies are less well-characterized and understood than we would like and they're going in to treat a pathophysiologic condition that in this case is maybe less well understood than we would like as well. So, that does lead us with some quandaries. Dr. Gold.

Dr. Gold: Yeah just a quick comment to Dr. Shah. So, look you're right. We don't have a complete understanding of ALS. We don't have a complete understanding of depression and schizophrenia, but we still managed to get effective drugs out there. But when you don't have that kind of detailed knowledge and you want to address multiple pathological pathways at the same time, that's where it becomes really clear. You got to know exactly what it is you're giving.

Dr. Ahsan: Thank you.

Dr. Gold: We don't know and it's unclear that compounds that go after very single selective targets, other than these kinds of monogenic disorders like SOD-1. Right? That's an exception. But for sporadic ALS, these kind of multi-modal or multi-pathway approaches make sense. But like I said, you really have to understand what it is you're giving a patient.

Dr. Ahsan: Right. It's hard to work with two unknowns for sure.

Dr. Gold: So, they tell me. That was my first science lesson, right? Only modify one factor in an experiment, right?

Dr. Ahsan: Exactly. Scientific method comes back. Okay. So, I think we are running a little bit behind, but I do feel like everyone on the committee has gotten the chance to voice their opinions on this discussion question. There are no more raised hands. So, I think at this point, we need to go to the vote. Marie.

Ms. DeGregorio: Yes, when you are ready to proceed, we will.

Dr. Ahsan: Yes, I think we're ready to proceed to the vote.

Vote

Ms. DeGregorio: Okay. Sounds good. We're on the next slide. Thank you, everyone, and Dr. Ahsan. At this time, I will explain the voting process.

Only our 7 regular committee members and 12 temporary voting members, a total of 19 individuals, will be voting in today's meeting with respect to the voting process. Dr. Ahsan will read the voting question for the record. At this time, the FDA AV will move all non-voting members out of the main Zoom room. For those non-voting members in the Zoom room, please do not log out of Zoom. We will move you back into the main Zoom room in a few minutes after the voting is conducted. When only the voting members are present in the main Zoom meeting room, the chair will read the voting question again for the record. At this time, all voting members and temporary voting members will be asked to cast their vote by selecting one of the three voting options on their screen, which consists of yes, no, or abstain. To all voting members, you will have one minute to cast your vote after the question is read by the chair. Please note that once you have cast your vote, you may change your vote within the one-minute time frame before you press the submit button. Once the poll is closed, all votes will be considered final. Once all votes have been cast and non-voting members are put back into the main Zoom room, we will display the voting results and read the individual votes allowed for the public record. This process may take a few minutes and so before we start, does anyone have any questions related to the voting process?

Dr. Tuszynski: I'm sorry, where do we vote?

Ms. DeGregorio: We will provide a pop-up screen once all of the voting members are within the room minus any non-voting members. So, once we have you all arranged in the room as a group, AV will pop up a pop-up message and there will be radio buttons where you'll be able to

vote. So, it'll come up automatically. And if anyone has any trouble, just put it in the chat immediately, and then we'll work on a solution for you.

Dr. Tuszynski: Thank you.

Ms. DeGregorio: Alright. Okay. Dr. Ahsan, could you please read the voting question for the record?

Dr. Ahsan: So, the voting question is, do the data presented demonstrate substantial evidence of effectiveness for treatment of mild to moderate ALS? The options are A. Yes. B. No. C. Abstain.

Ms. DeGregorio: Okay, thank you. Okay we now need to prepare the Zoom room for the vote. Voting members and TVMs, please stay present. At this time, FDA AV will move all non-voting members out of the main room into a separate Zoom room. For those non-voting members in the Zoom room, please do not log out of Zoom. We'll move you back into the main Zoom room in a few moments once we're finished conducting and collating the vote.

Ms. DeGregorio: Okay. I think everyone's back. Welcome back. Thanks for being patient for that slight delay there. Okay, so we have a display of voting results. So, there are a total of 19 voting members for today's meeting. The results are one member voted yes. 17 members voted no. And one member abstained. Okay. So therefore, the voting question does not pass. Now next I'm going to wait for the queue of results to come up. Here we go. Okay, so you should see on the screen an Excel list of the voting responses of each voting member. I will read them aloud for the public record. Lisa Lee, no. Narali Shah, abstain. Jan Nolta, no. Ronald K. Liem, no. Joseph Wu, no. Nick Johnson, no. Rajiv Ratan, no. Andrew Buckley, no. Kathleen O'Sullivan-Fortin, yes. Donald Kohn, no. Lynn Raymond, no. Jun Li, no. Richard Kryscio, no. Wendy London, no.

Caleb Alexander, no. Mark Tuszynski, no. Gil Wolfe, no. Taby Ahsan, chair, no. Kenneth Fischbeck, no.

Okay, great. Thank you. This concludes the voting portion of today's meeting. Next slide, we begin with the committee vote explanation. Thank you.

Vote Explanations

Dr. Ahsan: Great. If you could put the Excel spreadsheet back up, alright Marie?

Ms. DeGregorio: Yeah, sure. That would be good too.

Dr. Ahsan: So, at this stage, we're going to go through each individual and they will have the opportunity to give the explanation for their vote. So, I'll take the prerogative of going last as chair, but we'll start at the top. Dr. Lisa Lee.

Dr. Lee: Thank you again. In my earlier comments, I think the data taken together do not provide enough substantial evidence. Not confusing, but conflicting information that was presented led to less clarity. And for the reasons I suggested in my previous comments, I voted no.

Dr. Ahsan: Thank you. Dr. Shah.

Dr. Shah: Yeah, so I'll echo to what I had said right before the vote. I think that there is just a fair amount of conflicting information that was presented today and a lot of emphasis on the mechanism of action for something that we don't entirely understand. And ultimately, the reason I abstained is I'm a little bit just worried that we're asking for the impossible and don't really know what it is that would be needed to be able to move this forward. And so, I struggle with just even the question. I was very compelled by the patients, but even more so, I was compelled by the providers who are taking care of these patients. Many who have decades of experience treating these patients. That leads me to believe that there is something there, but I don't know that it fits the regulatory platform that we currently have.

I think the CMC concerns are legitimate. But I also did not get any clarity on what it would be that it would take for a mesenchymal stem cell product to be approved. And so, I think that in ongoing discussions with the sponsor, those attributes really need to be understood. And so, I felt that I was not able to provide a vote.

Dr. Ahsan: Thank you, Dr. Shah. Dr. Nolta.

Dr. Nolta: Yes, I do work in the field of MSCs and I was very compelled by the patient's testimony. We always have responders and non-responders in the MSC field. I wanted to be able to approve this, but in the end, I just did not see the data there. I did not see overwhelmingly substantial evidence of effectiveness there and I just did not see the statistical data. So, at this point, I had to say no.

Dr. Ahsan: Thank you, Dr. Nolta. Dr. Liem.

Dr. Liem: Yeah, I too was very impressed and moved by the statements from the patients and their providers, but ultimately, I did not think the data was there. Therefore, I had to vote no.

Dr. Ahsan: Thank you, Dr. Liem. Dr. Wu.

Dr. Wu: Yeah, so I have to agree with the FDA scientists who did a great job in terms of presenting the data. I think, despite the patient's testimony, the data just doesn't substantiate the company's claims about efficacy. So, I voted no as well.

Dr. Ahsan: Thank you, Dr. Wu. Dr. Johnson.

Dr. Johnson: Like others said, very compelled by both the clinicians and the patient testimony. But unfortunately, the clinical data did not bear out the appropriate level of efficacy that would be required to move it forward. So, I had to vote no.

Dr. Ahsan: Thank you, Dr. Johnson. Dr. Ratan.

Dr. Ratan: I similarly was extremely moved by patients and their caregivers and just wanted to let them know there's a huge amount of hope in this field, that there's incredible amounts of science and actively moving towards patients going on, but I was not compelled by the clinical data presented or the evidence of quality control of the stem cells were target engagement and I voted no. I would encourage the company, I think that there are now many examples of the earlier you treat that there may be more opportunities for intervention. So, the company may be using a milder disease as a proxy for earlier, but maybe thinking about protonormal ALS. And a targeted population would be a reasonable next step.

Dr. Ahsan: Thank you, Dr. Ratan. Andrew Buckley.

Mr. Buckley: So, I looked at this through the lens of is this drug safe and is it effective? I didn't find that it was effective. It seemed to me like there's more evidence to the contrary. And then as to the issue of safety, it seems to me it's not as safe as maybe the sponsor would like it to be given the number of deaths in the neuron group versus the control group. As a person living with ALS, I certainly hope that should this drug ultimately not be approved, that the efforts made by the sponsor aren't for nothing. That there is some good that can come out of their studies to help move the ball down the field. But I'm very sensitive to approving a drug that may work on some people. I think that could ultimately result in more harm than good in the long run and set back the cause in general.

Dr. Ahsan: Thank you. Kathleen O'Sullivan-Fortin.

Ms. O'Sullivan-Fortin: Hi, this isn't a surprise. I voted yes. I think it is very clear that I include data that no one else considers as real data, which is obviously fine. I think there's no bigger risk than imminent certain death from ALS, and these are unique and desperate circumstances that would require us to exercise flexibility. I wish, with everyone else here, that

the sponsor's data was definitive and broad and fixed and helped and saved everyone. And it wasn't going to be that, but I still think there was a value.

Dr. Ahsan: Thank you. Dr. Kohn.

Dr. Kohn: Yes. So, I also want to mention once again, the FDA, I think, has done a very thorough detailed review. Really meticulously looking at the data. And of course, also I find the patient and family testimony was very compelling and we feel the pain that they're going through and the anecdotes of improvement. I hope those are true and I hope there is efficacy in there, but I think the substantial evidence of that effectiveness just wasn't there in the clinical data from the trials. So, I think based on that question, we had to vote no. And, I think one of the issues is the mechanism of action of the drug isn't clear whether it's anti-inflammatory, whether it's neurotrophins. And therefore, even the CMC issues that were discussed briefly of how you assess the potency of the drug product is difficult. So, I think those things need to be looked at. And then the right trial needs to be done to show efficacy.

Dr. Ahsan: Thank you, Dr. Kohn. Dr. Raymond.

Dr. Raymond: So, I voted no despite the compelling anecdotes and experiences, which I'm very sympathetic to. So, it's possible that this therapy has some benefit for some patients, but we look at the total when we have to decide whether this goes forward to public market, and there wasn't evidence that, for the whole group, this was effective. And there was evidence to potentially suggest it was actually deleterious, at least for those who are maybe more advanced with ALS causing more deaths, causing more bulbar dysfunction. So, for that reason, I would vote no. And to the last point about even if we had all the best evidence, if we don't have assurance that this effect, which may have worked for some people can be reproduced in a bigger market and a

bigger number of people because we know about the manufacturing process and how reliable it is, then we can't go forward either. So, both of those things made me vote no.

Dr. Ahsan: Thank you, Dr. Raymond. Dr. Li.

Dr. Li: Hi, as a physician, I see patients for the past more than 20 years, I would be thrilled if someone tell me there is a treatment effective for ALS. But unfortunately, what I see so far is not only that we don't have evidence for efficacy, but also, we have safety issues. And I'm particularly concerned about increased mortality in the treated arm, which is an independent influence of the floor effect that the company tried to make an argument on. And the mortality itself will not be affected by floor effect, but it's there. And it is quite concerning. And these two combinations just makes me really hard to say yes. So that's why I choose no.

Dr. Ahsan: Thank you, Dr. Lee. Dr. Kryscio.

Dr. Kryscio: Yes. I voted no, for several reasons. One is I felt that the data was not very strong. I was particularly concerned about the lack of efficacy in terms of survival and looking at all these different groups sizes and also compelled by the conversations we had from the clinicians who are on the panel and treat these patients. They didn't seem to think that this was a step forward. And although I will also reiterate that I have a very strong feeling for all the patients who are out there who are hoping for a cure for this disease because it is pretty bad. Thank you.

Dr. Ahsan: Thank you. Dr. Kryscio. Dr. London.

Dr. London: Yes, I voted no. I applaud the efforts of the applicant to seek an effective treatment for ALS and I found the testimonials compelling and moving. And so, I encourage the sponsor to identify a quality of life instrument that could capture this anecdotal benefit in an objective fashion and use it as a key secondary endpoint in a trial. I voted no because of the statistical evidence wasn't presented to me through regulatory requirement. The trial wasn't

designed or powered to detect the small treatment effect within the post hoc subgroup analysis of patients with an ALSFRS-R score greater than 35, and this was an exploratory analysis. It was post hoc and unplanned, uncontrolled type one error with an increased chance of a false positive result. The sponsor spent a lot of time examining the floor effect, and I think that this just adds evidence that the ALSFRS-R score is a poor endpoint, at least within the patients with the most severe disease to try and detect a treatment effect and perhaps should investigate a potential new primary endpoint.

Dr. Ahsan: Thank you, Dr. London. Dr. Alexander.

Dr. Alexander: Yeah, I voted no. I think the clinical evidence or lack thereof of clinical efficacy is actually quite clear and if you measure that up against statutory thresholds, I think it's a pretty clear call. I do think there is also a lot of additional uncertainty in my mind that was generated regarding the process, manufacturing process and quality controls. And, we talked about six or seven different important sources of uncertainty and open questions regarding, the consistency of the neurotrophic factor secretion. Dose to dose, person to person, across people, across different neurotrophic factors, the degree to which these persist in vivo. Whether they make it to the target area, how long they are there, and then all of those levels of uncertainty all can interact with each other as well. So, there's a second order and higher levels of uncertainty as well that I think just really complicate matters. So, I thought both the sponsor and FDA did careful jobs of making their case, but I think that the FDA has it right here with the concerns that they raised about this product at the current time.

Dr. Ahsan: Thank you, Dr. Alexander. Dr. Tuszynski.

Dr. Tuszynski: I also voted no. This was based on the absence of clear efficacy and the presence of potential harm. The exploratory analyses were marginal. And even with that, even if they were

valid, the effect sizes were extremely small or, as said by the sponsors, incremental. So, given the marginal nature of the analyses that were leading to potentially incremental changes, it just wasn't enough to get over the threshold.

Another issue was the absence of mechanism. If there are growth factors involved, they're extremely unlikely to reach the spinal cord parenchyma. And just for the whole program, it would be very nice to have a better concept of mechanism. Another issue was the poor manufacturing process and quality control substantiation in the documents that we saw. And I'd just like to say too that the presentations by the patients were just passionate and compelling. And my heart, like that of everybody else, goes out to the families and the patients that are dealing with this. And you never know if some independent patients aren't benefiting that it's possible that they are. But what's clear from these data is that for all comers to the trial, there was no evidence of an overall benefit and potential harm to non-responders. So, to approve this could be approving harm to the majority of patients who would enter the trial, even if there's a subset who are benefiting.

And finally, I bear in mind that approval of a marginal therapy impedes the progress of what's clearly needed at the end of the day, which are far better effective therapies than we have for ALS. Thank you.

Dr. Ahsan: Thank you, Dr. Tuszynski. Dr. Wolfe.

Dr. Wolfe: Yeah, as others have said, my heart bleeds for the ALS community. It's been a difficult day. The points that have been made about manufacturing, quality control, targeting, efficacy, and I'll add, I could not decipher a clear subset consistently going from what was seen in the Phase II studies to the Phase III studies with the various sub analyses. I just couldn't see it, of where it might work. And then the safety issues that have been raised. I voted no based on

for effective therapies. And obviously we'll go back from today and review the comments to the docket further and review the transcript from the meeting. And as Dr. Witten said put everything together. But I want to just say that the FDA does hear the tremendous need here for effective therapies in this space. And that's not lost on us. So, with that, I want to thank our chair and thank everyone for hanging in there through a long day. Really appreciate everyone's participation today. I'll turn it back over to the chair.

Adjournment

Dr. Ahsan: Great. I think we're at the end and I can, again, thank everyone. It's been a long day, but I think it was very fruitful. So, I'll pass it to Marie. Did you have some final comment before we do?

Ms. DeGregorio: Sure, I just want to thank you, Dr. Ahsan, Dr. Witten, and Dr. Marks. In closing, I want to thank this committee, CBER staff, including all AV staff for working so hard to make this meeting a successful one. I now call this meeting officially adjourned at 6:37 PM Eastern time. Have a wonderful evening. Thank you.