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CORPORATE PARTICIPANTS

Armando Anido *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

James E. Fickenscher *Zynerba Pharmaceuticals, Inc. - CFO, VP of Corporate Development & Treasurer*

Joseph Palumbo *Zynerba Pharmaceuticals, Inc. - Chief Medical Officer*

Terri B. Sebree *Zynerba Pharmaceuticals, Inc. - President*

William C. Roberts *Zynerba Pharmaceuticals, Inc. - VP of IR & Corporate Communications*

CONFERENCE CALL PARTICIPANTS

Charles Cliff Duncan *Cantor Fitzgerald & Co., Research Division - Senior Analyst*

Lin Tsai *Jefferies LLC, Research Division - Equity Analyst*

Michael John Higgins *Ladenburg Thalmann & Co. Inc., Research Division - MD & Senior Biopharmaceuticals Equity Research Analyst*

Scott Robert Henry *ROTH Capital Partners, LLC, Research Division - MD, Senior Research Analyst & Head of Pharmaceuticals Research*

Sumant Satchidanand Kulkarni *Canaccord Genuity Corp., Research Division - Analyst*

PRESENTATION

Operator

Ladies and gentlemen, thank you for standing by, and welcome to the Zynerba Clinical and Regulatory Update Conference Call. (Operator Instructions)

I would now like to (inaudible) today's conference call, Mr. Will Roberts. You may begin, sir.

William C. Roberts *- Zynerba Pharmaceuticals, Inc. - VP of IR & Corporate Communications*

Thanks, Kevin. Good morning, everyone, and thank you for joining us on this call. We issued a press release and 8-K this morning disclosing the outcome of our meeting with the FDA to discuss our clinical and regulatory path forward for Zygel in Fragile X syndrome, or FXS. This press release can be found on our website under the News section.

Before we begin, I'd like to remind you that today's webcast contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These statements reflect Zynerba's current expectations regarding future events, including, but not limited to, statements regarding the company's cash runway, the design, initiation, timing, continuation and/or progress or results of the company's clinical trials, the need for additional clinical trials, whether additional clinical trials will confirm prior clinical trial results or be sufficient to support the filing of an NDA and the company's ability to obtain and maintain regulatory approval for its product candidates and/or the label claims that seeking from FDA.

Actual results could differ materially from those expressed in or implied by these statements as a result of various important factors, including those discussed from time-to-time in the company's filings with the Securities and Exchange Commission on Form 10-K and our periodic filings on Form 10-Q and Form 8-K and other filings made with the SEC. Links to these documents are available in the Investor Relations section of our website. And as always, we encourage you to review these materials. Any forward-looking statements represent our views as of today, December 17, 2020.

With me on the call this morning are Armando Anido, our Chairman and Chief Executive Officer; Terri Sebree, our President; Dr. Joe Palumbo, our Chief Medical Officer; and Jim Fickenscher, our Chief Financial Officer.

I will now turn the call over to Armando Anido. Armando?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Thanks, Will, and good morning, everyone.

We issued a press release earlier today announcing the outcome of our Type C meeting with the U.S. Food and Drug Administration's Psychiatry division. During this meeting, we discussed the results of the CONNECT-FX trial in Fragile X syndrome, including the consistent clinically meaningful improvements in behaviors we observed in the preplanned ad hoc analysis of pediatric and adolescent participants in the trial, with a 90% or greater methylated FMR1 gene treated with Zygel. As you may recall, these patients represented approximately 80% of the CONNECT-FX trial population and approximately 60% of the Fragile X population overall.

In summary, we believe that if we are able to confirm the positive results observed in the responder population of the CONNECT-FX trial with a single prospectively defined double-blind placebo-controlled confirmatory pivotal trial in patients with Fragile X syndrome, who have a highly methylated FMR1 gene, we would have the basis for submitting a new drug application or NDA for the approval of Zygel to treat the behavioral symptoms associated with Fragile X syndrome.

Before providing some additional details, I want to again thank the participants in the CONNECT-FX trial, their families and caregivers, along with the clinical investigators and their staff. I also want to thank our patient advocacy group partners, including the National Fragile X Foundation and the Fragile X Association of Australia. We appreciate your remarkable efforts on behalf of the Fragile X community.

To the parents and families who struggle with realities of this disorder, I want to say very clearly that we remain dedicated to supporting your community, and that completing the development of Zygel in Fragile X syndrome and preparing for a successful launch will be our primary focus.

Our analysis of the patients with Fragile X syndrome who have 90% or greater methylation of the FMR1 gene showed a statistically significant improvement in the social avoidance subscale of the aberrant behavior checklist community for Fragile X, which was the primary endpoint in CONNECT-FX. Zygel was associated with several statistically significant improvements in core behaviors of Fragile X syndrome as measured by caregivers and clinicians. And additional psychometric analysis conducted indicate that these improvements were both relevant to caregivers and clinically meaningful.

Importantly, significantly more patients achieved a clinically meaningful change and social avoidance and irritability with Zygel and placebo. The data in this population of patients appear to be clear, consistent and supportive of the potential for Zygel to be a very important drug to improve core Fragile X behaviors.

Our discussions with the Psychiatry division was interactive, and we appreciate our ongoing constructive dialogue and their continued partnership in our development program in Fragile X syndrome, a patient population with a high unmet medical need and no currently FDA-approved therapy. As a result of the feedback from the FDA, we plan to conduct a double-blind placebo-controlled pivotal trial in patients with Fragile X syndrome who have a highly methylated FMR1 gene to confirm the positive results observed in this population of responders in the CONNECT-FX trial. The primary endpoint will again be improvement on the Social Avoidance subscale of the aberrant behavior checklist community for Fragile X.

We are already well along in designing the protocol for this planned clinical trial. Our plan is to review the trial design and protocol for the new trial through a Type C meeting with the FDA in the first half of 2021 prior to initiating the trial before the end of '21. Once we have the FDA's feedback, we will be able to clarify further the timing for the initiation of that trial and provide further details around the trial design.

Switching to our 3 other development programs. We expect to achieve meaningful milestones in each of them throughout 2021. We look forward to resuming recruitment in the 14-week open-label Phase II INSPIRE Trial in children and adolescents with genetically confirmed 22q dilution syndrome, once the COVID-19-related restrictions in Australia are eased. After recruitment is resumed, we will provide a time frame for completion of this trial.

Regarding our autism program. In the first half of 2021, we plan to discuss data supporting the potential efficacy of Zygel in ASD with the FDA to determine the regulatory path forward. This discussion will include the previously reported positive results of the Phase II BRIGHT trial in children and adolescents with moderate to severe autism spectrum disorder. We will provide an update on this program once we receive the minutes from that meeting.

Finally, regarding our program in developmental and epileptic encephalopathies, or DEE. Our evaluation of potential target indications is well-advanced. We expect to conduct an observational trial that will help us finalize target syndrome selection in one or more DEE syndromes in 2021. We look forward to providing more information on these targets once our work is completed.

With respect to our cash position. By focusing our resources on initiating and completing a confirmatory Fragile X trial and bringing the other programs to the next milestones, as I just described, we expect that our cash runway will extend into 2023.

In conclusion, Team Zynerba remains energized to achieve our goal to bring the first pharmaceutical product indicated for the treatment of patients with Fragile X syndrome to market. The path to submitting an NDA will require a lot of hard work, but the positive results we observed in patients with 90% or greater methylation of their FMR1 gene gives us confidence in the potential for success of a confirmatory trial. We look forward to updating you as we move forward, and thank all of our shareholders for their continued support and confidence.

With that, let's move to Q&A with our analysts. Operator, can you please give the instructions on how to ask a question?

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from Sumant Kulkarni with Canaccord.

Sumant Satchidanand Kulkarni - *Canaccord Genuity Corp., Research Division - Analyst*

First, I know it's been fairly early yet, but what is the number of patients you might expect to enroll in this new pivotal trial? Will it be around the same as in the FX -- the CONNECT-FX trial? And if you had to enroll a similar number of patients, do you expect the time line from initiation to announcement of top line results to be similar to the CONNECT-FX time line?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Great. Thanks for the question, Sumant. And I think that it is somewhat early. We are in the process of trying to evaluate what the absolute number of patients we will need in this trial. And I think that it's probably going to be similar to what we did with CONNECT-FX.

Terri, do you want to comment relative to time lines and our ability to recruit this population?

Terri B. Sebree - *Zynerba Pharmaceuticals, Inc. - President*

Yes. Sumant, I think the time line will be similar to what we experienced with CONNECT-FX. We have learned a lot about how to support the families and work with the Fragile X community, but we will be providing more of that information as we finalize the protocol and meet with the FDA.

Sumant Satchidanand Kulkarni - *Canaccord Genuity Corp., Research Division - Analyst*

Got it. And a quick follow-up, what geographies do you expect to have this trial in? And what is the rough cost associated with conducting the new pivotal trial?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. So first, we usually don't comment on the exact cost of the trial. And I think that as we are trying to determine the exact number of patients in that trial, we'll maybe give a little bit further clarity in the future. But we are probably going to expand beyond the territories that we covered previously, which was Australia, New Zealand and the United States. And we'll probably go into a few English speaking countries, primarily because of the validity of the ABC in English.

Operator

Our next question comes from Charles Duncan with Cantor Fitzgerald.

Charles Cliff Duncan - *Cantor Fitzgerald & Co., Research Division - Senior Analyst*

Yes. Armando, I had a couple. First is on the protocol that you intend to pursue with Fragile X. I know that you are still currently designing it. But I guess I'm wondering, if you think about the sample enrollment criteria that you may be targeting, it makes sense to me that you probably have some methylation status. But also what are some of the criteria for behavioral baseline and age that you'd be looking at in that sample?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

So Charles, I would think that as we are developing this confirmatory trial, there will be some similarities to what we did in CONNECT-FX. And obviously, based on some of the lessons that we learned in the -- in that trial as well, we will be making some adjustments. I think that I would hold comment at this point until we have a firm protocol that we have discussed with the FDA. And sometime in the first half of this year, we will communicate an outcome of a Type C meeting with the FDA on this.

Charles Cliff Duncan - *Cantor Fitzgerald & Co., Research Division - Senior Analyst*

Okay. And then with regard to the FDA interaction. Frankly, we're -- we've heard this kind of similar response from at least two other companies I can think of off the top of my head. Seems like it was constructive feedback from the division. But what was the key point of debate, if you will, for the division suggesting that you do a double-blind placebo-controlled study, just to confirm what you had observed in CONNECT versus just going ahead with an NDA, in this very difficult-to-treat patient population?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. Terri, do you want to add color on that?

Terri B. Sebree - *Zynerba Pharmaceuticals, Inc. - President*

Sure. Charles, the biggest issue with FDA that it was as we call it, an ad hoc -- preplanned ad hoc analysis, they called it a post-hoc analysis, and the analysis was not in the statistical analysis plan. So they're just -- we're following the rules for demonstration of efficacy. They were very -- I think they were very interested and pleased with the results but said that we needed to -- confirm it in a prospective study, which we will do.

Charles Cliff Duncan - *Cantor Fitzgerald & Co., Research Division - Senior Analyst*

Okay. That makes sense to me. And then final question. With regard to cash, Armando, you mentioned focusing the resources, so the cash extends through 2023. First of all, would you anticipate data from -- in Fragile X by that time? It seems like it could do given your answers to the previous question. But also, what are the changes in spend that allow that to occur? Is that in the R&D line? Or can you provide color on it?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. So clearly, in our previous guidance with cash, we had anticipated being able to file an NDA pretty quickly after our meetings with the FDA, and we had built in their headcount change. We had built in launch expenses and everything. So I think one of the biggest areas that we have extended our runway with is that we are not hiring all of these folks and not spending the money for a prelaunch at this particular point.

In addition, clearly, in 2020, we have a fairly high investment in the Fragile X, CONNECT-FX trial because the study will not begin until after we have had our Type C meeting with the FDA. Our expenditures on the R&D line,, predominantly from the Fragile X trial, will be reduced this year.

So that does give us another additional amount of capital that helps us send us into 2023. And I'll ask Jim if there are any other areas that we should help Charles with on this.

James E. Fickenscher - *Zynerba Pharmaceuticals, Inc. - CFO, VP of Corporate Development & Treasurer*

I think those are the main areas. It's not building up the commercial and prelaunch costs and the change in -- when we're going to spend money on the nature of. So nothing else to add.

Operator

Our next question comes from Michael Higgins with Ladenburg.

Michael John Higgins - *Ladenburg Thalmann & Co. Inc., Research Division - MD & Senior Biopharmaceuticals Equity Research Analyst*

A lot of good questions asked so far in early days. I understand it's tough to get too detailed for us. Question in this morning's press release, we noticed you described the patients is highly methylated, whereas in the past, they were described as fully methylated. Is this any change coming from the discussions of the FDA? Or are we just overthinking it?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. I think I'm going to comment real quickly and then ask Terri or Joe to jump in. But I guess they did not fully appreciate the full methylation, and they prefer the term highly methylated. So it's almost as simple as that. Terri or Joe, do you want to add any commentary there?

Terri B. Sebree - *Zynerba Pharmaceuticals, Inc. - President*

I think, Armando, you answered this exactly right. They just like highly methylated instead of fully methylated.

Michael John Higgins - *Ladenburg Thalmann & Co. Inc., Research Division - MD & Senior Biopharmaceuticals Equity Research Analyst*

Okay. I appreciate it, guys. Just trying to clarify as we can here, knowing that we're not getting a lot of detail from you this morning, and that's understandable. Second question would be the guidance seems pretty conservative to start in 2021. So just to clarify obviously it's possible that you're being conservative, but do you have enough product supply to start this trial and the other trials? If not, when might that be ready?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. I think that, Michael, we do have enough product supply in order to get a study started. I think that the time lines on establishing a Type C meeting with the FDA are pretty well-known, and then waiting for the final minutes from them adds another 30 days or so after that. So I think that establishing a meeting in the first half is doable. And then from that point, after we get the final feedback from the FDA and buy-in on the trial design, we will then be in a position to give a little bit more clarity on the exact timing in 2021 when we can initiate this trough.

Operator

Our next question comes from Andrew Tsai with Jefferies.

Lin Tsai - *Jefferies LLC, Research Division - Equity Analyst*

Appreciate you sharing the updates. I guess, first question on FXS is just, I guess, should we expect you to make changes to your secondary endpoints in the confirmatory study? I guess, what I'm trying to say is, would you still evaluate irritability, lethargy as your key secondary endpoints? Or might you even consider other ones? But I appreciate if you cannot mention that since this is...

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. Andrew, thank you very much for the question. And I think it is a little premature to give you more specifics around what potential secondary endpoints could be used. There clearly were a lot of lessons that we learned from the conduct of the CONNECT-FX trial that we will be incorporating into the trial design for the confirmatory trial. And we will give a lot more clarity on exactly what we may be doing on secondary endpoints as we announced the results of our meeting with the FDA in the first half.

Lin Tsai - *Jefferies LLC, Research Division - Equity Analyst*

Makes sense. Makes sense. And maybe if I can switch to DEE then. I guess, maybe talk about how you're strategically thinking about the program. I mean, on one hand, [LGS-Dravet] patients made up a good chunk of your Phase II data set. But on the other hand, there is competition within those populations. So I guess maybe talk about how you're thinking about which targeted syndromes you might want to pursue.

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. So clearly, and you've outlined some of the issues in selecting exactly what syndromes to go after, they are clearly our friends at another company have indications in Lennox-Gastaut and Dravet syndrome. And in our BELIEVE trial, we actually had more than just those two. About 75% of the patients were non-LGS or Dravet. So we are looking at -- and they're now looking at kind of more rare types of syndromes. So I think that our plan is to kind of do an observational study that will help us really define the ability to go forward in some of the other syndromes.

Operator

Our next question comes from Scott Henry with ROTH Capital.

Scott Robert Henry - *ROTH Capital Partners, LLC, Research Division - MD, Senior Research Analyst & Head of Pharmaceuticals Research*

Just a couple of questions. You mentioned in the press release that this will be the primary focus of the company. Do you anticipate deprioritizing any of the other programs, just with the idea of conserving cash to move this program on?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. So I think, Scott, a great question. We think that obviously the Fragile X syndrome has made some dramatic steps. And I think that now knowing with one confirmatory trial in this highly methylated patient population that we are one step away from potential submission of a new drug application. I think that is a wise thing for us to do is try to focus on that and get it completed.

We've got some data points and milestones coming with the other indications right now that I think can be very encouraging. And whether it is the completion of the 22q or the meeting with the FDA on Autism Spectrum Disorder or the final selection of the various syndromes or one or more syndromes for DEE, are pretty important milestones for us. And I think that as we get to those milestones, then we will look to continue to evaluate whether or not we move forward with some more.

So clearly, getting to the finish line with Fragile X syndrome seems to be the most logical place to focus our energies, but the other indications are pretty valuable if we can get the milestones and then go beyond there.

Scott Robert Henry - *ROTH Capital Partners, LLC, Research Division - MD, Senior Research Analyst & Head of Pharmaceuticals Research*

Okay. Great. And then I think you may have mentioned this already in the call, but what percent of the CONNECT-FX patients would be classified as the highly methylated FMR1 gene?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. So in our study, using 90% and above as the percent methylation. It was 80% of the CONNECT-FX population. And our preliminary estimates on how that translates into the full population is that it's probably about 60% of the entire Fragile X community.

Scott Robert Henry - *ROTH Capital Partners, LLC, Research Division - MD, Senior Research Analyst & Head of Pharmaceuticals Research*

Okay. And then, I guess this question has already been asked a little bit, but I'm just trying to get this sense. At this point, do you expect any changes from the CONNECT-FX to the next trial, whether that be from the FDA, or perhaps there's some things that you learned in the first trial that I think can give you a more favorable outlook in the next trial? Just trying to get a sense of how things will change from CONNECT-FX to the next trial.

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. So maybe, Terri or Joe, we can talk about kind of the top line on some of the lessons learned?

Terri B. Sebree - *Zynerba Pharmaceuticals, Inc. - President*

Yes. Joe, you want to do that?

Joseph Palumbo - *Zynerba Pharmaceuticals, Inc. - Chief Medical Officer*

Yes. I'm happy to do that. I think the most obvious focus is going to be on these patients who have full methylation or highly methylated. So that's the focus of the study.

I think we also learned a lot about what the needs are in the community. It would have -- and what we've learned during COVID-19 is that we need to bring the study to the families and bring the study to the patients as best we can.

These are families that have a lot of challenges, so with children who are highly impacted by the disorder. And what we've learned during COVID-19 is that we could do that, that we could bring the trial closer to them. We made partnerships with organizations that allowed us to collect laboratories in the patient's own neighborhoods. We did a lot of work via virtual means. So I think those are some of the things we've learned.

And Terri, if there's anything else we need to add, please do so.

Terri B. Sebree - *Zynerba Pharmaceuticals, Inc. - President*

Yes. Yes. I think that's good. We just learned operationally how to run these studies efficiently.

Operator

Our next question is a follow-up question of Sumant Kulkarni with Canaccord.

Sumant Satchidanand Kulkarni - *Canaccord Genuity Corp., Research Division - Analyst*

So we know that Tetra, which is now part of Shionogi, recently announced Phase II results for their product in adult males with FXS. So could you comment on how you see the competition on patients -- for pediatric patients for trial enrollment might evolve with others in industry also planned pediatric trials?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Yes. So Terri, do you want to hit on patient enrollment? And our focus is going to probably remain on pediatric and adolescent patients that we get in to CONNECT-FX, but talk a little bit about any challenges with enrollment based on competitive agents.

Terri B. Sebree - *Zynerba Pharmaceuticals, Inc. - President*

Yes. Yes. Sumant, I -- we had some competition with other studies while we were enrolling. We did not think that affected us too much. I think we -- we're going in girls and boys, which will help enrollment. I just do not see that it will. There's quite a few, even though it's rare disease, with the -- at the FXS consortium sites, there's quite a few patients. So I don't think we will have any extra issues in enrolling patients.

Sumant Satchidanand Kulkarni - *Canaccord Genuity Corp., Research Division - Analyst*

Got it. And my last question is on autism spectrum disorder. What are some of your learnings -- given that there are some overlaps in terms of behaviors and things like that, what are some of the learnings from CONNECT-FX that you might be able to apply to the ASD program that you have ongoing?

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Right. Joe -- maybe Joe Palumbo can hone in on the ASD.

Joseph Palumbo - *Zynerba Pharmaceuticals, Inc. - Chief Medical Officer*

Yes, I'm happy to do so. The learnings are exactly what I mentioned. It's close collaboration with the community. It's understanding very much what are the primary symptoms that -- about which people are most concerned and being able to make sure that we measure those symptoms. I'll stop there. That's it. Thanks.

Operator

And I'm not showing any further questions at this time. I'd like to turn the conference back over to Armando for any closing remarks.

Armando Anido - *Zynerba Pharmaceuticals, Inc. - Chairman & CEO*

Wonderful. Thank you all for your participation this morning, and we look forward to a very productive 2021. So we will be in touch. Thank you.

Operator

Ladies and gentlemen, this does conclude today's presentation. You may now disconnect, and have a wonderful day.
