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EDITED TRANSCRIPT

PFE - Pfizer Inc Conference Call to Review DMD Data Presentation at
ASGCT Annual Meeting

EVENT DATE/TIME: MAY 15, 2020 / 2:00PM GMT

OVERVIEW:

Co. provided an update on DMD treatment.



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PRESENTATION

Operator

Good day, everyone, and welcome to Pfizer's analyst and investor call to review the DMD data presentation at the American Society of Gene & Cell Therapy 2020 Annual Meeting. Today's call is being recorded.

At this time, I would like to turn the call over to Mr. Chuck Triano, Senior President of Investor Relations. Please go ahead, sir.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Thank you, operator. Good morning, everyone, and thanks for joining us to discuss the preliminary results from our ongoing Phase 1b DMD gene therapy study that were presented earlier today. I'm joined today by Mikael Dolsten, Chief Scientific Officer and President, Pfizer Worldwide Research Development in Medical; Seng Cheng, Chief Scientific Officer and Senior Vice President, Rare Disease; Bob Smith, Senior Vice President, Global Gene Therapy, Rare Disease Business Unit; and Mike Binks, Vice President, Rare Disease Clinical Research.

Before we start, I want to remind everybody that we'll be making forward-looking statements about the preliminary data on today's call, and actual results may differ from those statements. Forward-looking statements speak only as of the original date of this presentation, and we undertake no obligation to update or revise any of the statements.

Mikael and Mike will make some prepared remarks, and then we'll move to a Q&A session with the Pfizer team. With that, I'll turn the call over to Mikael Dolsten. Mikael?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Thank you, Chuck, and thank you to all of you who are joining us on the call today. We are very excited to share with you what we believe may be one of the most promising and comprehensive sets of investigational gene therapy data in DMD as determined by improvement in measures of



muscle function, and improvement at an age where stagnation or decline in muscle function is the natural expectation. The preliminary functional data from this Phase 1b program are accompanied by improvements on measures of muscle health, as indicated, as measured by exploratory recording of fat fraction by MRI. The gene delivery of mini-dystrophin also appeared to provide durable and statistically significant improvements across multiple efficacy-related endpoints measured at 12 months post infusion. So while we recognize that there is much to learn about this potential therapy as we continue to monitor patients from this Phase 1b program and plan to initiate our Phase 3 program, we are very excited about the potential this program has to help us deliver on our mission of breakthroughs that change patient lives. Before we review the data in detail, I would like to provide some overarching comments on our program, gene therapy pipeline and state of the art manufacturing capabilities and facilities.

Now on this slide, you can see that DMD is a devastating and life-threatening x chromosome-linked disease that's caused by a mutation in the gene-encoding dystrophin needed for proper muscle membrane stability and function. Consequently, patients present with muscle degeneration that progressively worsens with age, such that they require wheelchair assistance when they are in their early teens, and unfortunately, often succumb to their disease by the time they are, on average, 28 years of age. As you can see on this slide illustrates the loss of muscle function and motor achievement. It's estimated that there are between 10,000 to 12,000 individuals affected with DMD in the U.S. alone. And despite significant investments by both private and public sector to develop potential solutions, it's fair to say that there remains a high level of medical needs to these patients. What is important about today's data is that the data suggests the potential impact of our therapy may have not just been on surrogate endpoint, such as dystrophin concentration and distribution within muscle tissue, but also on the overall function of patients with DMD. Based on the data we're sharing today, we are excited that this investigational treatment, so far, appears to live up to Pfizer's mission of developing breakthroughs that change patient lives. And we are happy to report that we are planning to progress our DMD gene therapy program to Phase 3 testing as quickly as we can, subject to regulatory approval.

As we have previously stated publicly, we're working on plans to begin dosing in the Phase 3 program in the second half of this year. The planned Phase 3 study for DMD will be a multicenter pivotal study with 99 ambulatory boys between the ages of 4 to 7 who will be administered commercial-grade drug product at the Phase 1b high dose of 3E14 vector genomes per kilogram. We look forward to providing further details about our Phase 3 trial design in the near future.

At Pfizer, we are a leading innovator in rare disease, pioneering breakthrough therapies that have a profound impact on the lives of underserved patient population. We're building a broad and diverse pipeline, including in gene therapy, where we currently have 12 ongoing programs in both clinical development and preclinical research. Within Pfizer, we have also structured rare disease as one of our autonomous business units in terms of research, development and commercialization, which demonstrates our commitment to rare disease as a key development area.

To further illustrate that point, we expect to have 3 Phase 3 gene therapy development programs ongoing by the end of this year in hemophilia A, hemophilia B and Duchenne muscular dystrophy, which I believe will make us the only company in the world with that number of gene therapy programs in Phase 3, and all of them will be using drug product manufactured with a commercial process at commercial supply scale.

Concerning manufacturing. One of the key differentiating features of our approach to gene therapy in DMD is our manufacturing capabilities, and this may be an area of potential differentiation that's not fully appreciated in terms of its impact on commercialization. We have proactively invested in manufacturing at the scale to support rapid drug development, and importantly, urgent and timely access to these potential medicines.

Over the past 2 years, we have made a very significant investment, totaling approximately \$800 million to ready 3 manufacturing facilities which offer a combined space of about 300,000 square feet in North Carolina. It is our expectation that these facilities will have the potential to support commercial manufacturing of sufficient amount of vector so that if this program is successful, we will be positioned to treat all eligible DMD patients upon regulatory approval and that we also anticipate that these facilities would be able to support commercial manufacturing of not only the DMD vector but multiple other gene therapy programs, in parallel, by 2022.

To support drug development, we have also assembled an end-to-end infrastructure across the research to development and commercial axis in an effort to enable efficient advancement and delivery of new gene therapy programs into the clinic, and ultimately, if approved, our patients. We look forward to sharing more details with you about these capabilities and our position of strength in rare disease at our rescheduled R&D Day in September.



Now I'm pleased to turn the call over to Michael Binks, who will walk you through the data.

Michael Binks - Pfizer Inc. - Vice President, Rare Disease Clinical Research

Thanks very much, Mikael, and thank you, everyone, for taking the time to dial in today to hear more about our research. I'm Mike Binks, VP of Clinical Research in our Rare Disease Research Unit based in Cambridge, Mass. Along with the authors listed here and many other contributors at Pfizer and at our clinical sites, I'm very pleased to share with you this new data from our ongoing Phase 1b DMD program that was presented this morning at the ASGCT for the first time.

Next slide, please. So we've been working on developing a potential gene therapy solution for DMD using recombinant AAV9 vectors to deliver and reconstitute the affected muscles with a truncated dystrophin transgene, referred to as mini-dystrophin. This construct includes a muscle-specific promoter designed to preferentially express mini-dystrophin in cardiac and skeletal muscle cells. I'll also note here that the preclinical studies showed a very clear dose response with this vector on rat -- in a rat mdx model of disease, particularly on cardiac and skeletal muscle transduction with improved muscle strength and echocardiographic parameters. These vectors are manufactured using a triple transfection technology in HEK-293 suspension cell line, which we have successfully scaled up, as Mikael has described, to a 2,000-liter bioreactor scale for commercial manufacturing readiness, if the therapy is approved.

Next slide, please. We previously reported our preliminary findings of a Phase 1b trial at the Parent Project Muscular Dystrophy conference in June last year. The design for that trial is illustrated here. Since then, we've dosed an additional 6 patients, for a total of 12: 3 in the low-dose and 9 in the high-dose cohort. Now at the time of the snapshot of data that I'm reporting here where we have more than 3 months follow-up on patients, there were 6 patients in the high-dose cohort, but we have now dosed another 3.

Next slide, please. So the -- we're running the study at 3 sites in the U.S. We have a mean age of participants of 8.8 years, and about 10% of those boys who were screened for the study were excluded on the basis of neutralizing antibody positive testing.

Next slide, please. So the preliminary safety -- sorry, back one. The preliminary safety findings are described here. The intravenous infusion was well tolerated. We had, throughout the period of follow-up, no evidence of any hepatic dysfunction or clinically relevant anti-dystrophin immune response using the daily glucocorticoid regimen. Among the 9 patients, we've seen 3 serious adverse events, and these all occurred within the first 14 days following administration. Two of these we reported previously. There's one more that is new, and that is thrombocytopenia, which occurred in association with complement activation and required a half-unit platelet transfusion and treatment with eculizumab. The prior adverse events that we described last year, one was a persistent vomiting and dehydration, which required admission for IV antiemetics and fluids; and then second, which involved an acute kidney injury with atypical -- general picture of an atypical hemolytic uremic syndrome associated with complement activation and required hemodialysis and treatment with eculizumab. That was the first time we've seen any evidence of complement activation in our program. So we've amended the clinical study protocol to include increased monitoring and management regime based on the experience in this study. Because of heightened monitoring that was implemented after the first and second SAEs, the third SAE was detected much more promptly and intervention occurred earlier, allowing a much more rapid recovery, following a brief 24-hour admission to a hospital at the weekend, as determined -- as required by local site procedure.

So we're cautiously optimistic that because our complement activation events are both monitorable and manageable in the clinical trial setting going forward, we'll be able to manage and mitigate these SAEs, should they occur. It's important to note that we've checked and not observed any evidence of liver damage or a clinically meaningful immune response to dystrophin in any of our treated patients, so far, including the 2 additional patients that we've dosed most recently and have more than 4 weeks follow-up for them.

Next slide, please. Today, I'm thrilled to share with you new data on the biochemistry based on analysis of muscle biopsy that expands from -- on a data set presented at Parent Project Muscular Dystrophy last year. As you're aware, we had reported on the biopsy of 6 boys at 2 months posttreatment and had shown expression of meaningful amount of mini-dystrophin as measured by immunofluorescence and liquid chromatography mass spectroscopy, or LCMS assays. So I'm pleased to report new data from 3 additional patients in the high-dose cohort, similar -- showing similar expression levels of mini-dystrophin at 2 months, which we believe may be clinically meaningful. In the Phase 1b trial, new results from the open muscle biopsies of the biceps of the 3 participants in the low-dose cohort show that the mean percentage normal dystrophin at 12 months was

24%. For the 3 participants in the high-dose cohort, for whom 12-month data are available, the mean percent normal is 51%. Comparisons between baseline and posttreatment measures were significant, and an increase in mini-dystrophin concentration was observed in 5 out of the 6 participants between the 2- and 12-month time points. In the 6 high-dose patients, on average, expression was noted to be distributed in approximately 50% of muscle fibers, and the concentration of dystrophin was approximately 40% of that, over the normal level. Based on our understanding of the biology of this disease, we anticipate that the changes from baseline values that we've observed in our study may confer a clinical benefit to patients. Importantly, data for the first -- for the 3 high-dose patients, for whom we have 12-month data, show that similar levels of expression were sustained when the muscle biopsies were outlined at 12-month posttreatment.

So what I'm showing here are the images of muscle biopsies that we've stained for the presence of dystrophin, which are illustrated here as a red signal. The top row are representative samples taken at baseline. The middle samples at 2 months, and the bottom row at 12-month posttreatment. As you can see, the number and intensity of positively stained cells on rows 2 and 3 are notably higher than at baseline, indicating expression of greater amounts of dystrophin in the treated patients, as we showed with our quantitative mass spec assay. Importantly, the pattern observed in the data 12 months is similar to that at 2 months, suggesting that the expression -- the distribution of expression remained at a similar level at this time interval. These results, while early, suggest that durable expression of potentially therapeutic levels of mini-dystrophin following a single administration may be achievable. These data have been updated since last year based on an updated digital platform and analysis algorithm, which -- using a new algorithm, which, actually, is not directly comparable with previous or other measures.

Next slide. We're further encouraged because these levels of dystrophin are supported by new additional evidence of potential efficacy based on 2 separate metrics. It should be noted that functional assessments in this trial are considered exploratory due to the small number of planned study participants and the risk for bias and an open-label study. The first metric is the North Star Ambulatory Assessment score, which is a composite of 17 measures of ambulation. When the first 6 treated patients were examined at 12 months using the North Star Ambulatory Assessment tool, an improvement in the measurement was noted in 5 out of 6 participants. The only exception being a participant in the low-dose cohort. We don't think data yet -- we do not have data yet for the other 3 participants as they've not yet reached the 12-month mark.

When we look at the scientific literature regarding the mean trajectory of the North Star score in relation to the age of patients with DMD, it shows that children with DMD can experience an improvement in their motor function up until 6 to 7 years of age. After which, they typically exhibit a rapid decline to the point that they become non-ambulatory in their early teens. In our study, the patients, on average, showed a marked improvement in their North Star scores. In fact, we see a statistically significant difference at both dose levels compared to external control groups, which consists of placebo groups from blinded clinical trials matched for age, weight and baseline function provided by both TransCelerate and our own DMD programs for domagrozumab. These observations, albeit in small numbers, provide hope that treating patients who would typically be losing function may benefit from this potential therapy.

Next slide. Importantly, supporting our belief that gene therapy may have conferred a benefit in motor function, a second metric, MRI analysis, showed a reduction in fat fraction in the thighs of the first 3 boys treated with the high dose at 12 months posttreatment. Boys with DMD typically exhibit a progressive loss of contractile or lean muscle and replacement with fat or fibrotic tissue. In our study, a mean reduction in fat fraction was noted in these 3 boys from the high-dose-treated cohort when compared to an external placebo group, suggesting that gene therapy had improved the muscle fiber health and quality in these boys. We observed a higher level of visible fat fraction in the size at baseline than when they were examined 12 months posttreatment. If we continue to see evidence of the extent of muscle preservation in additional patients, we believe we have the potential for a truly transformative treatment. We also observed a significant reduction in the creatine kinase, both at the 2- to 3-month and at the 12-month time points.

Together, we believe these data support the view that administration of our potential gene therapy can lead to expression of potentially therapeutic levels of mini-dystrophin that translate to a measurable improvement in muscle function and health in these patients.

So in summary, we're very excited about our DMD gene therapy program which we believe has the appropriate attributes of potential safety and signals of efficacy to advance into pivotal Phase 3 trials, subject, of course, to regulatory approval. Importantly, with our state-of-the-art manufacturing facilities and end-to-end capabilities, we're confident that, if this program is successful and approved, we're on a path to providing this potentially transformative medicine for the DMD community as quickly as possible following that regulatory approval.



We extend our heartfelt thanks to all the study participants, their families, researchers, investigators, other clinicians and patient advocacy organizations from around the globe for their passion, expertise and engagement, helping to advance clinical research and care for the Duchenne muscular dystrophy community.

I'll now turn the call back over to Chuck to begin our Q&A.

Charles E. Triano - Pfizer Inc. - SVP of IR

Great. Thanks, Mike and Mikael, for the prepared comments. Operator, could we please poll for questions now? Thank you.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Your first question is from Vamil Divan with Mizuho Securities.

Vamil Kishore Divan - Mizuho Securities USA LLC, Research Division - MD

Great. So I was wondering if maybe you could just clarify a little bit more in terms of new monitoring management steps that you're taking to address the potential side effects here. And also, I guess, just thinking about the real world, so of what level of sort of steps would you think would be acceptable to patients and families given the amount of efficacy that you are seeing here?

And then maybe my second question. If you could just maybe put some clinical perspective on the NSAA endpoint, this 3.5 point increase that you saw in your patients. Can you just put some sort of perspective on what that actually means, just because I was less familiar with that endpoint?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you, Vamil. Mike, do you want to start responding to this question?

Michael Binks - Pfizer Inc. - Vice President, Rare Disease Clinical Research

Sure. So in terms of the mitigation strategies to try and reduce the frequency and the severity of any safety events that may occur, we've increased the safety monitoring over the first 2-week period, in particular, increase both in the breadth of monitoring, the domains that we're monitoring. Now obviously, having seen that there could be complement activation, monitoring the complement compartments directly, particularly over the period from day 7 to 10, which seems to be where problems are emerging, if there are going to be problems. So we've implemented that in the protocol, an increased intensity and frequency of monitoring over this period. We've given guidance to our investigators in terms of intervention strategies. We've seen the effectiveness of neutralization of C5 with a monoclonal antibody, eculizumab, with rapid turnarounds in any complement activation that's going on. So we've given guidance there. We've also allowed some flexibility around the co-medication regime from the outset of administration, allowing higher doses of steroid to be administered or potentially other medications that may be appropriate to attenuate the risk of complement activation. So I think that covers the activities around risk mitigation.

The other thing -- one other thing, perhaps the flag is that in moving to a younger cohort, the total vector load that we're going to be delivering to the boys in the Phase 3 study is likely to be lower, and perhaps that will result in a reduced event rate here.

In terms of the efficacy in the North Star -- so the North Star Ambulatory Assessment has really been developed in Europe. It's a highly validated scale and has broad acceptance with a lot of interest from the FDA. The -- as we've shown, the natural history for boys using this scale is that their



scores increase between the age of 4 and 6 and then start to decline after the age of 7. So the increase in North Star score that we're seeing is over a background where we would expect the scores to be falling. And in our comparison with this external placebo control group which was matched to our study population on the basis of age, weight and baseline function, we're seeing highly statistically significant differences relative to this external control group of 60 patients derived from a recent placebo-controlled studies. And that difference of 7.5 points that we're seeing, relative to what we would expect in this population, is highly statistically significant, even though we're looking at small numbers at the moment.

In terms of what that means long term, obviously, we have data over 12 months. We need -- we will be generating data over longer periods. If we're able to delay ambulation through this treatment by many years, that will be a significant impact on this patient population. If we're able to delay the time to requirement for ventilation because of respiratory muscle weakness, that will be a major impact. And of course, if we're able to delay the mortality in this disease, that would be fantastic for this population. But until we have longer-term studies, the extent to which these very clear, measurable changes on the ambulatory scale translate into a long-term delay of major disease progression milestones, we're going to have to wait for the data to come in.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you, Mike. And let me just punctuate 2 things. On the monitoring, as you have noted, we have now gained experience proactively that we believe will allow us in a convenient approach for medical practice that is common to be able to intervene, if necessarily, and resolve potential adverse events. And what's key for this population that we hope to give many years and possibly decade benefit is, of course, the dose you chose to maximize likelihood of benefit. The SAE that Mike Binks spoke to are related to a higher dose, while we also got a favorable benefit on numerous markers related to muscle functions with a lower dose. But given that we think that management of any adverse event can be quite conveniently performed over days to up to 2 weeks, we feel pretty optimistic about rather going with a dose that we believe maximizes long-term gain for these patients is the right way to go.

And then finally, I believe this is actually the first convincing data set shown that gene therapy can, in boys, gain significant improvement of multiple tests related to muscle health. First, the North Star now performed at an age where you are expecting decline makes the value much more persuasive from what I interpreted. Data on earlier boys, 4 years of age, it's -- in our experience, much more difficult to interpret, whether you have a real effect or whether it's more normal gain. So again, this data set was supplemented, as you heard from Mike Binks, by exploratory endpoints of MRI, which I think is the first to be shown, and we also have favorable trends in creatine kinase. So altogether, I think it's the largest data set on boys where gain is not what you expect to be shown and the most consistent efficacy parameters shown year-to-date, and we obviously hope to gain more data as we continue into Phase 3. Thank you very much.

Operator

Your next question is from David Risinger with Morgan Stanley.

David Reed Risinger - Morgan Stanley, Research Division - MD in Equity Research and United States Pharmaceuticals Analyst

Yes. So could you provide some more color on the baseline characteristics in -- of the patients in your data set, including the age of the patients and other details? I know that you commented previously, but if you could add more color relative to the Sarepta data sets. And then separately, could you just provide a framework for the timeline for Phase 3? And when you think that you could issue results from Phase 3?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

You want to start, Mike?



Michael Binks - Pfizer Inc. - Vice President, Rare Disease Clinical Research

Sure. So the population we look at where boys between the age of 4 and 12, but actually, the population we're reporting on is between 6 and 12 or almost 13. They were all walking, still able to walk and on daily glucocorticoids for at least 6 months on a stable dose of at least 3 months. The mean age was 8.8 years with a range from 6.2 to 12.8. The mean body weight was 27 kilos with a range of 18 to 42 kilos. And the mean functional measure that we use to -- for inclusion purposes, is the time for a boy to get up from lying on the floor, and it had to be under 7 seconds to be eligible for the trial, but the mean time of these boys was 4 seconds. And as I said, we've -- in our external placebo comparisons, we've used the same inclusion criteria to select the comparator group.

Relative to other studies, I think the Sarepta study, this is obviously an older population. I think the oldest boy in the Sarepta study was -- that we've seen so far, was 6 years. Does that answer your question?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Yes. Thank you, Mike. And I think your thorough answer punctuates my previous comments that these data are the most comprehensive shown to date, particularly in a population that is assumed to decline. And that, I think, puts, what I believe, a unique standing of excitement around this data.

Now on the Phase 3 timeline, we have previously said that we are planning to start Phase 3 in the second half of the year. I think given the progress we have had in preparing gene therapy manufacturing and in our strength of the data we have accumulated, we will look at ways to do that in the earlier part rather than the later part. And I think we are likely just a few months away from a potential Phase 3 start, so it's coming quite soon. And we are reviewing various options to be able to pull data across all of our studies as fast as possible to share with the proper regulatory agencies, and we're trying to look at what's the best way to have multiple options for this given that this is a group of boys with tremendous unmet need. And we feel we have now a good benefit risk profile, supported by the most comprehensive data set shared yet. Thank you.

Operator

The next question is from the line of Chris Schott with JPMorgan.

Christopher Thomas Schott - JP Morgan Chase & Co, Research Division - Senior Analyst

Great Just 2 for me. Sorry, if I missed this. But can you just talk about the age of patients you're targeting for the Phase 3? So what's the -- is there a criteria that specifically looks at a younger population? Or how do you balance the age of those patients? And the second question is just digging into the efficacy you're seeing a little bit more. Is there any color in terms of the benefit you're seeing in the younger patients versus older patients? I know the older patients are in a more difficult position. But are you seeing the same level of relative benefit when you look at that, I guess, external placebo that you're using versus the data in the study? Or is more of the signal coming from the younger part of the cohort here?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Mike?

Michael Binks - Pfizer Inc. - Vice President, Rare Disease Clinical Research

Okay. So to deal with the second part of your question first. We're dealing with such small numbers. It's very difficult to make comparisons within this group of 6 boys dosed at the high-dose cohorts and only 3 in whom we have 12-month follow-up to evaluate function, very, very difficult to draw any conclusions from those 3 patients. But you're right to say that older patients are likely to have more damaged muscle and are further



down the function curve and deteriorating at a faster rate. So -- and in terms of comparisons with our external placebo group, I don't think there's anything to add there, just the numbers are too small to start dicing.

And I'm sorry, what was your -- the first part of your question?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

The last part was related to age in the Phase 3. And currently, we are planning a multicenter pivotal study with 99 ambulatory boys between ages of 4 and including up to 7 who will be administered a high dose explored in Phase 1b. Anything you want to add to that, Mike? I think the question was about the age range, 4 to 7.

Michael Binks - Pfizer Inc. - Vice President, Rare Disease Clinical Research

So the age range is, yes, 4 to 7. We believe that in this population, it may be possible to have less heterogeneous data and hence the selection of a narrower age range for this pivotal efficacy analysis that we intend to do.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

This is an ambulatory population, but we are also preparing additional studies in other DMD patient populations. This is just the first that we hope to start at the Phase 3 within a few months. Thank you very much, Chris.

Operator

Your next question is from Vincent Chen with Bernstein.

Vincent Chen - Sanford C. Bernstein & Co., LLC., Research Division - VP

Great. Congrats on the data. Maybe just 2 quick ones for me. So the first one is what were your assumptions around the powering of the Phase 3 trial and how's the results you've seen here compared to the ongoing assumptions? It seems to me that the effect size you're seeing in these initial patients is actually, potentially, well exceeds what's necessary to demonstrate benefit. And then the second would just be what's your sense for the half-life of micro-dystrophin? And is it reasonable to think that the micro-dystrophin levels could actually continue to increase somewhat further beyond 12 months given the long half-life of dystrophin?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Mike, you want to start with the first, powering of Phase 3 and the half-life observed. And maybe Seng, you can speak about micro-dystrophin and its potential for further changes in a favorable direction.

Michael Binks - Pfizer Inc. - Vice President, Rare Disease Clinical Research

And so the Phase 3 study is powered on the basis of the primary endpoint, looking for change in the North Star Ambulatory Assessment. And obviously, it's a well-powered, robust study. If we were to see the magnitude of effect size that we think we're seeing in the Phase 1, then we're maybe slightly overpowered in that study. But certainly, we felt it was important to ensure that we were able to detect whatever clinically meaningful difference in North Star was likely to be relevant. So I think that's all.



Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Seng, any comment to micro-dystrophin that was shown to increase and the question on half-life and what to expect next? Seng?

Seng Cheng - Pfizer Inc. - Chief Scientific Officer and Senior Vice President, Rare Disease

Mikael, this is Seng here.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Okay.

Seng Cheng - Pfizer Inc. - Chief Scientific Officer and Senior Vice President, Rare Disease

Yes. I can say that we believe that the half-life, at least of the wild-type dystrophin, is approximately 100 days. But we are clearly not sure if that's different for the micro-dystrophin that we're using in our construct. So the longevity that we're seeing at the 1-year time point probably reflects a steady state of expression and degradation of micro-dystrophin. But the fact that we're seeing expression at the 1-year time point basically reflects the fact that with the gene therapy vector that we had used and employed, we are continuing to express micro-dystrophin over this time period.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you, Seng. And I believe that seeing such a sustained expression at the year in boys of older age and have been studied by any other companies reporting data of this type is also encouraging given what you heard from Mike Binks that you expect degeneration of muscle to happen, but we sustain a very robust level. And that, I think, give further encouragement that the Phase 3 that we hope to start in just a few months, as you heard, is well powered, and if anything, maybe overpowered because we think the current data were very encouraging. And that may give us an opportunity for looking at ways to rapidly extract data across all our studies for a potential way to increase speed to access for this type of product to a broader population.

I thought I wanted to ask Seng also to comment on that being in the field a lot of discussion around comparing the technology that we use, high-end LCMS technology, highly quantitative versus western blot, and I know that you have also performed western blot data. And could you just share with the analysts and the colleagues listening to this call what made you stick with LCMS? And your somewhat, I think, concern about western blot being similar accurate technology.

Seng Cheng - Pfizer Inc. - Chief Scientific Officer and Senior Vice President, Rare Disease

Yes. So sure, Mikael. I think that we can all agree that the western blot method is not exactly a standardized method that we use in the different organizations, so it's really difficult to make comparisons between data sets that generated at one site relative to another site. The LCMS method that we have developed, as Mikael had indicated, is designed to provide what we believe would be a more qualitative measure of dystrophin levels. It offers a significantly higher sensitivity and reproducibility, and importantly, also a wider dynamic range. And we've worked quite hard over the last period to validate this assay. We believe it is clearly a more precise, sensitive and selective way by which we can measure dystrophin levels. And we've had actually discussions with the FDA who's clearly encouraged that this clearly is a path that we should pursue going forward. As you indicated, Mikael, we have made comparisons of our samples using both methods of western blot as well as LCMS. And in general, we have seen a tendency to overestimate the values of dystrophin when we use the western blot to the point where, in some instances, it exceeds 100% normal value that we see in our assays. So that's the main reasons that we are pursuing, going forward, the use of the LCMS method.



Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you, Seng. So I thought that was a very important aspect that, in our hand, western blot most frequently give higher values. So we have had some concern that it would give maybe some overoptimism of the levels. And we found, at least, in our experience, that LCMS is more consistent and seems to, we think, more accurately reflect the level. So that's why we used LCMS and found concern that, western blot in our hands give much higher values than we thought was reasonable to expect. And that's good to keep in mind when you do cross-trial comparison, although, of course, different companies may use different type of western blots. So we do not comment on others, but I thought we wanted to share our experience. Thank you.

Operator

Your next question is from Terence Flynn with Goldman Sachs.

Terence C. Flynn - Goldman Sachs Group Inc., Research Division - MD

Maybe a couple for me. First, on the North Star data, trying to think about how to correlate this with the dystrophin levels. You mentioned there was one patient, I believe, at the low dose that didn't improve between 2 and 12 months on the North Star. Was that the same patient that had no change in dystrophin levels? And then the -- one question on safety, just with respect to the 3 additional high-dose patients that were not included in today's presentation. I think you commented on this front, but I just wanted to be sure here. There were no additional cases of complement activation in those patients. Is that correct?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Mike, I think these are clinical questions in the trial you're leading. Please start with the North Star and then on the 3 additional patients and the safety.

Michael Binks - Pfizer Inc. - Vice President, Rare Disease Clinical Research

So no evidence of complement activation in the 2 additional patients in whom we have follow up outside of the cohort that we reported. So that's the first point.

And in terms of the levels of expression in the boy whose North Star score over 12 months in the low-dose cohort declined really at the same rate as the population, I don't think he was an outlier in terms of the dystrophin concentration.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you. And one needs to remember, North Star is a very comprehensive, integrated analysis of the function of multiple muscle groups, particularly in the lower extremities and other parts of the body, including head movement. While the biopsies are of usually as one single muscle group. So that's why, I think, particularly the functional data and supplemented by exploratory MRI that measured a sizable part of a muscle and also creatine kinase data that was stable altogether come to a quite encouraging indication of gain in muscle health and function. So that's, I think, pretty encouraging for us. Next question.

Operator

Your next question is from Umer Raffat with Evercore ISI.



Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

I'm very intrigued by your comment that the whole thigh MRI improvements, the 12 months, have never been observed in matched, placebo-controlled population. But I was curious if you could speak to why the low dose did not have any MRI improvements? And also considering that there's a discrepancy in MRI between low versus high dose, perhaps you could speak to how the MRI is trending pre-12 months for the 3 patients that you didn't report at first? And then separately, on immunofluorescence with the percentage positive fibers, the high dose used to be at 70% normal in the data you presented previously at 2 months. Now it's 50%. And I think you hinted at some algo changes in measuring percentage positive fibers. Can you speak to what exactly was changed, why it was changed and if there's different muscle locations that are being measured now?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Mike, you want to start on the first, and then maybe Seng can speak about immunofluorescence? The first was related to the MRI and the low dose versus high dose.

Michael Binks - Pfizer Inc. - Vice President, Rare Disease Clinical Research

Yes. Right. And so in the low dose, at 12 months on the MRI in the low-dose cohort, there was one outlier who had progressed in terms of their fat fraction, and that probably pulled the mean up. But we have to be cognizant that these are still small numbers. We do not have an analysis of earlier time points than 12 months. Throughout this, we've been very concerned that the steroid -- the increase in steroid doses at the time of administration and for a couple of months after the administration may have an effect on improvement of a range of biomarker and functional parameters. So we're focused on the 12-month time point as being more meaningful from a long-term perspective but also less likely to be confounded by short-term medication.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you. Seng?

Seng Cheng - Pfizer Inc. - Chief Scientific Officer and Senior Vice President, Rare Disease

Yes. So in terms of the change in absolute immunofluorescence positive numbers, it does reflect a change in the algorithm that we used to measure the signal. So with the new algorithm that we use, we impose a higher threshold on what we would constitute a positive. So in terms of the intensity of the signal that we saw that we qualified as a positive. So it essentially reflects a change in the algorithm that we use to select what we would constitute as a positive signal, a more stringent approach to the question.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you, Seng. And I think it underscores the difficulty in cross-trial comparison, depending on exactly how you analyze some of these techniques that are more qualitative and quantitative based to some variability, but it's a very impressive change from baseline if you look at the immunofluorescence data sets.

And I think as you spoke to the MRI, it also, as a very quantitative instrument, may help to feel confident about the advantage of going with a high dose for patients that need to benefit over many decades and that we are -- what we think in a really good benefit to risk and feel very confident now how to easily monitor early signs of complement and, if required, intervene, simple laboratory blood tests that can be performed at any hospital or physician office. Thank you. Next question.



Operator

Your next question is from Andrew Baum with Citi.

Andrew Simon Baum - Citigroup Inc, Research Division - Global Head of Healthcare Research and MD

A couple of things. Just going back to the duration of the dystrophin expression. I just want to make sure I understood correctly. So you're confident about prolonged expression is a function that children are rapidly growing, and therefore, there's a rapid turnover of myocytes. So if I've misunderstood, then that would be helpful. And then second, going back to the patients who have complement activation. Mechanistically, I'm assuming it's not the AAV. So presumably, it's either the oligonucleotide or it's the protein. I think you said the -- it occurred 7 days, so I'm assuming it's micro-dystrophin itself. But anything you could add mechanistically on the complement activation patient would be helpful.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Mike, you want to start on this?

Michael Binks - Pfizer Inc. - Vice President, Rare Disease Clinical Research

So in terms of duration of expression on growth where we can reflect the data that we have showing, if anything, an increase in expression in the biopsies from 2 to 12 months. We do not have data on biopsy going out further. We're encouraged by that, that there was no loss of muscle fibers expressing over this time period, which could have accrued from growth or immunological events. So we're not seeing anything there.

In terms of the complement activation events, we do believe this is related to the immune response to AAV. The data that we have, so far, in these 2 individuals suggest that their neutralizing antibody levels rose higher and faster than others in the cohort. But the numbers are very small to get down to a mechanistic dissection, and we're being pragmatic about how to best intervene and prevent.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you, Mike. And that your view on complement activation related to probably AAV capsid proteins fits very well with the issues we've seen early of infusion and 2 weeks after infusions, all the patients, including the SAEs, have recovered from this. So it is something that's happening if there is a rapid antibody response to a capsid. And in this case, the complement is something that could give a typical complement disease but can easily be monitored, such as platelet consumption and intervene very resolutely, if required. We know AAV can, in other cases, lead to liver function tests, and that requires quite careful monitoring and possible intervention for that. Fortunately, for our cases, it's been really clean for any issue of liver injury, while that's something that many companies have reported for their vectors. So we feel pretty good in understanding the profile of this drug, how to minimize and mitigate and take care of the safety. We believe we have a good picture that we can now implement in Phase 3. And while we've been very encouraged by the efficacy, particularly seeing this also in larger boys with higher age but still ambulatory, meaning we can prefer possibly then over time, as we have shown, improved motor function, even in advanced cases here. Thank you.

Operator

Your final question is from Geoff Meacham with Bank of America.

Scott D. Puckhaber - BofA Merrill Lynch, Research Division - Research Analyst

This is Scott on for Geoff. Just had one. Given the high SAEs on a percentage basis, do you think this will impact your ability to enroll in the Phase 3 trial? And then are you actively monitoring for damage to the CNS and other neurotoxicity given the AAV9 has been associated with neurotoxicity?



Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Mike?

Michael Binks - Pfizer Inc. - Vice President, Rare Disease Clinical Research

Okay. So in terms of neurotoxicity first, we've seen -- our investigators are looking out for issues, and I have reported no CNS-related adverse events that could be, in any way, connected with the high-dose AAV9 publications that you're referring to. And so that's -- that was the second part of your question.

The first, in relation to recruitment challenge, well, this is a very savvy patient population. They think about the criteria for enrolling their boys very carefully. And it's our view that these are managed in a controlled way, and we are getting better at detecting and alleviating these types of adverse events. We have very close links with the patient community, and we do think that there's a lot of interest in our therapy. And we're not anticipating any enrollment -- any particular enrollment challenges related to this particular adverse event profile in the first 14 days after the treatment where people are closely monitored.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you, Mike. And if I can, Geoff (sic) [Scott], just to punctuate here, our learning from this patient community that maximizing efficacy is very important to bring long-lasting benefit, as we have shown, by far, the most comprehensive number of boys studied with the largest panel of endpoint that are measuring muscle function or biomarkers for muscle function and health. We have, in general, felt a strong interest for our trial, and we feel very much comforted that we have a manageable approach in medical practice to safety events if they may emerge, and we think that can be well managed and easily monitored. And they all happen over a couple to -- a few weeks after infusion, so we feel very good about getting through that. What we focus is long-lasting durability.

And I should punctuate, even during the era here of COVID-19 concern in the community, we have been able to continue to enroll and monitor and follow up on our Duchenne boys, and we have seen significant interest for our trial. And I think that adds a further dimension to the eagerness for many to explore our products. And of course, we'll look forward and hope we'll see that we can enroll fast in the Phase 3 that we'll be starting in a few months, and our ambition is to be -- hope for being the first Phase 3, starting with commercially available product and moving swiftly to be a leader in this space.

Thank you very, very much for your interest for this product and for Pfizer.

Charles E. Triano - Pfizer Inc. - SVP of IR

Thanks, everybody, for dialing in on the analyst and investor side. Thanks to the Pfizer team. And operator, this will conclude our call. Thank you.

Operator

Thank you for joining today's conference call. You may now disconnect.



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