Sarepta Therapeutics, Inc. - Special Call *(Edited version)*

Call Participants

EXECUTIVES

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Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

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Presentation

Operator

Good morning, and welcome to Sarepta's conference call to discuss the safety update for ELEVIDYS and steps to strengthen safety in non-ambulatory individuals with Duchenne. As a reminder, today's program is being recorded.

At this time, I'll turn the call over to Doug Ingram, President and CEO. Please go ahead.

Douglas S. Ingram
President, CEO & Director

Thank you, Michelle. Let's move to Slide 3, please. Before I begin, I'd just remind you that we'll be making some forward-looking statements today. Please refer to our various public filings for the risks and uncertainties that come with making predictions about the future. Let's move to Slide 4.

Well, thank you, everyone, for joining Sarepta's call today to update you on important steps we are taking to enhance the safety of ELEVIDYS treatment for non-ambulatory individuals. It is with great sadness that I must report that a non-ambulatory patient dosed with ELEVIDYS has passed away from acute liver failure.

We have by now dosed over 900 patients with ELEVIDYS across a broad range of ages and weights and ambulatory status and spanning over 7 years of infusion experience. While liver injury is a known risk with the use of any AAV-mediated gene therapy, historically, we have not had a signal that would lead our safety committee to conclude additional measures were necessary or appropriate.

However, following this second tragic event, we have immediately taken steps with the goal of enhancing further the safety profile of ELEVIDYS in the non-ambulatory patient population. You will hear shortly from our Head of R&D, Dr. Louise Rodino-Klapac, who will provide the preclinical results of a study conducted by Sarepta on the use of sirolimus. The data from these studies suggest that an immunosuppression regimen employing sirolimus could significantly mitigate the risk of elevated liver biomarkers and therefore, ALF in connection with dosing of an rh74-mediated gene therapy.

With that in mind, we have taken the following steps. We immediately took the decision to pause our non-ambulatory study ENVISION or Study 303, while we seek a protocol amendment to add the prophylactic use of sirolimus in connection with future infusions. We have temporarily suspended commercial shipping of ELEVIDYS for non-ambulatory patient infusions until such time as we have completed the following 2

activities: we have called an expert panel to share the data and align on the use of sirolimus and its protocol in connection with future infusions; and second, we have had an opportunity to take feedback from the FDA on the recommendation of additional immunosuppression as a prophylactic addition to the treatment protocol for ELEVIDYS in the non-ambulatory patient population.

Our goal is to complete both activities as rapidly as possible as we know that non-ambulatory patients are waiting for treatment and as with all DMD patients, time is not on their side.

Let me now turn the call over to Dr. Louise Rodino-Klapac, who will provide more detail on the preclinical data that support our proposed enhanced immunosuppressive regimen and will explain how this data underpins our confidence that this approach can effectively mitigate the risk that we have observed. Louise?

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

Thanks, Doug. Our mission at Sarepta is to support those living with Duchenne. And with over 900 individuals treated with ELEVIDYS, patient safety is and always will be our absolute top priority. In light of today's heartbreaking news, we are acting swiftly and decisively. Our immediate actions, as Doug just outlined, are directly informed and supported by robust preclinical data, which I'll now outline for you.

Next slide, please. Our current understanding is that the safety events we've observed are likely related to the AAV vector in the liver, which triggers a T cell-mediated immune response. This response then causes inflammation, which in severe cases, can lead to acute liver injury and in very rare cases, acute liver failure. We believe sirolimus can mitigate this risk because it's a potent inhibitor of T cells. This mechanism of action is crucial as it helps suppress the activation of T cells, thereby mitigating the immune-mediated liver inflammation that can lead to liver injury. Our proposed regimen, which includes sirolimus is therefore designed to address the underlying immune response, which we believe will be responsible for these events.

Next slide, please. And the next slide. We performed a study in nonhuman primates to test the effect of sirolimus on antibody formation and immune response to AAV-Rh74 and transgene. Animals were monitored for approximately 12 weeks. The significance of this study includes that the data highlights the effects of sirolimus on the immune system, specifically its ability to lower T cells.

As shown on the left of the slide, transgene AAVrh74 was administered along with ImmTOR, which is just sirolimus delivered via lipid nanoparticle, we observed a clear suppression of the immune response to AAV. The data on the right further confirms its effectiveness in suppressing the immune response to the transgene.

Next slide, please. I'd like to turn your attention to this slide, which provides evidence of how sirolimus impacts liver health in our preclinical studies. Here, we are tracking key liver biomarkers, ALT, AST and bilirubin. Elevated levels of ALT and AST are common signals of liver cell stress or injury, while high bilirubin can indicate problems with liver function. The results demonstrate that across all of these vital measures, sirolimus effectively moderates or significantly reduces these liver enzyme elevations in nonhuman primates.

Next slide, please. It's also important to evaluate how adding sirolimus for safety reasons might impact ELEVIDYS expression. The data from these charts clearly demonstrate that expression is not negatively impacted by including sirolimus in the regimen. The chart on the left shows strong protein expression in the heart and skeletal muscle, measured via an ELISA assay. The chart on the right further illustrates robust expression in the heart, diaphragm and skeletal muscle through immunofluorescence, or IF. These findings collectively confirm that the addition of sirolimus maintains the desired expression across key tissues.

Next slide, please. And next slide. So to summarize, our preclinical data provides a critical foundation for these next steps. As data demonstrated that our proposed enhanced immunosuppressive regimen with the addition of sirolimus was effective at suppressing liver enzyme elevations. This finding gives us strong rationale for its potential to help mitigate liver-related safety events in patients and has informed the actions we have announced today.

In summary, our commitment to patients and patient safety is unwavering. As we learn more, we will update the community and others thoroughly and with expediency.

I'll now turn the call back to Doug for any final remarks and Q&A. Doug?

Douglas S. Ingram
President, CEO & Director

Thank you, Louise. Let me reiterate that our goal is to implement this enhanced risk mitigation plan as rapidly as possible as we know that time is muscle for all patients living with Duchenne, and that certainly includes our nonambulatory patients.

Of course, we don't yet have visibility into the exact time line to resume dosing in the nonambulatory population, and we're going to need more time to assess its impact. Thus, we were required to suspend our revenue guidance. We plan to provide an update on guidance in our second quarter results call.

As we look at 2025 performance, we will assess the impact on revenue and then we're going to take a careful look at our cost structure to ensure that we remain financially disciplined.

And with that, Michelle, let's open the call to questions.

Question And Answer

Operator

[Operator Instructions] And our first question comes from Brian Abrahams with RBC Capital Markets.

Brian Corey Abrahams
RBC Capital Markets, Research Division

Sorry to hear the news here. Is there anything more you can say about this particular case in terms of whether this was somebody who was receiving ELEVIDYS in the commercial setting or in the ENVISION study? Anything you could say about dosing and weight?

And I know in the prior case, the management and mitigation measures were done and were done to very high standards. Was this the same thing here, where the monitoring -- I guess, maybe talk a little bit about how this -- what the course was like and how the patient was managed?

Douglas S. Ingram
President, CEO & Director

Brian, thank you. I'll just make one comment before I turn this over to Louise, and that is that this patient was cared for at an absolutely stellar site by an absolutely stellar physician, and they received very good care. With that, Louise, perhaps you want to comment?

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

Sure. This particular patient was a nonambulatory patient in our ENVISION study. So it was in a clinical trial setting. As Doug mentioned, received the best care possible. This was an individual that's 15 years old. There was similarities to the previous case what we have. We're not going to provide too many details on the exact case just for privacy reasons, but there were similarities in the first case and there were some differences as well.

So this patient was well cared for. We are currently evaluating this case in the context of this case alone and then in comparison to the previous case. We haven't identified a single risk factor, but we are working expeditiously to identify anything that we could potentially point to. In the absence of that, we've obviously

talked about our intention to include immunosuppression. As I mentioned, sirolimus will limit liver enzyme elevations, which will then limit the ALI signal.

Operator

Our next question comes from Tazeen Ahmad with Bank of America.

Unknown Analyst

This is Daniel on for Tazeen. I was just wondering if you could maybe help us understand, what gives you confidence that this is not going to happen with younger patients? And what's giving you confidence that you can maintain the same kind of immunosuppressive regimen for those patients when you only need to adopt it for the nonambulatory ones?

Douglas S. Ingram
President, CEO & Director

Louise, would you like to take this question?

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

What we could say right now is the signal -- the safety signal was seen in nonambulatory individuals. As you know, ambulatory status is really a surrogate for the severity of disease progression. And so we've only seen the signal in this nonambulatory population. It's certainly something that we will evaluate as we go on and continue to evaluate in this population. We have not seen it in the ambulatory population, but it's certainly something that we will continue to evaluate the immunosuppression in nonambulatory population and certainly continue to look at it more broadly as well.

Operator

Our next question comes from Ry Forseth with Guggenheim.

Ry Roger Forseth
Guggenheim Securities, LLC, Research Division

Given the potential implications of the 2 deaths and what they may have on the overall ELEVIDYS brand reputation, do you anticipate that younger ambulant patients will want to wait for next-gen gene therapy technology rather than dosing with ELEVIDYS?

Douglas S. Ingram
President, CEO & Director

Look, I'm not going to speculate on the near-term impact of this announcement other than to note, the best of my knowledge, there is no obvious next-gen gene therapy that's coming right around the corner. Please remember that this issue that we have now identified and seen a signal for relates to liver stress, which is a known risk of any AAV-mediated gene therapy. And we're not aware of a single development stage non-AAV gene therapy that's currently in existence.

Operator

Our next question comes from Gena Wang with Barclays.

Huidong Wang
Barclays Bank PLC, Research Division

I'm very sorry for this unfortunate event. So my question is, I know you presented the preclinical data. But we do know REGENX also actually using sirolimus in their prophy regimen. Will you be able to use some of the

clinical data, the human data that -- I think FDA has all these data as well. Sorry, bottom line, the question is, what kind of a human data you need to run a study? And how many patients, like what kind of data that will be sufficient for FDA to consider this regimen will be safe? And how long follow-up that you need to have in order for FDA to think this regimen will be safe?

Douglas S. Ingram
President, CEO & Director

I will turn this over to Louise to comment. Your; point is a very good one, Gena, which is that there are other gene therapies that have employed the use of sirolimus because it's -- anyways, in the patient setting, I think as you mentioned, there's one gene therapy from REGENX that uses a cocktail of immunosuppressive and other complement suppressive pretreatments. And then, of course, there's also a gene therapy for GAN that existed that use this as well. That data -- given the amount of that data, one might consider that to some extent anecdotal. But it certainly provides additional conviction that the use of sirolimus could greatly mitigate the stress on the liver and elevated liver biomarkers and therefore greatly reduce the risk of ALS in these patients. Our goal is to meet rapidly with the FDA to discuss this and to put this in place now. First is a protocol for our Study 303, our nonambulatory study as well as in the commercial setting.

We have not yet had the opportunity to have those discussions with the FDA. We want to have them as rapidly as possible. We want to have an expert panel as absolutely rapidly as possible to nail that protocol and then to put it in place. One thing I will say is that the FDA has proactively asked us if we have considered the use of additional immunosuppression. And I believe, and Louise will correct me if I'm wrong, actually mentioned sirolimus itself. So our hope is that we're going to have a very constructive discussion with the FDA about getting this in place right now to mitigate the risk in the nonambulatory patient population.

But Louise, feel free to add anything or correct me if I've made a mistake.

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

You've covered most of it. The only other thing I'll add is, and as Doug mentioned, you mentioned a few, but there are several clinical programs that have used sirolimus. And it's been used pretty commonly in gene therapy. There are slightly different protocols. So one of the things that we'll be confirming with the expert panel that we meet with is the exact regimen. Sirolimus is not without any risk. There is some effect on the immune system. So we want to make sure that we're being thoughtful about the balance between suppressing the liver toxicity but also not making any of them [susceptible] to more infections than needed.

So the protocol typically will have a start shortly before dosing and then continue for several months. And so we'll be confirming that exact regimen and the dosing with both the panel and then with the FDA.

Operator

Our next question comes from Andrew Tsai with Jefferies.

Lin Tsai
Jefferies LLC, Research Division

Sorry about the tragic news. So as we think about the outlook ahead, why should investors feel confident ALF will only be limited to the nonambulatory population? And are you aware of any other patients being hospitalized for serious cases of liver injury right now?

Douglas S. Ingram
President, CEO & Director

What we can say is that the signal for ALS is obviously exceptionally rare and has only emerged in the nonambulatory patient population right now. To remind you, we have dosed well over 900 patients. We've been dosing for 7 years. At the time of our first approval and our broader approval, we had no signal of this

serious ALS concept. We had elevated liver enzymes in a minority of patients. They responded very rapidly to modest increases in steroids.

So we're following the available objective evidence that we have right now. Obviously, as Louise mentioned, the ambulatory status is very likely a surrogate for disease progression. And certainly, once we have developed this protocol and we were able to implement it with the nonambulatory patient population, physicians can use their judgment to determine the circumstances in which they see it as a valuable additional prophylactic for other patients as well in their medical judgment.

So that's where we are right now. Is there anything I missed in that, Louise?

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

No.

Operator

Our next question comes from Mike Ulz with Morgan Stanley.

Michael Eric Ulz
Morgan Stanley, Research Division

Sorry about the news as well. Maybe just a quick follow-up on one of the prior questions regarding dosing. And if you're willing to share, just curious if the second patient might have been on a higher dose versus the first patient.

Douglas S. Ingram
President, CEO & Director

Louise?

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

No. The dose was the same between the patients. Dose per kilogram, yes.

Ian Michael Estepan
Executive VP & CFO

Yes, and just to add on to Louise's point, the dose is always the same for patients. It's weight-based dosing. The first patient was 70 kgs. The second patient was 50 kgs. So obviously, you got a lower dose overall. But obviously all the patients get the same dose based on their weight.

Operator

Our next question comes from Louise Chen with Scotiabank.

Hannah Grace Liu
Scotiabank Global Banking and Markets, Research Division

This is Hannah Liu on for Louise Chen. We wanted to ask, since your March safety update, it looks like you dosed an additional approximately 100 patients. What was the feedback like from those patients and their physicians? And why did they feel comfortable going ahead with treatment despite the known safety risk?

Douglas S. Ingram
President, CEO & Director

Well, I'm not going to comment on the number of patients we've dosed. Obviously, we'll update you on all of that in our second quarter conference call. I will note that versus our second quarter guidance, we were modestly tracking at the time before this event to exceeding that. I think that, at least based on the discussions we've had with physicians and families, regarding the therapy, folks understood the risk benefit. They understood the potential value of ELEVIDYS, the patients who I would remind you, are suffering from a devastating degenerative disease that invariably results in death, understood the risk profile and the number of patients that have been dosed and the signal. And that's what we've heard so far.

Operator

Our next question comes from Kostas Biliouris with BMO Capital Markets.

Unknown Analyst

This is for Phil on for Kostas. Sorry for the tragic news. So our question is about the ratio between the ambulatory and the nonambulatory commercial patients you have treated so far. And also, what is the expected contribution of the nonambulatory patients to the latest 2025 guidance?

Douglas S. Ingram
President, CEO & Director

Yes. On the latter half, I'm obviously going to -- I'm going to refrain from answering that question, We'll do more work and then we'll talk to what our guidance -- what impact this will have on our 2025 guidance, which we're suspending right now. And we'll discuss that hopefully in the second quarter conference call, we'll have some update on that.

I can just give you the broadest of strokes epidemiologically and otherwise with respect to ambulatory, nonambulatory. Broadly speaking, if you look epidemiologically, it's 50% ambulatory, 50% nonambulatory. If you look at the number of patients treated with ELEVIDYS since our initial launch, it's more like 85% ambulatory, 15% nonambulatory. If you look at just narrowly this year, we're tracking to more like 70% ambulatory, 30% nonambulatory. So there was a greater percentage with the broader label, obviously, this year than before.

Again, we will do the work. We'll do all the analytics both on the guidance and as well on our cost structure, and then we'll provide an update to everyone when we're able to do that. Hopefully, we'll have some update at the second quarter conference call.

Operator

Our next question comes from Ritu Baral with TD Cowen.

Joshua Seth Fleishman
TD Cowen, Research Division

This is Joshua Fleishman on the line for Ritu. So curious, what is the window of suspicion after ELEVIDYS treatment for these severe adverse reactions to occur? And what percentage of the 140 dosed nonambulant patients are currently in this window of suspicion? And you've indicated that the safety signal has only been identified in non-ambulant patients, but we believe it's been seen younger patients, too. So should the enhanced regimen also be a discussion point for those younger patients? And if so, why not?

Douglas S. Ingram
President, CEO & Director

Yes. We haven't seen a signal in ambulant patients as we sit here today. But nevertheless, Joshua, to your point, I think once the protocol is in place for the use of sirolimus for the nonambulatory patient population, I would imagine that physicians are going to reflect on that and then make some risk-based decisions about

whether it makes sense in other cases, late ambulatory or other risk factors where they decide that the use of sirolimus might make sense even for ambulatory patients.

With that, I'll turn the remainder of your question over to Dr. Louise Rodino-Klapac.

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

Yes. The question was around the timing of when we might see these events. And so typically,with any liver enzyme elevation, that typically occur within the first 90 days, as most of our AEs do. So that's typically the window that we would be looking at as far as percentages of patients, I don't have a percentage to provide you as far as how many patients are currently in that window.

Operator

Our next question comes from Brian Skorney with Baird.

Brian Peter Skorney
Robert W. Baird & Co. Incorporated, Research Division

I'm very sorry to hear about the tragic death of this young man. I know all our thoughts are with his family. I guess to push a little more on the question of liver safety differential between ambulatory and nonambulatory. If you don't expect sirolimus use to impact expression, why not add it in the ambulatory setting as well?

I understand acute liver failure has only been seen in nonambulatory patients. But these are really small numbers. And in the past, you had indicated that you had not seen any difference in LFTs based on age or weight, which would imply that potentially, the acute liver failure risk is functionally the same. So why shouldn't risk mitigation be the same?

And I'm just wondering, do you have any additional analysis for peak bilirubin and ALT broken out by ambulatory and nonambulatory? And can you provide that to us?

Douglas S. Ingram
President, CEO & Director

Well, Brian, to your -- you have a very good point. Look, the ambulatory status is very likely a surrogate for disease progression. We are required to follow the evidence. And right now, the signal that we've seen is ALF in the nonambulatory patient population. But to your very point, once a protocol is in place, it will be available for its physicians to consider the use of sirolimus in other patients, including ambulatory patients.

We are going to be, with respect to the nonambulatory patient population, more prescriptive, assuming that we get to this expert panel and the FDA confers in our view. But that doesn't foreclose the ability to use rapamycin in connection with even ambulatory patients as the protocol is published. And so we would leave that to physicians. And we'll provide them with all of the evidence that we have available to us that can help guide those decisions.

Operator

Our next question comes from Gil Blum with Needham & Company.

Gil Joseph Blum
Needham & Company, LLC, Research Division

Allow me to add my condolences to the family here. So following up on something that was asked previously, and I just want to clarify this point. What additional clinical development would be required at add sirolimus to your protocol?

Douglas S. Ingram
President, CEO & Director

Our goal is to add it now and then to additionally have a protocol amendment for Study 303 or ENVISION to put it in place for ENVISION as well. So our goal is to implement it as a risk mitigation plan now. We have not had formal discussions or even informal live discussions with the FDA yet to take their input on that. I would note, however, that the FDA proactively asked us about whether we were considering the use of additional immunosuppression, including the use of sirolimus to risk mitigate elevated liver enzymes and therefore a signal of ALS.

So while I can't say in advance how those discussions will proceed. We are hopeful given that this is also on the mind of the FDA, that those discussions could be very constructive and that we could add this as a risk mitigation strategy right now for our nonambulatory patients who are waiting. That is important to us because, remember, for all Duchenne patients, as we often say, time is muscle. They lose muscle, they cannot get back on a daily, weekly, monthly and yearly basis.

And that is no less true. In fact, muscle is even in some regards, more precious for these nonambulatory patients who have already lost an enormous amount of muscle. So we will have that dialogue with the FDA. Our goal is to have it as soon as reasonably possible. And then we'll provide updates on those discussions once they have concluded.

Operator

Our next question comes from Joe Schwartz with Leerink Partners.

Joseph Patrick Schwartz
Leerink Partners LLC, Research Division

Please accept our condolences as well. So given the PPMD meeting is later this week, it seems like it could be a very important venue to interact with parents, patients and the community. Can you talk a little bit about your strategy heading into this meeting and how you plan to rebuild the trust of the community? What will be your main messages? And how do you plan to assuage concerns?

Douglas S. Ingram
President, CEO & Director

Well, yes, we're still -- obviously, there is an opportunity at the PPMD conference this week to have discussions with the patient community and provide information to the patient community. We're looking at that and looking at other mechanisms to engage.

Our number one strategy is to provide accurate and, to the fullest extent possible, complete information on the risk benefit, both the risk and the efficacy benefits of ELEVIDYS, first and foremost, to treating physicians and then referring physicians so they are armed with good information to have thoughtful discussions with the community and, of course, also to directly dialogue, to the extent possible and compliant, with the patient community itself to ensure that they have their questions answered as they are reflecting on these important treatment decisions.

So we are going to take the opportunity. There will be a number of Sarepta individuals and representatives at PPMD to provide accurate and complete information to the extent we have it to PPMD folks that will be in attendance.

Operator

Our next question comes from Salveen Richter with Goldman Sachs.

Salveen Jaswal Richter
Goldman Sachs Group, Inc., Research Division

Maybe just stepping back here in the context of this news. What are your steps in just overall strategy here for the company holistically? Thoughts about diversifying the pipeline as well as just the underlying base exon skipping business, just confidence in that kind of providing support here on the forward?

Douglas S. Ingram
President, CEO & Director

Well, let's start very -- let me start with a few issues in front of us. Our first goal is to ensure that we do the right thing by patients now. And while some might have seen this -- our approach as a conservative one, we do not because we think it is the right answer for the patient community right now. That's why even though the signal is still in the context of well over 900 patients dosed, a very rare one, we think we're doing the right thing, which is pausing dosing in 303, getting a protocol amendment to add a thoughtful protocol for the pretreatment with sirolimus.

Given the data we have today, we are -- we have a lot of conviction that, that is going to greatly reduce the risk not only of ALF but even of an elevated liver biomarkers. And then pause commercial shipments of ELEVIDYS for the nonambulatory patient population as painful as that is, because there were nonambulatory patients waiting for that therapy. But we need to do that for them, pause it and as rapidly as we can, get a risk mitigation strategy with sirolimus in place so that those patients can have the opportunity to consider the use of ELEVIDYS in the context of this devastating and deadly disease that they are currently living with.

The next thing we have to do, of course, acutely is look carefully at our guidance for the year. First, our revenue guidance for the year. What is the impact on this? Again, we're prioritizing the patients first, and we'll prioritize looking at the revenue guidance and figuring out what impact that has on our revenue for the year. And then, of course, we're going to have to look at our cost structure to make sure that we remain financially disciplined in the context of this. And then beyond that, we will drive forward the rest of our plans.

We are a very mission-driven company. We have a lot of programs to hopefully bring a better life to patients across an array of other diseases. As you will know, in addition to our gene therapies, we have programs limb-girdle programs that are moving forward right now. We have siRNA platform and we're driving that as well as. That's a lot of unmet need inside of those programs. And I think as you know, we have a DM1 and FSHD readout for proof of concept, proof of biology later this year. We have IPF and we have Huntington's disease. We have the [SCAs] and a number of other things in addition to our gene therapy.

So we have a lot of really exciting platforms and pipeline programs that we're focusing on. But our focus right now today is, first, to ensure that we rapidly do the right things for our patients that we -- which required us to pause both the 303 and the shipments for nonambulatory, get the risk mitigation in place and then think about what that means from a revenue perspective and a cost structure perspective. Get all that done. And then of course, our R&D colleagues will continue to drive those other platform programs and pipeline programs forward at the same time.

Operator

Our next question comes from Yanan Zhu with Wells Fargo Securities.

Yanan Zhu
Wells Fargo Securities, LLC, Research Division

Sorry to hear this news. So based on your dialogue with FDA, could there be any regulatory actions on the ambulatory patients or any indications of such actions? And also, any thoughts on why the signal only started emerging after you've treated 100-plus nonambulatory patients? Any changes in manufacturing or any other factors that you could think of? Because it feels quite unusual to not have seen this in 100-plus patients, within 3 months, 2 patients?

Douglas S. Ingram
President, CEO & Director

I can only speak to what we know now. First, with respect to the ambulatory patient population and the nonambulatory patient population, I think that as painful as this is, and I think that I'm very proud of the team for having made what is, I think, a very, very swift and very appropriate but potentially, conservative set of actions, including immediately pausing Study 303, pausing the commercial shipments for nonambulatory and working as rapidly as possible to put in place a protocol for the use of sirolimus to mitigate risk.

So I think with all that said, I think this is very appropriate. And I'm hoping the FDA will agree with this. And I think that there would be no obvious reason why someone would want to go further than what we're already doing, which I think is appropriate and definitely focused first and foremost on patient safety, patient well-being.

On the fact that we haven't seen this before, first, I will note on manufacturing. My tech ops team have looked carefully at all of this. We've seen no signals that there's anything in manufacturing that would explain this. Very likely this is the result of the fact that this signal is a very, very rare one. We have dosed, I said, 900 - well over 900 patients by now, and this has only emerged very recently. Even if you look just down at the nonambulatory patient population, we've dosed just about 150 nonambulatory patients. So obviously, even inside of the nonambulatory patient population, it is a very rare signal.

And it's no greater signal, I should note, than other full-body gene therapy infusions that are commercially available today. So this may very well just be a reflection of the rarity of this. I mean to your point, we've been dosing patients since January of 2018. And it was only in these last 2 cases that we've seen this sort of signal that's required us to take these actions that we are announcing today. Thank you for your question.

Operator

Our next question comes from Anupam Rama with JPMorgan.

Anupam Rama
JPMorgan Chase & Co, Research Division

So sorry about the news. Doug, I know you guys are still working through the guidance and then the revenue trajectory here, but just wondering if you could comment on how you plan on managing the 2027 convert and repayment there?

Douglas S. Ingram
President, CEO & Director

Sure, I'll have Ian comment on that.

Ian Michael Estepan
Executive VP & CFO

Sure. Thanks, Anupam. Yes, and managing our liabilities is something that we're always focused on. I think you know that 2027 notes become due in September. So we still have over -- a little over 2 years to manage them. And then we have multiple pathways available to us to address it. Doug touched upon it. But in the context of the converts specifically, we're proactively managing our expenses, and we're going to prioritize our portfolio in a way only to focus on the programs that have the highest probability of success and can reach the greatest number of patients.

The ambulant population alone supports profitability for us. And so if our EBITDA ratios, therefore, support access to our $600 million revolver. So we have -- so we remain in a very strong financial position, and we have multiple ways to address the converts.

Operator

Our next question comes from Biren Amin with Piper Sandler.

Biren N. Amin
Piper Sandler & Co., Research Division

I'm sorry to hear about this latest event. Have you considered lowering the weight-based dose or the max dose on the nonambulatory side to reduce the risk of ALS?

Douglas S. Ingram
President, CEO & Director

The signal that we've seen doesn't look like it would relate specifically to the weight or the total path. We've dosed patients significantly heavier than the patients in issue, as one example. So with that, I'll turn it over to Louise, who can provide more color on that.

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

Yes. I mean you've basically covered it. So we've seen no correlation with total dose in terms of the [ILI] signal, which prior to progressing to ALS, we haven't seen any correlation with the total dose. So it would -- we would not change the dose at this point based on that.

Operator

Our next question comes from David Hoang with Deutsche Bank.

David Timothy Hoang
Deutsche Bank AG, Research Division

So I wanted to ask, I know there was a plan to, I think, dose patients under the age of 4 and maybe have a discussion with the FDA on that topic. So what is the status of the plan to treat those younger age 2 to 4? And then would you consider a risk mitigation with sirolimus for your LGMD gene therapy programs?

Douglas S. Ingram
President, CEO & Director

Yes. Just I'll handle the under 4 question. Real quick, we are going to have discussions with the FDA on the patients under 4. We haven't had it yet. So I can sort of answer that question. But it is upcoming. And when we have more information, it might be more than one meeting. We'll provide an update on that. I will note, we're very excited about the potential opportunity to be able to bring this therapy to kids under 4. The data that supports the expression data that we saw was absolutely fabulous.

So with that said, we'll continue working on that. When we have an update on that, we'll provide it. With respect to sirolimus and its use in connection with the LGMD population, I will leave that to Dr. Louise Rodino-Klapac.

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

For LGMD, I think it's important to remind that the disease progression is different and unique in LGMD as compared to DMD. We have not seen a signal of ALF in this population. We have seen elevated liver enzymes. Another difference is that there is an overall lower dose in the limb-girdle programs versus DMD as well. With all that said, it's certainly something that we will consider as we implement the immunosuppression with sirolimus in the DMD population. We will consider it for a limb-girdle, but it would be a data-driven decision if we decide to go there.

Operator

Our next question comes from Uy Ear with Mizuho.

Uy Sieng Ear
Mizuho Securities USA LLC, Research Division

I'm also sorry to hear about the tragic event. Doug, you mentioned a couple of times that the FDA has asked you to perhaps consider additional suppression regimens -- immunosuppression regimen. Could you maybe just help us understand when was this, how long ago? And also, are there any either examples outside or within, I guess, gene therapy that -- where you present maybe sort of preclinical data and the FDA allows for a change in, I guess, administration protocol of some sort? Just wanted to get a sense of what could be the hurdle in terms of getting the protocol agreed by the FDA.

Douglas S. Ingram
President, CEO & Director

Yes. The answer to your first question is very, very recently. They were asked about it. So I mean, second of all, just the actual attitude of the FDA and the view of the FDA on these risk mitigation strategies will be known with certainty once we've had a lot of discussions with the FDA, and we'll provide that update once we've done it. As I've said before, our goal is to rapidly both have an expert panel to provide a protocol. Again, this has been done practically in connection with other gene therapies.

So while there are some nuance as to what that exact protocol ought to look like, and we'll take some advice on that, generally speaking, there's a good path forward to know exactly how one would put a protocol like this in place and do so very rapidly. Then the second thing is we need to have that dialogue with the FDA and take their views. And then we can have a better view on how fast we can bring this to the non-ambulatory patient population, which as I've told you, are waiting toward this therapy. And so we'll do that as rapidly as we can.

Operator

Our next question comes from Eliana Merle with UBS.

Tejas Manubhai Wein
UBS Investment Bank, Research Division

This is Tejas on for Eli. And our condolences for this tragic event. I know there's been a lot of discussion about weight. Can you just remind us of the weight range in ambulatory patients versus nonambulatory patients? And maybe what percentage of patients are getting that max dose in ambulatory versus nonambulatory?

Douglas S. Ingram
President, CEO & Director

Louise, do you have that data available to you?

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

I don't have the data. The average weight, I think somewhere for ambulatory 35 kg. I think on the -- no one's hitting max dose in the ambulatory status. So it would be a nonambulatory, where we're hitting the weight cap of the 70 kg. And [Dallan] you could correct me or Doug, if -- but based on that, we haven't -- there's no weight cap in the ambulatory population. Because those are all underweight under the max dose.

Operator

Our next question comes from Mitchell Kapoor with H.C. Wainwright & Company.

Daniel Robert Smith
H.C. Wainwright & Co, LLC, Research Division

This is Dan on for Mitchell. And our condolences for the situation as well. So we were curious, what percent of nonambulatory patients that you've seen signs in ALF versus what percent typically experience elevated liver enzymes? And this is specifically nonambulatory patients.

Douglas S. Ingram
President, CEO & Director

We have not seen -- on elevated liver enzymes, I think it's about the same across all patients. These -- so I don't know, Louise, do you have any more information than I just provided?

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

No. It's about 30% of patients have elevated liver enzymes across the board.

Operator

Our next question comes from Sami Corwin with William Blair.

Caleb Kawun Stubbs
William Blair & Company L.L.C., Research Division

This is Caleb on for Sami. So from the preclinical data, we sort of had a question on the liver enzymes. I think you guys are showing that those enzyme levels were elevated between days 20 and 50. We were sort of wondering how good these NHP models are for evaluating ALF in humans, which happens a little bit more rapidly.

Douglas S. Ingram
President, CEO & Director

Louise?

Louise R. Rodino-Klapac
Executive VP, Chief Scientific Officer and Head of Research & Development

So the nonhuman primate model is relatively good in terms of the timing and duration. ALF is not -- follows an ALI signal. So it's not any quicker than you would see ALI. I think that was the question.

Operator

There are no further questions at this time. I'd like to turn the call back over to Doug Ingram for closing remarks.

Douglas S. Ingram
President, CEO & Director

Thank you very much, Michelle, and thank you all for your questions today as we announce this very difficult, but I believe appropriate set of actions to address this issue.

I will reiterate again, our goal is to move as rapidly as possible to implement a risk mitigation strategy, which would allow us both to safely commence Study 303 and continue to be providing what I believe to be a life-enhancing therapy to boys and young men who have Duchenne muscular dystrophy in the United States. We will continue to work on this. And as we have updates that are material and appropriate, we'll provide updates to the investment community as we also provide it more importantly to our physician and patient community. So thank you all very much.

Operator

Thank you for your participation. This does conclude the program, and you may now disconnect. Everyone, have a great day.