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Novartis AG

Avidity Biosciences, Inc., Novartis AG - M&A Call

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Event Participants

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Analysts 10

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Operator Operator

Good morning, and good afternoon, and welcome to the conference call and live webcast Novartis agrees to acquire Avidity Biosciences. [Operator Instructions] The conference is being recorded. A recording of the conference call, including the Q&A session will be available on our website shortly after the call ends. With that, I would like to hand over to Ms. Sloan Simpson, Head of Investor Relations.

Please go ahead, madam.

Sloan Simpson Executive

Thank you, Heidi. Good morning and good afternoon, everyone, and welcome to our conference call on the proposed acquisition of Avidity.

The information presented today contains forward-looking statements that involve known and unknown risks, uncertainties and other factors. These may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. Please refer to the company's Form 20-F on file with the U.S. Securities and Exchange Commission for a description of some of these factors. The discussion today is not the solicitation of a proxy nor an offer of any kind with respect to the securities of Avidity Biosciences [indiscernible] Health.

The parties intend to file relevant documents with the U.S. SEC, including a proxy statement for the transaction and a registration statement spinoff. We urge you to read these materials that contain important information when they become available. [Operator Instructions] And with that, I'll hand across to Vasant.

Vasant Narasimhan Executive

Great. Thank you, Sloan, and thank you, everybody, for joining today's conference call. We're very excited to go over with you the proposed acquisition of Avidity Biosciences, which we think has a strong strategic fit for the company, builds our presence in neuromuscular diseases, builds our RNA technology platform and materially improves the medium and long-term growth profile of Novartis.

So moving to Slide 4. I want to give you first an overview of the transaction. Novartis proposes to acquire all outstanding shares of Avidity for $72 per share. This represents a 46% premium to the October 24 closing price. Avidity will separate its early-stage precision cardiology programs into a new SpinCo, including the relevant third-party agreements.

Novartis will acquire the neuromuscular franchise, follow-on compounds platform rights, and we do expect the closing in the first half of 2026, subject to the completion of the SpinCo and the usual customary closing conditions.

Through this acquisition, we'll acquire three late-stage assets, which I'll go through in turn, a preclinical neuromuscular pipeline and importantly, a platform for extrahepatic delivery of xRNA, an area that, as you know, a high interest to Novartis as one of the leaders in delivering xRNA for cardiology-related indications to the liver. This will give us the capability to deliver these technologies outside of the liver in the future.

Now moving to Slide 6. I wanted to start with the strategic rationale for the deal in a little bit more detail. We've articulated to you we want to do deals in our core therapeutic areas and our core technology platforms. And this is a deal that fits both. We strengthened our neuroscience franchise by adding three late-stage neuromuscular programs.

And this builds on the extensive experience we have with Zolgensma. It really complements the footprint that we have with Zolgensma. I'll go through that in a bit more detail later in the presentation.

It advances the xRNA strategy that we began by acquiring The Medicines Company and now have built over the last years a broad portfolio of RNA therapeutics targeting a range of cardiovascular targets. This now adds a unique platform for antibody oligonucleotide conjugates enabling us to deliver RNA to the muscle. It also adds a first-in-disease pipeline. We want to be in these areas where there are high unmet needs and a need for disease-modifying therapies. Del-desiran and Del-brax have the potential to be meaningful disease-modifying therapies for DM1 and FSHD.

As I noted, this enhances our growth profile, and I'll go through that in a bit more detail, but I already want to highlight that these are medicines without LOEs before at least 2042 and our IRA exams. And from a sales profile and return profile standpoint, unlock multiple near-term multibillion-dollar opportunities with three programs expected to launch before 2030.

Now moving to Slide 7. This transaction is also in line with the capital allocation priorities of the company. We've been consistent in saying we want to invest in our core business. We want to do value-creating bolt-ons like the Affinity acquisition. We want to consistently grow our dividend, which we remain absolutely committed to.

And of course, ongoing share buybacks with excess capital, and we have an ongoing $10 billion buyback, which we expect to complete by the end of 2027.

Now over the years, we have done value-creating bolt-ons in neuroscience to build out our capability in a range of areas, including as you see here, including areas in neuromuscular conditions, including DTx and Kate Therapeutics amongst others. So this really complements the efforts that we've had over the recent years. It strengthens the key therapeutic area. It's a best-in-class profile, and as I noted, the attractive sales and financial profile.

Moving to Slide 8 and just to say a bit more about the impact that we expect could have on Novartis. It raises our '24 to '29 CAGR from plus 5% to plus 6%. But even more importantly, in my mind, it adds multiple assets that can drive significant growth through the next decade. It adds to the portfolio of late-stage assets that we'll be talking about our recent management event in a few weeks, adding these additional large-scale assets, which can bolster that growth profile in 2030 and beyond. And as I noted, these are assets that have that outlook into the 2040s without exposure to IRA.

Now we did note in the release, we will have a few points of margin dilution of 1% to 2% we expect, and we expect to get back to our 40% plus core margin in 2029 with efforts, of course, as always, to get there sooner and continue our strong productivity efforts in the company. Lastly, I do want to note that this is a deal that we believe clearly exceeds our internal rate of return threshold, a clear value creation potential and will deliver, we hope, substantial returns to our shareholders over time.

Now moving to Slide 10. So now I want to take a moment to go into the core value drivers. And let's start with the technology platform. Avidity brings a pioneering AOC platform for RNA therapeutics, in particular, with the ability to deliver RNA to the muscle. This platform consists of monoclonal antibodies that target specific receptors on the target tissue.

Those monoclonal antibodies are combined with an oligonucleotide to create the AOC conjugate. This gives you the ability to target these RNA therapeutics to cells beyond the liver where normally RNA therapeutics acts. It gives you flexibility to deploy either siRNAs or other nucleotides of different structures to the relevant tissue. We believe that the technology can give you the capability to maximize therapeutic durability as well as infrequent dosing and it's reproducible and scalable.

So moving to Slide 11. Over the next few slides, I want to take each of the three assets in turn. This page hopefully is helpful to you in that it covers a lot of the key data that I'll be covering in more detail, giving you the patient populations, our base case time line and the mechanism of action. But let's dive into each one separately.

So starting on Slide 12 with DM1, Myotonic Dystrophy. This is a rare progressive neuromuscular disorder with a poor prognosis, no disease-modifying therapy, but with a relatively large patient population with an estimated 80,000 patients in the U.S. and the EU combined. There are no currently approved disease-modifying therapies for this. It's an underrecognized disease.

So the prevalence may ultimately be higher than what we currently model. It's progressive and often fatal. It primarily affects skeletal, cardiac and smooth muscle. It is autosomal dominant increases in severity from generation to generation. There's a significant impact on quality of life.

Some of the quality of life measures and things we look at in this muscle weakness and wasting, myotonia, it can be cardiopulmonary comorbidities. And importantly, there is a reduced lifespan in these patients. The current standard of care primarily consists of supportive care, physical and pharmacological symptom management and as I said, no disease-modifying therapies.

So Del-desiran is designed to address the root cause of DM1, and I'll go through that in a bit more detail. This is a medicine that's well recognized by the regulators. It has FDA Orphan drug designation, it has Fast Track designation and it has breakthrough therapy designation. And it also has in Europe Orphan drug designation.

So moving to Slide 13. Del-desiran, as I noted, is addressing the underlying cause of DM1. So DM1 is caused by CTG trinucleotide repeat, CTG repeat that expand within the DMPK gene. These expansions change the mRNA structure such that mRNA sequester splicing factors, including another splicing factor importantly called MBNL. This leads to loss of normal cell function and muscle wastage.

And so the goal here is to restore normal MBNL function. Del-desiran does that by degrading the DMPK mRNA apparent transcripts in muscle cells and restoring normal MBNL function in splicing.

The way this was studied in the clinic is in the Phase I/II MARINA study. The trial showed that the medicine is delivered to muscle, engages the target and restores splicing. In the study, there were a number of endpoints, which were also used in the Phase III program that's ongoing to assess myotonia, the video hand opening time, to assess strength, hand grip and quantitative muscle testing and to look at activities of daily living, a patient-reported outcome measure called DM1 active.

Moving to Slide 14. In the Phase I/II MARINA study, Del-desiran demonstrated the potential to be a transformational therapy in these patients with really meaningful improvements in all four measures. In the study, the comparison was to the natural history for these patients. But the video hand opening time you can see was improved -- significantly improved versus the natural history. The QMT composite and hand grip were also significantly improved.

And from a patient-reported outcome study, there were very positive feedback from patients who are in the trial.

So in total, in this Phase II study, efficacy endpoints were met. There was a reversal of disease progression compared to the natural history data, durable improvements in multiple functional endpoints over 1 year of follow-up, improvements across the domains that are relevant for the disease and also significant DMPK knockdown, which is not shown here on the study.

Overall, there was also a favorable safety profile. There were 37 patients enrolled that remain on the study and all related AEs were mild or moderate. The most common related AEs was nausea, and there was no study drug-related treatment discontinuation or serious adverse event.

So moving to Slide 15. The Phase III HARBOR study really tried to replicate the Phase II study that I just went over. It's a global pivotal trial with FDA, EMA and other regulatory authorities endorsement and completed enrollment already in July 2025. The participants are currently eligible to roll over into an open-label extension study. And it has 40 global sites.

And the endpoints you can see here on the clinical endpoint are aligned with what we used -- what was done in the Phase II study.

Overall, the study is a 54-week study with 159 patients randomized to placebo or the active group, and you can see here the population is targeting patients who are over 16 years old and with a significant number of repeats, over 100 repeats in the gene. We expect the 54-week readout in the second half of 2026 and global regulatory submission in 2027. There is an earlier look at the study in week 30. We'll certainly evaluate that, but our base case remains a

submission in 2027. And I think it's important to understand the study well because this is a key differentiator, we believe, of Avidity versus competitors.

This is the only fully enrolled Phase III study that will generate randomized placebo-controlled data. It's the only study that has participants from around the world, including the United States, and we think can generate a compelling data package that can be used with regulators, health authorities and payers.

Moving to Slide 16. Now turning to the second disease in the portfolio, FSHD. This is a rare hereditary disorder causing relentless loss of muscle in certain parts of the body as designated in the actual name of the disease, Facioscapulohumeral Muscular Dystrophy. It is estimated to be somewhere between 45,000 to 87,000 patients. But as with DM1, I think there will be better understanding of the number of patients as therapies become available.

No currently approved therapies. It's one of the most common forms of muscular dystrophy, causing again the progressive muscle weakness, pain and fatigue.

The onset typically occurs in the teenage or adult years. So what happens with these patients is there's a steady loss of independence and 20% of these patients ultimately become wheelchair bound. Now this particular disease is caused by aberrant expression of a gene called DUX4, which leads to cell death, immune response and oxidative stress. It is an autosomal dominant disorder, potentially affecting multiple generations. 20% to 30% of cases also arise from spontaneous mutations affecting the vessel or gene.

And Del-brax is designed to address this root cause of FSHD and it's the only asset to demonstrate disease-modifying potential in a Phase II study. Del-brax has Orphan drug designation, Fast Track designation and EMA Orphan drug designation.

Now moving to Slide 17. In the Phase I/II FORTITUDE study, Del-brax improved mobility, strength and upper limb function compared to patients that were treated with placebo. You can see here in the graph at 12 months with 13-week dosing. You can see the improvement in the 10-minute walk test, also improvement in other functional measures as well, including the RWS, which is reachable Workspace test is a timed up and go test, which again, is a measure of mobility in these patients as well as in the QMT test, which is a composite endpoint.

Overall, the study met its efficacy endpoints with improved mobility and muscle strength, consistent improvement in quality of life as measured by patient-reported outcomes. And from a pharmacodynamic standpoint, rapid and significant reductions in the levels of cDUX, which is a marker of DUX4 and creatine kinase, which is a key marker of muscle damage.

From a safety and tolerability standpoint, all participants remain on study, no discontinuation and mostly mild and moderate adverse events.

Now moving to Slide 18. Overall, this compelling data could support cDUX as a biomarker for an accelerated approval, though as I'll go through our base case remains the filing with the Phase III data. cDUX is a direct target of DUX4 and is elevated 6 to 9 fold in people living with FSHD. Elevated cDUX levels are also linked to worsening disease and muscle weakness. Significant and rapid reductions in cDUX like we saw in the study and creatine kinase in these participants was seen following treatment with Del-brax.

And with that, we saw, as you saw the improved functional mobility and muscle strength. So right now, there is a biomarker cohort ongoing for the FORTITUDE study to better understand the reductions in cDUX. And the FDA has confirmed the potential for an accelerated approval based

on demonstrating that reduction in cDUX combined with the clinical data, which I went through in the earlier slide.

So that readout is expected in the second quarter of 2026. Our base case remains filing with Phase III data, which I'll go through in a moment, but we'll certainly be looking at that biomarker cohort to see if there is a potential for an accelerated approval.

Now moving to Slide 19. The Phase III FORTITUDE study of Del-brax in FSHD is already enrolling. It's intended to serve as a confirmatory study for full approval. Participants are across 45 sites in North America, Europe and Japan. The registrational endpoints, you can see here are in line with what we saw earlier for the Phase II study.

In addition, there are signs and symptoms of FSHD as well as specific endpoints around the cDUX and creatine kinase biomarkers. It's a 200-patient randomized study. You can see here at Q6 weeks, 2 milligrams per kilogram versus placebo. And as I noted, our Phase III readout of global regulatory submission under a standard filing path is expected in 2028.

So moving to Slide 20. The third asset amongst the late-stage portfolio for Avidity is DMD, certain subgroup within DMD. You all likely well know that DMD is a severe early onset disease marked by progressive muscle damage and reduced life expectancy. There's estimated 10,000 to 15,000 patients with DMD. This is a monogenic X-linked recessive condition.

It means progressive muscle damage and weakness. Symptoms can occur very early by 4 years of age and leading to loss of ambulation for teenager, often teenage boys, with significant reductions in life expectancy caused by the mutations in the DMD gene, which includes dystrophin protein. So you're trying to restore proper dystrophin protein in these patients. 6% to 7% of patients have mutations to exon 44 skipping, DMD44, and that's what we're targeting here. So Del-zota designed specifically to skip exon 44 of the dystrophin gene and produce functional full-length dystrophin and restore the function of this protein.

Del-zota has Orphan Drug designation, Fast Track designation, Breakthrough Therapy and Rare Pediatric designation as well as EMA Orphan Drug designation.

Moving to Slide 21. So the Phase I/II EXPLORE44 registrational study Del-zota showed improvements across key biomarkers, endpoints. You can see on the left-hand side, I think from an expert community perspective, remarkable increases in dystrophin protein as well as striking reductions as well in creatine kinase. I think this is viewed as, in my mind, a very strong proof of principle of the overall platform, but importantly, also an important therapy to this group of patients. There was a 40% increase in the exon skipping across the dose cohort, 25% increase in dystrophin production.

As I noted, 80% reduction in CK levels and clinically meaningful improvements across functional endpoints with a favorable safety and tolerability profile.

So this is a program that's on track for FDA submission for accelerated approval in 2026. So also, I think an important part of this acquisition.

Moving to Slide 22. Now I think one of the most important things to note from a commercial standpoint and why we believe we can drive rapid uptake in these medicines is it's aligned with our commercial capabilities and the neuromuscular experience we've built up since the launch of Zolgensma. We have deep understanding of patient journeys in rare diseases in areas like spinal muscular atrophy as well as diseases like PNH and C3G. We've built up patient identification and activation capabilities. We have strong payer engagement capacity as well.

Our field structure is ready to deploy across neuromuscular indications. I'll come back to that in a moment. And we also have built a scalable support programs as we've gone through the launches of medicines such as Zolgensma, Fabhalta, Vanrafia, Scemblix, and also Elaris before this.

And when you think about coverage of diagnosing neurologists, we see here already with the first launch in DMD a 90% overlap. And already with FSHD and DM1, 60% and 40% overlaps of the primary prescribing physicians, which we believe will allow us to have a relatively small scale up to be able to fully cover the physicians in question in FSHD and DM1, and we're absolutely prepared to do that.

So taken together, Avidity is highly synergistic with our commercial footprint in the rare neuromuscular space and in rare diseases generally.

And moving to Slide 23. We also wanted to give you a perspective on external forecast. You can see here the mean, median and max. At this point, we would just highlight that both the assets in DM1 and FSHD have multibillion-dollar potential and certainly, we think very sizable potential given the size of the patient population and our expertise in launching these medicines. And as I already noted, we don't have LOE for either medicine before the early 2040s at the earliest and neither medicine is currently or expected to be subject to IRA.

So moving to Slide 25. So in closing and just to give you a summary, transaction, I think hopefully is clear, $72 per share. The total transaction value is estimated to be $12 billion on a fully diluted basis, representing an enterprise value of $11 billion at the expected closing date. We expect to close in the first half of 2026, subject to the separation of the SpinCo and other closing conditions. We believe this value -- this deal will bring substantial value to the company with multiple multibillion-dollar peak sales opportunities, near-term launches and exclusive rights to an exciting RNA platform outside of cardiology.

This enables us to raise our near-term sales guidance from plus 5% to plus 6%. But importantly, perhaps even more importantly, bolsters our growth profile 2030 and beyond. It does involve short-term dilution of 1% to 2%, but we expect to get back to the 40% plus core margin in 2029 with an aspiration to get there sooner. And we expect an IRR well in excess of our cost of capital with significant value creation if the assets are successful.

And then lastly, this fits with our capital allocation priorities, no change to our capital allocation strategy overall. So taken together, we think an attractive opportunity for Novartis, our shareholders and most importantly, for the patients that these diseases can treat -- that these therapies can treat. So with that, let me open it up for questions.

And maybe before I open up for Q&A, just to mention on the call with me, we have a number of folks have Harry Kirsch, of course, our CFO. Alongside that, we have Shreeram Aradhye, our Global Head of Development. We also have Dr. Norman Putzki, who is our Head of Neuroscience Development and Neurologist. And Dr.

Bob Baloh, our Head of Research in Neuroscience and Neuroscience in our Biomedical Research group and really one of the global thought leaders in muscular diseases such as the ones we talk about here. So with that, we can open the line for questions.

Operator Operator

[Operator Instructions] The first question comes from the line of Sachin Jain from Bank of America.

Sachin Jain Analyst

Question on accelerated pathways, which you touched on about maybe you could just detail a little bit more. So in FSHD, I think Avidity almost framed the accelerated as base case. So just trying to understand your reason for greater caution and you referenced you'd wait until the biomarker data. Do you have a specific benchmark agreed with the FDA as to what needs to be seen?

And then a similar question for DM1. Again, you slightly referenced it, but competitor Dine has talked to, accelerated path for your perspective on that and your competitive profile should they get to the market slightly ahead of you? Is it just a larger global study? Or is there anything else in the clinical profile.

Vasant Narasimhan Executive

Yes. Thanks, Sachin. So I think first on the accelerated pathway. We certainly think the company avidity has had very robust discussions with FDA. I think it's just our general experience always assume full clinical data sets are required for approval.

So that's our base case assumption. We certainly hit the CDC reductions are significant. I think there's a very good reason given the high end of the pathway forward for accelerated approval. . So no concern, but I think that we want to take, I think, a pragmatic, thoughtful conservative approach to how we think about the filing time line.

And then I think on DM1, I think it's really important here to note that report here, we believe, of placebo-controlled data and having a full Phase III program that involves as well as U.S. patients, which is something that we think Avidity has done very well, a fully enrolled Phase III study, a placebo-controlled data set. And so certainly, we will look as well as the 30-week end point. There is an opportunity to have an interim read and that would enable faster. We think we will enable differentiation is the robust data set and that will enable us to launch to both regulators, payers and physicians with the compelling data such that we think will enable a rapid update.

I think both medicines, of course, are very good at achieving the desired goals of symptom improvement and biomarker impact. And I also would say that these are large enough indications that it can be multiple competitors. Our goal, of course, is to be the market leader in each one of these three diseases, and that's what we'll be able to do.

Operator Operator

Your next question comes from the line of [Kirsty Cogley] from BNP Paribas Exane.

Unknown Analyst Analyst

It's [Kirsty Stewart] from BNP Paribas on behalf of Peter. Just on the kind of revised midterm guidance, I think it's implying a kind of $2 billion to $3 billion revenue contribution from the Avidity acquisition in 2029, and that's kind of ahead of current ability consensus. So just a bit of parity on what's driving your high conviction here? Is it kind of pricing leverage that you can bring commercially on patient identification, breadth of reimbursement or something else?

Vasant Narasimhan Executive

So maybe just generally the first came to Harry on the guidance.

Harry Kirsch Executive

Yes. So overall, of course, as you mentioned, right, a 1% 5-year CAGR on our business of our size was roughly $3 billion. And now we don't expect in 2029, $3 billion from these assets. Roughly half, I would say, of that is due to these assets. And then the overall the portfolio is overperforming.

So that's continuing the other half. These are large ranges. But it also should not distract the most important year is the contribution as of 2030 well into the early 40s to further bolstering our long-term outlook. And we just saw the update the 5-year as this comes in handy as we looked at our 5-year anyway being a bit stronger and then these assets expected to further contribute.

Vasant Narasimhan Executive

And maybe Kirsty, to the second part of your question, we do believe that our ability to drive uptake. And given our commercial profile, we do believe that we can drive substantial uptake in these medicines, given the expertise that we have in neuromuscular disease of the established footprint and relationships that we had. And of course, we'll provide appropriate T sales guidance as we launch these medicines and we're further along.

Operator Operator

Your next question comes from the line of Harry Sephton from UBS.

Harry Sephton Analyst

I'd just like to get your thoughts on the structure of the deal with the SpinCo and why the cardiology assets weren't directly included as part of the deal and whether you see any potential use of this technology for future implications and the platform value from the deal.

Vasant Narasimhan Executive

Yes, absolutely. So I'll have the platform potential to Bob Baloh in a moment. But first, on the structure of the deal, given the third-party agreements that Avidity has, we thought it would be the simplest and most straightforward structure to create a SpinCo that can enable those third-party agreements to be serviced we'd rather focus on the neuromuscular portfolio and related assets as well as releveraging the technology up platform in the future. So maybe, Bob, if you want to cover as well the potential of the technology platform.

Robert Baloh Executive

Sure. We're clearly very interested in utilizing CFR delivered different tissues, including brain, muscle, and we found that it has done an incredible job in tuning the ability of these different shuttles to target different tissues over time. This one is clearly targeted to muscle and it does an effective job for skeletal and cardiac muscle. And they have further generations of that technology to sort of bring to next-generation even therapies to these diseases. So we think it can be more broadly used, but really the focus for this first generation is in these key lead diseases where we've seen such an effective delivery of the agent to the muscle and hitting targets.

Operator Operator

Your next question comes from the line of Seamus Fernandez from Guggenheim.

Seamus Fernandez Analyst

So as I was just hoping you might be able to walk us through a little bit of the timing around when we'll have clear validation of the xRNA platform from your perspective, that does seem like a major potential value-add opportunity here. Just wanted to kind of get your sense along those lines. It was our impression that sort of first half of next year was really going to be the major sort of stepping off point for Avidity in this context?

And then separately, in terms of SpinCo, is this really just being executed from the perspective of overlapping assets and to protect from FTC-related delays or issues in that regard. And if so, if you wouldn't mind just highlighting to us some of those overlapping assets where you are advancing your own targeted cardiology programs.

Vasant Narasimhan Executive

Yes. Thanks, Seamus. So first off, from a derisking standpoint, I mean, certainly, there will be important readouts next year. But in our mind, that the platform itself has been derisked with the DMD data set and then now FDA has aligned with the company is satisfactory for filing. So I think it's important to know, while that is a smaller indication, I mean, that has a huge validation that the company has successfully delivered on the promise of delivering the RNA therapeutics with antibodies to muscle having significant therapeutic effect and building a package that can ultimately be followed.

Maybe before I get to the SpinCo. Bob, do you want to just say a few words about why you think the DMD was such an important derisking of that for the technology.

Robert Baloh Executive

Yes, absolutely. I mean I think as you can see in the slide that was presented and really in the reaction from the community, the degree of dystrophin restoration as well as the CK levels that were observed is something that hasn't been seen before in exon skipping therapies for Duchenne. And it really opens up the possibility that while earlier generations of these have not really met the unmet need for these patients that may have simply been the lack of ability to deliver the medicine effectively to muscle. And that's why we really think that this and potentially future exon-skipping therapies using this platform could be highly effective for these patients.

Vasant Narasimhan Executive

And then on the SpinCo. SpinCo has nothing to do with FTC concerns. The company has research collaboration agreements with third parties which we simply think would be better served by SpinCo and Novartis executing research collaboration agreements. And so that's the primary driver. There's no other concerns with respect to FTC for the SpinCo.

Operator Operator

Your next question comes from the line of Richard Vosser from JPMorgan.

Richard Vosser Analyst

Just a question on the hypersensitivity that was mentioned on the slides for the Del-zota product in a few patients. I think avidity might have suggested that it was related to the antibody when they looked into it. So I just wanted to understand your thoughts around that and the thoughts on what data you've seen that suggests this is an isolated incident.

Vasant Narasimhan Executive

Yes. So maybe I'll turn it over to Norman Putzki, our Head of Neuroscience Development. Norman on the hypersensitivity part.

Norman Putzki Executive

Yes. Thank you, Vas. I think we're looking at probably a generic concern when you use a modality like that. It's still fairly novel to some inherent risk there. Generally, the overall AE profile was very favorable, and we have only seen a moderate side effects.

I think hypersensitivity is 1 of the things that you will be looking out for. But so far, we haven't had any concerns with the continuation of treatment who I haven't seen any severe effects to that end.

So far with the experience in the clinic, we have more than 100 patients dose in the Avidity program, some for up to 3 years at 4 mg per kg. So I think overall, a fairly mature safety profile in the program.

Operator Operator

Your next question comes from the line of Florent Cespedes from Bernstein.

Florent Cespedes Analyst

A question for Harry, please. Could you maybe generate some cost synergies when you will merge with this company as you have some overlap on some rare diseases. So is the 1% to 2% potential negative impact is something that takes potential savings from this merger?

Harry Kirsch Executive

Yes. Thank you for your question. I mean, as you know, usually bolt on biotech companies just in the cost synergies are limited. It is more important that we have synergies on the commercial side, on the medical, on the R&D side, and in terms of driving top line and pipeline execution.

Now the 1 to 2 points over the next 3 years is mainly due to it's [indiscernible], we have quite some expensive Phase IIIs ongoing. And initially before we take over the production of the product, the clinical trial material is quite expensive. So that's why this has a bit of an unusually high R&D cost impact for the next 2 to 3 years. As Vas said, we always look for productivity anyway, and we will see we can come back to the 40%, which we will basically achieve this year maybe even before 2029. But it's a worldwide investment given the expected huge returns and sales uptake in the '30s.

Operator Operator

Your next question comes from the line of Rajesh Kumar from HSBC.

Rajesh Kumar Analyst

The first one is after this deal, can you just ballpark give us an idea of how much more firepower you've got for dealmaking? And if the size of this deal is a template for deals going forward? Or this was an exceptional opportunity. That's why you deviated from your sounded bolt-on model.

Second one is just on the readouts in '26. Can you give us clear definition of what you would consider a success in terms of outcomes? Or just if it can't be quantitative, just a qualitative idea of what are we looking for when we see the readouts and then we can evaluate them better, it has met your expectations or not.

Unknown Executive Executive

So first on firepower.

Harry Kirsch Executive

Yes, Kirsch here. So I would still consider this to be a bolt-on for companies of our size and cash generation. Our EBITDA per year is roughly $22 billion. Our net debt is below onetime EBITDA at the moment. Now with this goes a bit up but still a super strong balance sheet.

So we have continued significant bolt-on M&A and BD&L firepower. So no concerns there. And it's not for lack of trying, if you want to do more of these or we cannot really predict size of bolt-ons. It always has to come with the strategic fit and the signs with the conviction on the science and what the patient impact will be in the return for it. So of course, all of these are a bit opportunistic.

But clearly, for me, this is absolutely an online with our strategy of bolt-on M&A to strengthen the pipeline of our [48].

Unknown Executive Executive

And then, Rajesh, on the readouts, look, there is the -- as I mentioned, the CBS biomarker readout in FSHD. And assuming we see compelling impact on the biomarker would be absolutely our intention to go to FDA and have a discussion to see if we can get an accelerated approval. But the Phase III study is continuing to enroll, and we'll continue to ensure that enroll as fast as possible. And then I think for DM1, it's relatively clear, but we know the primary endpoint that we need to hit and we need to hit those primary endpoints as well as have the functional benefits in the secondary. And what aligned with what we saw in the Phase II study.

And assuming we see that at the end of study 54-week readout with the 30-week interim, but our goal would be to deliver this at the 54-week readout, then that would also create a compelling filing is the Phase I end points are aligned with what we're studying in Phase III. So we have, I think, a pretty good road map here of what we're trying to achieve in the Phase III studies, and that's what we're going to aim to do.

Operator Operator

Your next question comes from the line of James Quigley from Goldman Sachs.

James Quigley Analyst

I've got two, please. So as you mentioned, Harry, this is a fairly opportunistic deal and it's difficult to sort of time when you can pull the trigger on these things. But -- and clearly, this is going to have a positive impact on the long term and through the 2040s. But how comfortable would you feel now with the portfolio as a whole is fairly obviously highly high-profile LOEs that are coming up in the next sort of 4, 5 years. How are you sort of thinking around your ability to grow through those as well as the balance between M&A going forward and your current mid to -- early to mid-stage pipeline.

Second question, how broadly applicable could this technology be? And where do you think the key differentiators are in the technology. So it is the antibody targeting sort of neuromuscular system. Is it the linker or RNA combination? Or for example, is there an ability to have a plug-and-play asset here where you can substitute the antibody substitute the linker for a different payload, et cetera.

sort of how much does [Fiona] have to play with when she bolted into a development organization.

Vasant Narasimhan Executive

Yes. Thanks, James. I think, first from a growth standpoint, it's important to note, we have full confidence in the internal pipeline and internal assets that we have. And if you just look this year, we're launching Remibrutinib, which we believe will be a multibillion-dollar asset. We have a positive readout for homosensitive prostate cancer with Pluvicto.

We have the lanalumab readout, which I know, I mean different views in your view, so we have a very optimistic view that we can drive significant growth with lanalumab as well. So three major launches. And then we expect a very robust mid-stage pipeline as well behind that gives us confidence going in. So the goal then is to bolster the code more, of course, because we want to continue to drive that dynamic growth into the next decade.

So we did deals like Tourmaline, we did deals like Anthos. And now with this deal, we bring in three more late-stage assets, a total of five additional late-stage assets, all with 4 out 5 of them on those with multimillion dollar potential. So of course, we'll continue to evaluate when we find highly attractive deals, but we're not in a situation where we're going to reach the deals. We feel like we have to do a deal. But we find something that's very aligned with our technology interest aligned with our therapeutic area interest force, we're going to go after it and ensure that we put Novartis in the best possible position.

Now in terms of the technology here, I think there's many applications. I mean, here, you've already seen in these three drugs, both an antibody linked to an siRNA as well as antibody linked to an oligo, you have the ability to do both siRNA and oligo. All these assets, the antibody is using the targeting to the transferrin receptor, but as Bob mentioned, there's a potential to use this sort of antibody technology to target other targets for SR delivery. We know Bob has a substantial portfolio of assets that you're pursuing for other neuromuscular conditions as well as other disease targets. So we think there's a possibility to hopefully address a number of different organ systems in the body over time.

Bob, anything else you'd want to highlight on the platform?

Robert Baloh Executive

No, I think you said it well. And just as they have even further iterations with novel formats that we're really excited about exploring even further into the future.

Operator Operator

Your next question comes from the line of Michael Leuchten from Jefferies.

Unknown Analyst Analyst

It's Ben Jackson from Jefferies. Look, I get the reason internally for why you did the acquisition and the overlay with the existing portfolio. But could you perhaps touch on to what extent the macro overlay it takes the therapeutic areas of focus for M&A? Is rare neuro easier to do at the moment versus kind of cardiovascular and I&I. So any thoughts on that would be useful.

Vasant Narasimhan Executive

Yes. Thanks, Ben. No, I don't think it was based on a relative view. I mean, we have a strong expertise with Bob and his team in neuromuscular disorders. And if you've looked over the history, we've done acquisitions like a DTx, like Kate Therapeutics.

We have an internal portfolio. We work, of course, with Zolgensma and follow-on programs. So I think this is very much aligned with our long-term interest in neuromuscular diseases. So I don't think it's necessarily easier per se. I think it's just a very huge strategic fit for what we've been investing in and want to leave it in the long run.

Operator Operator

Your next question comes from the line of Paul Gallant from TD Securities.

Steve Scala Analyst

This is Steve Scala. Several questions. Just to be clear, Harry, I think you said half of the sales guide boost was from Avidity and half was from Novartis' existing business. Is that true of the margin hit as well? So half is from the acquisition and half is from Novartis' existing business?

So that's the first question.

Second question is what were the three most important questions during Novartis' due diligence process for the deal. So what were the three things that you had to kind of get over in order to move forward?

And then third, I don't know if we're allowed three questions, but if we are, Thinking back to the AveXis acquisition a number of years ago, it never really lived up to initial expectations set by Novartis. So why will this acquisition be different?

Unknown Executive Executive

Thank you, Steve. So first, on the half and half questions.

Harry Kirsch Executive

Yes. No, the margin expected impact over the next 2, 3 years is totally due to the R&D expenses year of this deal. The rest of the portfolio is on a fully driving forward and offsetting also some negative gross margin mix via very good productivity programs and expected top line growth.

Vasant Narasimhan Executive

Yes. Thanks, Steve. I'm not going to get into our due diligence, but I can say that we did absolutely thorough due diligence on the profile of all the assets and of course, all the standard area in the safety efficacy. As always, there's risk with all programs that are in Phase III studies. And so there's risk, of course, always.

There's no guarantees in this business. But I think based on what we saw in the Phase II, where we saw the design in the Phase III studies, the regulatory feedback, the mechanism of action, the biomarkers, everything aligned. So we think it's a reusable bed.

I would also say we have great expertise in this area. I think Bob and his team and Norman and their teams know the space extremely well. So we feel confident that this is a phase appropriate bet but -- and a base appropriate investment, but there's risk, I think it that's your point.

And then I think, look, with AveXis, actually, it's over $1 billion of sales, and we are about to launch the IT indication. So I'll invite you to look back in 3 years as to what your viewing of the deal then you always need to cherry pick in the middle. But I think actually, the two deals are unrelated in some ways, right? I mean this is a completely different technology I think RNA therapeutics here and the Phase II data in the Phase III and a huge unmet need, similar unmet need in novel technology but completely different technologies. So I think trying to read through this way deals are probably not very productive.

Operator Operator

Your next question comes from the line of Sachin Jain from Bank of America.

Sachin Jain Analyst

Two, just on topics we sort of touched on. So first, in the due diligence I wonder if you could just comment on your level of comfort with the safety of the technology platform mechanism given the clinical hold ability has I know it's lifted a while ago, but just you let comfort there.

And then second, if we have a couple of questions around the LOE and midterm growth. You've obviously raised the 24%, 29% today. We've got the CMD around the corner, is there still an intent to roll that guide to include 2030, which obviously the post COSENTYX impact. Any thought there?

Vasant Narasimhan Executive

Yes. So we -- just on the second question, we will roll forward the guide to 2030 at the meet of management. Then on the clinical hold, Norman, do you want to cover that?

Norman Putzki Executive

Thanks Vas. Yes, I think you alluded to the fact that safety was an important consideration during the due diligence is we're looking at a novel mode of action with a novel platform. The partial clinical hold occurred in 2022 due to a serious rare neurological event that was fully investigated and then the clinical hold was lifted in 2024. After that, full investigation was completed.

In the meantime, we are looking at a -- really a fairly established and mature safety profile. This is based on about 100 -- more than actually more than 100 patients dose with more than 500 [drug rates], some of these patients for up to 3 years. And that is at the dose of 4 mgs per kg, which was the dose that was implicated previously. So I think at this point, we were confident that we're looking at an idiosyncratic event, and we feel good about the overall safety profile. There are no discontinuations in the study because of side effects and overall AEs were mild to moderate, also good level of confidence at this point.

Operator Operator

Great question. Your final question comes from the line of Gena Wang from Barclays.

Huidong Wang Analyst

Congrats on the deal. So my question is, why now given the Phase III data will read out in like a half year or less than a year. And I know the Phase I/II data is very convincing. But still you have a risk of a Phase III. So why not wait for a little longer, so that would be completely derisked before the full acquisition?

Vasant Narasimhan Executive

Yes. Yes. Thanks. I mean this is always the question, right? If you do go in at the clinical stage or after the readout, the valuation, of course, could more than double and then you're looking at a transaction that quite substantially larger than this one.

So I think that is a judgment call. You, of course, couldn't wait, but then you're looking at a very, very large transaction potentially twice as big. And in our view, that the phase appropriate risk was reasonable given the data that we've seen. We also have two shots on goal of significant assets, either one of which would pay back the deal and most of which hit a very large value creation for our shareholders. And so we feel good about that as well.

And so we think it's an appropriate risk to take. But I think there is always that question. But if you wait, of course, the valuation will run away from you. And I think that's why we thought this is a prudent move to do.

Okay. Great. Thank you all for joining. I'm sure we'll be speaking with most of you tomorrow as well in our earnings call. So we'll look forward to connecting with you then.

Thank you again.

Operator Operator

This concludes today's conference call. Thank you for participating. You may now disconnect.