Biogen Inc.

Biogen Inc. - Q4 2023 Earnings Call

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Event Participants

Executives 4

Charles Triano, Christopher Viehbacher, Priya Singhal, Michael McDonnell

Analysts 10

Marc Goodman, Salveen Richter, Umer Raffat, Evan Seigerman, Unknown Analyst, Philip Nadeau, Michael Yee, Colin Bristow, Christopher Raymond, Mohit Bansal

Operator Operator

Good morning. My name is Katie, and I will be your conference operator today. At this time, I'd like to welcome everyone to the Biogen Fourth Quarter and Full Year 2023 Earnings Call and Business Update. [Operator Instructions] Today's conference is being recorded. Thank you.

I would now like to turn the conference over to Mr. Chuck Triano, Head of Investor Relations. Mr. Triano, you may begin your conference.

Charles Triano Executive

Thank you, Katie. Good morning, and welcome to Biogen's Fourth Quarter and Full Year 2023 Earnings Call. Before we begin, I'll remind you that the earnings release and related financial tables, including our GAAP financial measures and a reconciliation of the GAAP to non-GAAP financial measures that we will discuss today are located in the Investors section of biogen.com. Our GAAP financials are provided in Tables 1 and 2, and Table 4 includes a reconciliation of our GAAP to non-GAAP financial results. We believe non-GAAP financial results better represent the ongoing economics of our business and reflect how we manage the business internally.

We have also posted the slides on our website that will be used during this call. I'd like to point out also that we'll be making forward-looking statements, which are based on our expectation. These statements are subject to certain risks and uncertainties, and our actual results may differ materially. I encourage you to consult the risk factors discussed in our SEC filings for additional detail. On today's call, I'm joined by our President and Chief Executive Officer, Chris Viehbacher; Dr.

Priya Singhal, Head of Development; and our CFO, Mike McDonnell. Chris, Priya and Mike will each make some opening comments, and then we'll move to our Q&A session. To allow us to

get through as many questions as possible, we ask that you limit yourself to one question.

With that, I'll now turn the call over to Chris.

Christopher Viehbacher Executive

Thank you, Chuck. Good morning, everybody. A year ago, I had the -- an opportunity of presenting Biogen's quarterly results for the first time. At that time, we expressed the objective of returning Biogen to sustainable growth. And I think in the intervening year, we've made substantial progress.

And today, it is a great -- with a great amount of prior and pleasure that we can announce earnings guidance, which Mike will go into in greater detail, which says that we will -- we are expecting to see positive earnings per share growth. And as I have said on a number of occasions, once we can get Biogen growing, we really see Biogen becoming a growth company for the foreseeable future. We have very little we have, in fact, no exposure to Inflation Reduction Act with our current portfolio. We don't have any new patent expiries really coming in anytime soon other than those that are already known. And I think we've undertaken a number of other measures that really repositioned Biogen for growth.

And if I just review some of those things. The first is -- was really to refocus the company on growth drivers, in particular, our new product launches. Biogen had 4 new product launches from -- approvals from the FDA last year. That's the second highest of anyone in our industry. And that required though quite an awful lot of cultural change.

The multiple sclerosis franchise has been the stalwart of our company for -- since its inception, 45 years ago. Our people are passionate about the physicians to treat multiple sclerosis and the patients who have multiple sclerosis. And we are still the market leader in this space. However, that is a franchise that is facing increasing competition and we have to embrace new therapeutic categories and new businesses. And so we have really had a major shift in resources and focus, particularly towards LEQEMBI, ZURZUVAE, SKYCLARYS and QALSODY.

We also, though, have still some products with patent protection, again, with substantial competition. And if I take a product like SPINRAZA, analyst forecast had shown forecast that this product would decline, particularly proud of our teams and demonstrating that they could bring this product back to actually even modest growth. Obviously, the mode of administration of products is -- can be a competitive advantage. So if you have a pill, you're going to be a lot more preferred than if you have an infusion for example. But what we see in some of these really devastating diseases, is that efficacy is still the most important factor.

And that is why SPINRAZA continues to be a leader in this segment. And Biogen is extremely good at being able to develop the medical evidence to support the value proposition of its products. As many of you told me when I first came into the company, you've got a mature product portfolio, but you've got one of the highest cost bases in our industry and we took steps to address that. We -- but it wasn't just around reducing cost. We wanted to reengineer the business.

We were shifting our focus, entering new therapeutic categories and we needed to think

about capabilities. We needed to think about the agility of the organization, the number of layers of management that we have. And so we implemented a Fit for Growth reengineering project. We've already achieved $200 million of savings and we're on track to realize approximately half of the $800 million of net savings by the end of 2024. That's, of course, a gross savings of $1 billion.

And then we had to look at research and development. And Biogen is an extremely interesting company. All of the diseases that Biogen targets are really devastating diseases. And we target -- and there's a lot of pride in the fact that we go and try to find solutions for diseases where nobody else is doing that. But of course, we do that by you are pioneering -- you are pioneering because we don't really understand often the underlying disease biology of these conditions.

And so we end up taking a lot of risk and these trials can be really quite expensive. And yet we do need a company like Biogen in our world. And so our objective has been to really focus research and development investments on those products that will have the greatest impact. And of course, we have to manage the risk in the portfolio. We have to have Biogen as a sustainably growing company and one which is attractive to investors.

We need the capital to go and invest in new projects. And so I think with Prius Health, we've been able to take an extremely disciplined and objective view of the pipeline. We have 4 data readouts this year, again, on extremely important illnesses, and Priya will talk more about that. And as we go into next year, we're going to be looking at how do we reinforce that pipeline, how do we rethink our research efforts. A lot has changed in science, but we haven't necessarily done that kind of change at Biogen.

So I think research and development is extremely important to Biogen and I think continue to be a source of growth for the future. Now as we look at what does drive growth, clearly, we have LEQEMBI. And I'll remind everybody that, again, we are not just pioneering in science but pioneering in commercial. One of the interesting things about this disease is that if we talk about the efficacy of the product, in a lot of cases, we're looking at the characteristic of a product. But actually, when you talk about efficacy, you're talking about, are you in the right patient.

And in fact, for decades, our industry invested in drugs, which failed to demonstrate a benefit in Alzheimer's disease. And there were 2 main problems with that. One was we couldn't get enough drug across the blood-brain barrier, and we weren't in the right patient. Clarity was the first study to really convincingly demonstrate the importance of reducing plaque and the impact on cognition. But we know that some data that we showed at CTAD that we believe that the earlier you can go, the more likely it is you're going to show even greater efficacy because we're not -- we're really in the business of trying to protect neurons or create an environment where injured neurons can recover.

And so we have a huge investment in our AHEAD study to look at presymptomatic patients. We're investing in what happens when you remove the plaque and looking at maintenance. We're trying to make this more convenient for patients by having a subcutaneous formulation. And so this -- the pioneering continues and the pioneering also is out there in the marketplace. Patients with Alzheimer's are not in the system today and are coming into

the system.

So we've got approximately 2,000 patients on therapy at the moment. Now we don't have as companies direct access to the patient registries. You all know about the CMS registry. But there are a few other registries out there like Altinet, for example. And we have seen some analysts have been able to access that data.

There was one analyst report of 3,300 patients on the registry, latest information that we have, and again, this is not perfect information, but we have an indication that there are about 3,800 patients as of last week on the registry. When you look at that, that suggests we're getting about 260, 265 patients per week in the month of January. And as far as we can tell, that's about a 56% increase over what we were seeing in December. So we are clearly seeing that there is demand for the product. We're clearly seeing that IDNs are moving to put in place the care pathways and the treatment protocols to improve access.

70 out of the top 100 IDNs have had positive P&T committee decisions. 80% of those have now actually ordered LEQEMBI.

But if we talk to the people who are doing the PET scans, the MRIs, the people who sell the blood diagnostics, everybody is reporting increased activity and volume. And so -- and as you saw with Eisai's results, their belief is that for all the patients on treatment, they are at least three or fourfold of those who are actually in waiting rooms. So we do believe we're making a very solid progress. And we believe that we have validated the go-to-market model. And now that we have enough IDNs with reimbursement and care pathways in place, we believe it's also time now to increase our level of promotion out there.

And so as Eisai has announced, we will be expanding total U.S. field force by about 30%. And as was already previously agreed last year that once we had the go-to-market model really validated, that it's now time for Biogen colleagues to also go and visit physicians. And of course, we've seen the launch in Japan. I was there for the launch meeting, and Biogen is very proud to be working alongside our colleagues from Eisai on the launch in Japan.

And we've seen LEQEMBI approved in China and that launch will be for later this year. So everywhere we look with LEQEMBI, we are making solid progress. This is, as we have said before, and a launch that really doesn't have an analog. We have always guided investors to the fact that this would be a progressive ramp and that's what we're seeing. And we continue to believe in the long-term importance of LEQEMBI both to patients and to our financial results.

Moving on to SKYCLARYS. You've seen the launch numbers for the U.S. We have about 1,000 patients now on therapy. We don't have a pediatric indication yet. So the potential population is about 4,500.

So we've got a little over 20% of the patients on therapy within about 6 months of launch. There's an awful lot of complexity in launching these rare diseases. And I think this is where Biogen has an awful lot of strength. There's a lot of logistics issues with specialty pharmacy and reimbursement. And so we have already been able to demonstrate that we can reduce the time from the start form to shipment by 45%.

We've got about 2/3 coverage out there in terms of reimbursement. And of course, patients and their physicians need an awful lot of support out there. And so we have patient services and family access managers who are assisting patients and physicians to navigate the care pathways. One of the things that we see with SPINRAZA is that we do about 1/3 of our sales in the U.S. and 2/3 ex U.S., and we expect that to be a model for SKYCLARYS.

Last night, we announced the formal approval by the European Commission for SKYCLARYS. We have expanded access program in a number of European countries, and we are in the process of setting those up in the countries, including those outside of the U.S. We have a global filing strategy that is underway to make sure that all patients with Friedreich's ataxia and can benefit from SKYCLARYS. And of course, we are actively working on [indiscernible] that would be needed to obtain the indication for children under age 16.

ZURZUVAE, postpartum depression enormous unmet need. Tremendous media coverage. We're talking about maternal health and we're also talking about mental health. And those are 2 key trends in our societies today. It has been difficult often from others to seek treatment and get treatment.

This estimated about 80,000 women are diagnosed every year, but the incidence leave to be way in excess of 0.5 million.

So there's an awful lot of work to do to really get outreach to women who are suffering from postpartum depression. I have to say the initial indications of launch are well above expectations and very promising. But it's 6 weeks of data. So I think we want to see more data to really come to any firm conclusions, but everything that we are seeing is extremely positive. We were originally positioning this product for major depressive disorder and we pivoted to postpartum depression that meant we've had to go back and recontract with payers.

I have to say I'm highly appreciative of payers because they have actually been honoring prescriptions even though we haven't got all of our contracting in place.

And I think that is actually also helping with demand. So with that, I'll turn it over to Priya because I think increasingly, what we'd like to also start to talk about is not only what we're selling, but the new hope for patients that's coming out of our pipeline. So I'll turn that over to you, Priya.

Priya Singhal Executive

Thank you, Chris. As we previously discussed, we have focused on reviewing and prioritizing our development pipeline with a keen eye towards maximizing probability of success and increasing potential return on investment, as Chris noted. The intention was always to focus our pipeline to better represent a risk-reward balance and one that we believe could help Biogen reach the goal of achieving sustainable growth. While this effort resulted in a number of program discontinuations last year, specifically in areas we perceived significant regulatory development or commercialization challenges. We also highlighted areas where we had deep expertise and promising pipeline programs, and therefore, warranted an invest to win approach.

One such area is Alzheimer's disease, where we have an industry-leading pipeline, and we do expect to continue investing in order to expand our leadership. This starts first with building upon our opportunity with LEQEMBI. Our first priority is to continue working with Eisai to help ensure that LEQEMBI is available globally to patients suffering from early Alzheimer's disease. With approvals now obtained in the U.S., Japan and China and filings currently under review in 14 additional markets, we believe we are well on our way to achieving this goal. Second is creating additional treatment options for patients.

The data presented at CTAD last year on LEQEMBI suggests that there is continued benefit associated with treatment out to 24 months. And that treatment earlier in the disease course had a greater effect on clinical outcome. For this reason, we are working with Eisai to submit a filing for maintenance dosing with IV LEQEMBI or every 4-week treatment as well as evaluating LEQEMBI administration in preclinical AD, as Chris mentioned, in the AHEAD 3-45 trial, which is before the onset of symptoms. Eisai also aims to submit a filing for subcutaneous version of LEQEMBI by the end of March. Beyond LEQEMBI, Biogen is also advancing pipeline programs targeting tau.

We believe tau represents the next frontier in Alzheimer's therapeutics, and we are working to support the development of diagnostic tests and pathways. Our ASO targeting tau, BIIB080, represents a new mechanism for targeting tau distinct from prior antibody attempt. In the Phase Ib study, we saw a convergence of target engagement, reduction in tau pathology in the brain and improvement in exploratory measures of clinical outcome. We are very encouraged by these results and are currently evaluating BIIB080 in the Phase II CELIA study. We also have BIIB113, a Phase I small molecule aiming to reduce the aggregation of tau.

Importantly, [Jane] and the research organization is also focused on the future of Alzheimer's treatments and is pursuing a multi-modality approach to evaluate a number of other potential targets implicated in Alzheimer's disease biology. Looking beyond Alzheimer's disease, Biogen has an opportunity to expand our growing rare disease portfolio. We see rare disease expertise as a core competency at Biogen. I will now address BIIB121 in Angelman syndrome. Angelman syndrome is a rare genetic neurodevelopmental disorder that occurs in approximately 1 in 15,000 live birds worldwide.

It is diagnosed in early childhood and is characterized by symptoms such as severe developmental delays, speech impairment, problems with movement and balance, and may involve seizures. While there is no specific treatment approved, individuals with Angelman syndrome will generally have a near-normal life expectancy. However, they will generally require continuous care and are unable to live independently. Normally, the paternal allele of the UBE3A gene is silenced in neuron leading to expression of only the maternal allele.

In Angelman syndrome, the maternal allele is either absent or inactivated through genetic mutation, leading to loss of UBE3A gene expression and impairment of synaptic connections and brain network activity. This can be visualized by an increase in slow brain waves or called delta waves. BIIB121 aims to remove the silencing of the paternal allele in order to restore expression of the UBE3A gene. While the Phase I HALO study is designed as an open-label, multiple-ascending dose study across age groups and those levels to assess safety and tolerability. Importantly, the study also utilizes clinical measures that we can use to assess

therapeutic potential.

This includes objective EEG assessment as well as clinical assessments evaluating multiple domains of Angelman syndrome, like cognitive function and gross and fine motor skills. The HALO study has completed enrollment for the multiple ascending dose portion of the study. And last year, Ionis presented some encouraging early interim results. Overall, safety and tolerability support continued dosing in the long-term extension with no concerning safety trends having been observed to date. The EEG data was suggestive of early trends to a reduction of slow delta wave activity as compared to baseline.

And clinician-assessed clinical end points show a majority of participants demonstrating some level of improvement in overall functioning. Overall, we are encouraged by these early trends and look forward to sharing a more comprehensive top line study readout expected midyear. Following our review of those results, Biogen will be in a position to make its decision whether to opt in to conduct a pivotal study. Moving to lupus. This is another area with significant unmet medical need.

We currently have 2 Phase III assets in systemic lupus erythematosus or SLE. First is dapirolizumab pegol being developed in collaboration with UCB, where we expect a top line readout of the Phase III study midyear this year. If positive, we expect to conduct a second Phase III study. The second is litifilimab, our anti-BDCA2 antibody developed in-house at Biogen. We currently have 2 Phase III studies of litifilimab in SLE ongoing.

These studies are enrolling and utilize a 52-week primary endpoint. Litifilimab also has the potential to be a first-in-class biologic in cutaneous lupus erythematosus or CLE a skin-based autoimmune disease that can be associated with severe scarring and dispigmentation and can be distinct from SLE. As I've previously discussed, we have focused on reviewing our pipeline to identify and prioritize the areas where we believe we have both sufficient expertise and confidence in the science to deliver meaningful new treatments for patients. While this initial review is complete, this process remains dynamic, and we are committed to holding ourselves accountable to efficiently seeking out scientific insights and continuing to build the pipeline with what we believe is the right risk/reward balance. While we look forward to 4 important near-term readouts this year, we continue to focus on identifying additional near-term opportunities as well as continued expansion beyond neuroscience.

Through collaboration with Jane and research organization as well as Adam Keeney, our Head of Corporate Development, we are taking a holistic look across a spectrum of opportunities with both a research and development focus to identify strategic assets that we believe can contribute to Biogen's growth story now and in the long term. With that, I would now like to pass the call over to Mike.

Michael McDonnell Executive

Thank you, Priya. Good morning, everyone. I'm going to provide some highlights and color regarding our financial performance for the fourth quarter of 2023, and I'll follow that with some detail on our 2024 financial guidance assumptions. Please note that all the financial comparisons that you will hear are versus the fourth quarter of 2022.

Total revenue for the fourth quarter of 2023 was $2.4 billion. That's a decrease of 6% at

actual currency and 5% at constant currency. Non-GAAP diluted earnings per share in the fourth quarter was $2.95, and that includes a $0.35 negative impact from the recently disclosed closeout costs related to ADUHELM. For the full year of 2023, total revenue of $9.8 billion represents a decline of 3% at actual currency and 1% at constant currency, and that's consistent with our most recent guidance of a low single-digit decline. Full year 2023 non-GAAP diluted EPS was $14.72 and that's also consistent with our most recent guidance range of $14.50 to $15.

Total MS product revenue was $1.2 billion in the fourth quarter. That's a decrease of 8% at actual currency and 6% at constant currency. And that decline is broadly attributable to competition among the impacts from generic TECFIDERA. I'd like to now provide just a couple of quick updates to the MS business during the fourth quarter. First, for TECFIDERA in Europe.

In December, the European Commission revoked a centralized marketing authorization for generic versions of TECFIDERA. And in reaching this decision, the European Commission affirmed that Biogen is entitled to marketing protection for TECFIDERA until February of 2025, which makes TECFIDERA the only dimethyl fumarate treatment for MS that may be lawfully placed on the market for sale in the EU until that date. Also a TYSABRI biosimilar is now launched in a small number of countries in Europe. We expect that biosimilars will continue to launch in the first half of 2024 in other European geographies as well as in the U.S. Biogen has patents related to TYSABRI and we will continue to seek to enforce our IP.

And although VUMERITY grew modestly in 2023, we are seeing continued effects from pricing pressure and overall contraction of the oral segment of the market in the U.S., which we expect to continue to see in 2024. Now an update on our rare disease portfolio, which includes SPINRAZA, SKYCLARYS and QALSODY. In the fourth quarter, we reported revenue of $472 million, which is an increase of 3% at actual currency and 6% at constant currency. On our third quarter call, we noted that SPINRAZA outside the U.S. benefited from the timing of shipments in certain markets.

This prior period benefit negatively impacted fourth quarter performance.

While we expect continued shipment timing impacts for SPINRAZA in 2024, we remain encouraged by its overall performance. SPINRAZA outside the U.S. was also modestly impacted by pricing pressure and competition in Europe in the fourth quarter. As the market leader in SMA, we continue to believe that we can return SPINRAZA to growth over time. SKYCLARYS delivered $56 million of revenue in the first full quarter as a Biogen product, and we are encouraged by the continued patient growth that we've seen.

Biosimilars fourth quarter revenue of $188 million, increased 8% at actual currency and 10% at constant currency. We continue to explore strategic alternatives for this business and are working to ensure that we maximize its value for our shareholders. Our anti-CD20 revenue of $436 million included a $12 million operating loss related to our economics for LUNSUMIO. Contract manufacturing royalty and other revenue of $118 million in the fourth quarter was notably lower year-over-year, mainly driven by the timing of batches and I'll provide some additional detail on this dynamic shortly when I discuss our 2024 guidance. Now a few things to note regarding fourth quarter expenses.

Fourth quarter non-GAAP cost of sales was 25% of total revenue, and that includes $52 million of idle capacity charges. Fourth quarter non-GAAP R&D expense decreased $34 million and that's notwithstanding approximately $45 million related to our portion of the LEQEMBI collaboration and approximately $60 million in closeout costs relating to ADUHELM. Non-GAAP SG&A expense decreased $44 million in the fourth quarter, which was driven by approximately $110 million in cost savings initiatives and that was partially offset by an increase in commercialization expenses related to the launches of SKYCLARYS and LEQEMBI. Next, a brief update on our balance sheet. We ended the year with $1 billion in cash and marketable securities and $6.9 billion in debt, which puts us in a net debt position of $5.9 billion.

In the fourth quarter, we utilized approximately $1.3 billion of cash for final acquisition payment obligations related to the Reata transaction. We also paid down roughly $350 million of the $1 billion term loan that we put in place at the time of this acquisition. It's important to note that included in the $1.3 billion I just mentioned, $393 million was reflected in cash flow from operations for a onetime payment related to equity-based compensation for the Reata transaction. So absent this full year 2023, free cash flow of $1.3 billion would have been approximately $1.7 billion. We expect to continue to generate strong cash flow this year and expect to receive a payment of $437 million from Samsung in early Q2 of this year.

So now I'm going to discuss our full year 2024 guidance ranges and assumptions. We expect full year 2024 non-GAAP diluted earnings per share of between $15 and $16 and that reflects expected EPS growth of approximately 5% at the midpoint of the range compared to 2023. We -- while total revenue is expected to decline by a low mid-single-digit percentage, we expect our core pharmaceutical revenue or product revenue plus Biogen's 50% share of LEQEMBI revenue net of cost of sales and royalties to be relatively flat for 2024 as compared to 2023. This assumption is driven by the expected increase in revenue from new product launches over the course of the year, roughly offsetting the declines in our MS product revenue. As has been the case in previous years, we expect Q1 to be seasonally weaker quarter as compared to Q4 for our MS business in the U.S., and that's driven by higher discounts and allowances and some channel dynamics.

We also expect contract manufacturing revenue to be significantly lower throughout 2024 as compared to 2023. This is in part due to completing certain batch commitments in 2023 as part of the 2020 sale of Hillerød, which is located in Denmark. We had manufacturing operations there. And these batch commitments contributed roughly $320 million in 2023, which will not recur in 2024. The increase in revenue from new product launches and decrease in contract manufacturing revenue along with lower idle capacity charges are expected to have a favorable impact on cost of sales as a percentage of revenue for 2024.

We also believe we can grow our operating income at a low double-digit percentage in operating margins by a mid-single-digit percentage as compared to 2023. We expect this to be driven by improved cost of sales as a percentage of revenue as well as lower expected operating expenses resulting from our Fit for Growth initiative. On Fit for Growth, we continue to expect to generate approximately $1 billion in gross savings and $800 million in savings net of reinvestments by 2025. We have achieved approximately $200 million of savings in 2023 and are on track to realize another $200 million in 2024, which would put us at $400

million or half of the overall net savings by the end of this year with the remainder in 2025. In 2024, we expect our 50% portion of SG&A spend for LEQEMBI, which as a reminder is not included in our Fit for Growth assumptions and the reallocation of resources for ADUHELM to roughly offset.

With all of these considerations in mind, we expect our full year 2024 combined R&D and SG&A spend to total approximately $4.3 billion. We expect our other income and expense line to continue to be a headwind this year given the reduction in interest income and increase in interest expense as a result of the Reata acquisition. And so in 2024, we expect an improving revenue profile, improved margins and a return to non-GAAP EPS growth. Our #1 goal remains to return to sustainable growth and we remain committed to this goal and to creating long-term value for our shareholders. And now back to Chris for some closing remarks.

Christopher Viehbacher Executive

Thanks, Mike. So we have a number of milestones this year that we'll all be watching carefully. You've seen we have a scientific advisory group for LEQEMBI in the first quarter and assuming a positive result for the CHMP that should hopefully lead to an approval in -- by the European Commission in the first half -- later in the first half of this year. SKYCLARYS in the European Union, of course, we've just achieved, as we announced last night and the European approval for QALSODY, there's an expected decision by the CHMP and the European Commission in the first half. We have regulatory submissions coming up, as you know, with the subcutaneous formulation for LEQEMBI and IV maintenance dosing also for LEQEMBI.

And then as Priya has noted, we have 4 data readouts expected sometime midyear for core programs. As I said earlier, I think we are going to be spending an increasing amount of time focused on our pipeline and building out that pipeline. So Chuck, I turn that back to you for questions.

Charles Triano Executive

Right. Thanks, Chris. Katie, could you please open polling for questions?

Operator Operator

[Operator Instructions] Our first question comes from the line of Marc Goodman with Leerink Partners.

Marc Goodman Analyst

Can you walk us through just the subcu and the maintenance approvals, obviously, time lines, I guess, would be around the end of the year, but just talk about the impact into the market. Let's assume Lilly's on the market as well, they're going to get approved soon. So how do you expect this to change the dynamics and the uptake, and just give us a sense of that, please? And then also maybe you could just talk about the uptake in Japan that you expect?

Christopher Viehbacher Executive

Priya, do you want to just start with kind of the time lines and I can hit the commercial.

Priya Singhal Executive

Thanks, Marc, for that question. So overall, we shared our 6-month data for the subcutaneous formulation at CTAD last year. We believe we've achieved the bio-equivalents with the IV formulation. Eisai has communicated very recently about the FDA meeting that is on the book to finalize strategy for submission. And currently, the aim is still to file by end of March 2024 for the subcutaneous formulation.

In addition, there is data on the potential and need for IV maintenance, and that is also being aimed to file by Q1 2024. So that's the plan currently. I'm going to turn it over to Chris for the dynamics and the commercial implications.

Christopher Viehbacher Executive

Yes. So Marc, I mean the main benefit of subcutaneous is going to be convenience for patients. And as we talked about earlier, over time, we're looking at the AHEAD study, where we could potentially when they get an indication for much earlier-stage patients. We're looking at maintenance, where patients should continue on if we get approved, to prevent the recurrence of plaque. So the time on drug is expected to expand as we do these studies and having a subcutaneous formulation at any stage of this disease could be quite beneficial.

In terms of the actual competitiveness with donanemab, I think there's going to be a number of points. We do know that physicians are highly sensitive to ARIA and safety. And we have a significantly better safety profile with LEQEMBI than donanemab. There's an interesting thing with donanemab study, which their study actually followed patients until there was a decrease in plaques. So where CLARITY looked at an endpoint for everybody at the same time point after 18 months, there was a variable endpoint in terms of time on donanemab -- and so the stopping criteria are not quite clear.

And I think we need to see what those are if you need a PET scan, for instance, that could be quite onerous. Now we don't know whether that's going to be the case or not. But I think we're going to have a number of variables with which we can compete with donanemab. And subcutaneous at some point will be helpful. Obviously, Lilly guidance, looks like donanemab is an indicated is going to be on the market before the subcutaneous formulation is.

So we're going to be focused on some of those nonsubcutaneous factors and competition. And then once we see the label for Lilly, once we see the label for the subcu, then we'll develop our commercial strategy accordingly.

Charles Triano Executive

Do you want to comment on Japan?

Christopher Viehbacher Executive

In Japan. Yes, I think -- we certainly have a -- Eisai is basically putting all of its field force, not just the ones for LEQEMBI behind this. And you've got the government-managed health care system. So I think some of the complexity that we have in the United States with reimbursement and different actors could be simpler. We do expect that there will be some of the same constraints in terms of access to neurologists, the PET scans.

They will probably use a lot more of the CSF markers and PET scans in Japan. But I think we could potentially see a faster uptake in Japan than we saw even in the United States just because of the current system. So we're just out there since January, and we'll give an update, obviously, again at first quarter. But certainly, from what we're hearing from our own people in the field that there's been a very positive reception by physicians in Japan.

Operator Operator

We'll go next to Salveen Richter with Goldman Sachs.

Salveen Richter Analyst

I have one with regard to the bottlenecks on the LEQEMBI launch. Could you speak to maybe 2 of those aspects. One is your expectations for Medicare Advantage to get to the same level of coverage as traditional Medicare and over what time frame? And then secondly, just an update on the patient access to neurologists?

Christopher Viehbacher Executive

Yes. So I'll have to get back here -- I haven't heard anything that Medicare Advantage is any different than Medicare. So I haven't ever asked that question before, but I'll go check, but as far as I know, it's the same. The bottlenecks are still -- if you think about it, if the data from the patient registries are accurate and again, we don't have direct access to that. But it suggests that we've got almost twice as many people on the registry as we do on treatment.

And so that says that in addition to the bottleneck of getting into the neurologist that there's -- when you get to the registry, you've got a clear intent to prescribe because on the registry at least for CMS you have to describe how you actually validated the diagnosis. So by then, you've triaged the patient, you've done either the PET scan or the CSF markers, and you're looking for reimbursement. And what we're hearing a little bit is, is that there is some challenge in just scheduling the first MRI because when we initiate the infusion, you have to have the first MRI within the first 2 weeks. So people don't want to initiate the infusion until they've got that MRI scheduled. And the MRI -- there isn't an MRI capacity constraint per se.

But you are looking for a specific date and then you have to back up the infusion. So there's just, I think, until people get the hang of this, getting all that coordination, I think that seems to be where one of the bottlenecks is.

Operator Operator

We'll go next to Umer Raffat with Evercore ISI.

Umer Raffat Analyst

I thought I'd ask for something a little different today, your CD40 Phase III in lupus. And my question is 2 things. One, the trial size, this was shrunk from 450 down to 320. Could you speak to the recruiting challenges and whether they bode well or not well on efficacy? And then secondly, the primary endpoint, this 1 has 3 components, but the FDA guidance appears to want one clear index like [indiscernible] et cetera.

Is there alignment with regulator on that?

Priya Singhal Executive

I'll take that. So just starting off, I think we expect our results from the first Phase III mid-2024, we expect that we'll need a second Phase III if this is positive to generate the safety and efficacy to support a reg filing. We did make a protocol amendment. And this was really working very closely with Biogen and UCB looking at the study design, balancing our commitment to execute a well-designed informative study with a desire to potentially expedite the delivery of dapB if positive to patients in need. So we do think it's appropriately powered.

And we continue with regulatory engagements and facilitate a discussion on the next step. So we think, yes, it is positioned to give us a clear readout on the therapeutic potential as of now, yes.

Operator Operator

We'll go next to Evan Seigerman with BMO Capital Markets.

Evan Seigerman Analyst

Chris, can you walk me through some of the rationale for adding more Biogen resources to the LEQEMBI launch? And maybe kind of what's changed or evolved with your partnership with Eisai, where you think you needed to add more Biogen resources in the United States?

Christopher Viehbacher Executive

I mean to be clear, we're adding both more Biogen as well as more Eisai. A year ago, CEO of Eisai and I talked about the launch of LEQEMBI and for the U.S., just discussed the complexity of the launch. And we've been through all that and they won't necessarily bore everybody again with that complexity. But we just felt that we wanted to really make sure we understood the go-to-market model. In addition to these neurology account specialists you've got MSLs, you've got some patient care navigators, you've got some people looking after KMEs in the region.

And there's probably -- for every NAS, there's another 2 or 3 people who are actually out there in the field. And there's an awful lot of coordination that is needed. And even the role of the NAS is quite complex because you've got to go in there, you've got to work with the office around helping them to understand the safety. You have to help them understand what the care pathway is. You have to help them to understand the reimbursement, not just for LEQEMBI, but there's the reimbursement for the PET scans, the MRIs and further care.

And then finally, there's what people in the field have as a principal objective via LEQEMBI.

So we wanted to make sure we understood all of that. And to be honest, whenever you do these co-promotions, they require an awful lot of coordination between the companies. And we just felt that it would be simpler if one company went out at the start. We were sure that we knew exactly how the role of the NAS was going to work in relation to the other accompanying roles that are out there in the field. And we also needed to get a certain number of core IDNs ready and signed up because there's not a lot of point in increasing the number of people out in the field unless you've got enough sites that are activated and ready.

So now we're more than 6 months into the launch. I think we feel very comfortable about how the role of the NAS works. We understand how long it takes between going to visit a neurologist or an IDN and how long it's going to take for them to be activated because I say there's you can put an awful lot of resource out there but if you're not able to pull the drug through, it's not a very efficient process. So that's just where we are. We're confident in that model.

Obviously, it is -- we need to now reach out to more sites. So we're looking at this from both a geographic expansion. But also, I think even within certain geographies, perhaps reducing the territory side because when these NASs go in, they spend quite a long time with the specialists. So it was always the agreement between the 2 CEOs that when we scale up that Biogen would come in. But we both -- our objective is to make the joint venture as efficient as possible.

And so we just felt that the efficiency at the start would be maximized if we have had one company in the field. Now we've obviously learned from that, and that's what also gives us the confidence to put 2 companies out into the field immediately in Japan, for example, because while there are differences in the market, a number of the dynamics would be the same pretty much in most markets. So it is an increase. Eisai is increasing their resource and so -- and Biogen will be out there as well. And that could still evolve over time.

We're going to be in this business together for many years to come.

Operator Operator

We'll go next to Paul Mattias with Stifel.

Unknown Analyst Analyst

This is James on for Paul. Just one more on the lecanemab subcu and specifically in treatment-naive patients. Just wondering if you're confident that you have enough data from a regulatory perspective here, if you've aligned with regulators, you and Eisai aligned with regulators and specifically, if you have enough safety data in that treatment-naive patient population. Any color there would be great.

Priya Singhal Executive

So yes, overall, this has been a topic that we've discussed Eisai and Biogen have discussed with the FDA. And just to step back, the design was to add a sub-study, a subcutaneous sub-study in the Phase III CLARITY study open-label extension and the cohort that was treatment naive from lecanemab was about 72 patients. And then there was a whole cohort of 322 additional patients that provided safety and tolerability. So this was -- the 72 patients is the premise for the PK/PD and bioequivalents. But there's a larger subset of data that speaks to the safety data.

So yes, discussions are ongoing, but overall, these have been discussed with regulators prior to starting them.

Operator Operator

We'll go next to Phil Nadeau with TD Cowen.

Philip Nadeau Analyst

Question on SKYCLARYS following last night's approval in the EU. Chris highlighted the importance of the U.S. markets. Could you discuss the expected cadence and trajectory of SKYCLARYS' launch outside the U.S. and Europe, in particular, when will be available in the major territories?

And would you expect the uptake in those major territories to be as fast as it has been here in the United States?

Christopher Viehbacher Executive

So there's 2 aspects, I guess, to the launch. One is the early access programs and the other is the former launch. So for example, we'll be able to launch now in Germany with this approval. So we will -- this will be a formal launch. We still have an early access program and naive patients on that will now convert to commercial patients, remembering that actually, the patients in early access programs in Europe are expected to be revenue generating for the most part.

We have another program that's up and running in France. And we are negotiating the establishment of early access programs in 2 other European countries and there are some early access programs under discussion in countries outside of the EU. And the early access program is important because as we all know, in Europe, getting pricing and reimbursement can take some time. So it's a little hard to predict just because we have to understand the cadence of these early access programs. So I would expect that it's not going to be quite as fast as it was in the U.S.

That said, there is some suggestion that there are some patients, the warehousing effect could well be in Europe, but as I said and as a general matter, just because of the time to get reimbursement all increase in the fact that we are not going to be able to have early access programs in all countries that, that will be a slower uptake than in the U.S. That said, there's also probably more patients actually per capita. Remember, this is a disease that is related to European descent. And so the incidence of Friedreich''s ataxia is slightly higher in Europe than [indiscernible]. The next big market opportunity to be Latin America, and we are submitting in Brazil and perhaps, Priya, you can give us an update on the regulatory time lines there.

Priya Singhal Executive

Yes. I can comment on the fact that really, we are trying to expedite our regulatory filings in Latin America, Brazil, Argentina. We haven't yet communicated the time lines, but our teams are working very expeditiously, meeting with regulators to really define the pathways that could provide earliest access to patients.

Christopher Viehbacher Executive

We estimate, it's hard to get the numbers precisely, but we do estimate there's around 2,000 to 4,000 patients in Latin America. So -- and when we look at the experience of SPINRAZA,

we are expecting particularly Latin America to contribute substantially to our revenue outlook as well. As you know, there are very few patients in Asia just because of the genetics. So we don't intend to be filing or launching in Asia.

Operator Operator

We'll go next to Michael Yee with Jefferies.

Michael Yee Analyst

We had a question on SKYCLARYS. Can you maybe shed some more light on the dynamics of 800 patients to 1,000? And then the trajectory as we go forward into 2024, I know you mentioned there's about 4,000 patients, but how many of those are actually identified. Do you expect growth to moderate just from an expectation standpoint? Talk a little bit about the complexities in 2024 that you commented about.

Christopher Viehbacher Executive

Yes. Certainly, the growth is going to moderate. Remember, this was -- when this product was in hands of Reata, they had approval. I think it was back in the first quarter. I think it was February, if I remember accurately.

And -- but they were not able to commercially launch because of a manufacturing specification issue. So -- and that did not get cleared until July. So in other words, the market and physicians knew the product would be coming to the market that it was approved and they were just waiting for product availability.

So I think the warehousing effect was even greater than what you would normally see for any rare disease drug. Now we're back into the process of finding the patients. I have to say the Friedreich''s Ataxia Research Alliance, otherwise known as FARA, is an extraordinarily effective patient association and we're working with them to help identify patients. There is a requirement really to diagnose a patient accurately a genetic test. But this genetic test is not sold readily available.

And so we're having to look and make sure that the supplier of that test can make the tests readily available.

And then we're also doing the contracting really to make sure that as patients have start forms that they can quickly get on drug. So we'll be back to, I think, a regular growth cadence on SKYCLARYS in the U.S. I don't think we're necessarily going to get another 20% this year but we're growing every month. And certainly, SKYCLARYS is contributing significantly to our return to growth in 2024.

Operator Operator

We'll go next to Colin Bristow with UBS.

Colin Bristow Analyst

I just wanted to clarify something in your slides that says that the subcu that we can be filing is now first half of '24. But in your commentary, it sounds like it's still 1Q '24, so if you could

just clarify that? And just talk to specifically what FDA is waiting to see, I think it was a 12-month data last time we spoke. What is it within that? And then maybe just as a follow-on, AHEAD 3-45 study, what is the timing or thresholds for any interim analysis there?

Priya Singhal Executive

I can get started. So overall, I think with the subcutaneous, just to be very clear, Eisai has communicated as recently as their earnings a few days ago that we aim to file by Q1 2024, which is end of the first quarter this year. And just shifting gears to AHEAD 3-45, this is really a platform -- a set of platform trials with different amyloid levels for defining preclinical Alzheimer's disease. So at a very high level, A45 is preclinical Alzheimer's disease with an enrollment target of 1,000 patients and patients need to have an amyloid level of 40 centiloids or more. There are 3 phases of dosing with different doses, which is titration, induction and maintenance.

And in this particular trial, the outcome is a PACC5, which is a preclinical composite for Alzheimer's disease, where it's sensitive to patients who are still in the preclinical phase.

The A3 trial is -- has a target enrollment of about 400 and the preclinical amyloid cutoff is between 20 and 40 centiloids. And then again, it's got a different holding schedule of titration and then maintenance. Now the primary endpoint for the A3 trial is really a biomarker endpoint. We haven't really communicated exact time lines. These are very large trials.

I think the Eisai and Biogen are very pleased with how they are being enrolled. And I think we'll communicate more. There is an opportunity to do an interim analysis and Eisai has spoken to this, but we haven't communicated a time line yet.

Charles Triano Executive

And Colin, just a quick note on Slide 28, right. The docs that does show Q1, right? We have wordings as expected midyear, if there's something sort of in the middle of the year. So I get the confusion because it says half 1, half 2, but the docs are kind of at the end of the quarter there. So if you were looking at -- see if there was a disconnect, there's not it is.

They have said in the end of March is what we're looking at here. So Priya...

Priya Singhal Executive

I think there was the latter part of the question. I'll just wrap it up that with regards to FDA, I think I mentioned previously, there have been a lot of discussions. Eisai has recently mentioned the scheduling of more meeting another meeting. And so that strategy will be finalized. Looking at the 6-month data, we are very encouraged with what we saw.

We believe that the highest threshold, really, the biggest hurdle was to meet bioequivalence, which we believe we've met. So we'll continue to wait for more data. But we are very encouraged with what we've seen so far.

Operator Operator

We'll go next to Chris Raymond with Piper Sandler.

Christopher Raymond Analyst

I wanted to maybe circle back on the Angelman's program, and I wanted to understand a little bit better previous commentary around the program. Can you maybe clarify the calculus that goes into deciding to participate in future development. And obviously, there's a competitive approach with Ultragenyx's program. Curious how you're thinking about approvable endpoints? That's obviously been a big question mark.

And how you think this product, if successful, would sort of compare and any sort of commentary there in terms of the competitive set?

Priya Singhal Executive

Sure. Sure. So overall, just to step back, this is a program that Ionis, our partner is operationalizing and the way the contractual agreements are written, we have the option of opting in to take the data that we see midyear and decide whether we would like to do a pivotal program -- a pivotal study. So that's how it's set up. And then to step back, I described it briefly in my opening remarks that this is a Phase Ib trial.

So this is a Phase I trial that's being conducted in patients. It has a multiple ascending dose component for 3 months followed by a long-term extension. So we will get data. This is across different age groups and different doses. So we'll get a composite of data.

And importantly, we'll be looking for trends on EEG, which we know these patients suffer from the delta waves as I spoke to the slowing. So we'll be looking at that as well as clinical endpoints. And very specifically, there are quite a few clinical endpoints. There's the Bayley score, there's the CGI and there's a Vineland. We'll be looking at all of them.

Stepping out into what do we feel about the competitive landscape? We feel that this as designed the program is well positioned. Just from an ASO perspective, the backbone of the BIIB121 ASO, we believe, is different. That's one from the Ultragenyx ASO.

Second, we believe that the dosing may be needed at a quarterly level to really see the PK/PD impact that we need to have -- make an impact in this disease. And we do have a 3 monthly dosing in the LTE. So the MAD is 2 doses being given 1 month apart. And then the third dose, 2 months later, and then patients go into a 3-month dosing. So we are -- we feel that we will have a data set that we can look at and really assess whether we see an adequate signal to really take it into a Phase III.

And with regards to Roche discontinuing their program, we believe, again, that this is a different product and we believe we may have a competitive advantage. Ultimately, of course, we need to see the data.

Operator Operator

We'll go next to Mohit Bansal with Wells Fargo.

Mohit Bansal Analyst

Maybe I can -- if you can comment a little bit on the previous comments you made regarding SPINRAZA returned to growth. What is happening in the market right now? And how do you

plan to get back to growth on this product?

Christopher Viehbacher Executive

Sure. So as you know, we have an oral therapy out there. We have a gene therapy, and we have SPINRAZA with the intrathecal. So short term, I think one of the data points that was very important was demonstrating the efficacy of SPINRAZA following Zolgensma because there has been some feeling that Zolgensma wanes over time. So we're getting what we call switch packs, and the other on the oral therapy is that there has sometimes appear to be that the efficacy is limited to certain body weights.

So we can actually go after more adult populations.

We believe that only about 30% of patients with SMA are actually treated. Clearly, the pediatric patients are screened for and readily identified. But there are a number of adult patients where the disease is manifest, but it is sometimes difficult to diagnose. And so we're back to the rare disease job of hunting for patients. But we think, actually, we will be the most appropriate treatment for that patient population.

So that's one source of growth. And then longer term, as you know, we have a high-dose SPINRAZA program in development, which could, if it's successful, lead to just one intrathecal injection procured. And that would make an enormous difference to patients in terms of patient convenience and make SPINRAZA even more competitive compared to the others. Now that's still going to take a number of years, but we do expect that still to come to market before the patent on SPINRAZA occurs.

Michael McDonnell Executive

Yes. And I'll just quickly add to that, Mohit, that in the -- as we mentioned in our prepared remarks, there tends to be some lumpiness quarter-over-quarter, particularly outside of the U.S. with shipments. But overall, when you look at the full year of 2023, we actually saw modest growth in the U.S., modest decline OUS and overall, moving back toward the modest growth trajectory that we're hoping for, and we are pleased with how that franchise has stabilized over time.

Christopher Viehbacher Executive

Yes, there's a dynamic as sort of the oral comes into a market at one point or the gene therapy comes into a market. If you have 100% market share and the competitor comes in mathematically, you're going to lose market share. But what we see is that there is some churn for a year or 2. And then the markets settle out, and that's when people start focusing on efficacy and patient populations. And as I say, so far, we have been able to maintain leadership in SMA despite the competition.

And I think that's where they'll be. There'll be different products for different patients, but there's still enough of the patient population and even with the switchbacks that we can find reservoirs of growth.

Charles Triano Executive

And operator, can we move to our last question, please.

Operator Operator

We'll go next to Jay Olson with Oppenheimer.

Unknown Analyst Analyst

This is Matt on for Jay. Jason's regards. So we were wondering, I guess, it's still early, of course, with the PPD launch so far just in terms of any metrics or signals that you see that support your confidence in the launch so far. And of course, over the next few months to quarters, what kind of metrics do you believe will become meaningful and that you might plan to share? And maybe just your overall longer-term goals for that PPD launch and your general interest in the psychiatry space would be interesting to hear as well.

Christopher Viehbacher Executive

Sure. We -- there are a number of things that I think are quite encouraging. One is our initial target has been high-prescribing psychiatrists in this space as well as OB-GYNs. And one of the things that we are wondering about is, are the OB-GYNs really going to be willing to prescribe. And so one of the encouraging signs is that they, in fact, are doing so.

So we're seeing quite a high percentage of the prescriptions coming from them. Another has been, I think, as I mentioned earlier, that payers have really wanted to ensure access to patients, and I'm quite thankful to them.

I think Medicaid, for example, where 40% of births occur have moved very quickly on that in a number of states. And some of the large -- at least one of the large commercial insurers is moving much quicker than we expected as well. So I think the reimbursement is a key statistics. Now personally, I'm interested in knowing how many patients are treatment naive versus people who have been on treatment what is interesting is, is there a warehousing effect here as well. There's been an awful lot of media coverage.

The product was approved in July. We were not able to launch because of the DEA inspection until the very end of 2023.

So what we don't know is are we seeing a bolus of patients come in because these are patients, physicians have been following for some time, who've been identified as being particularly important for to have ZURZUVAE. So I think we'll need to see a little bit more data about who are the patients and where they're coming from. But I say so far, we're running for the first month, I mean we're certainly doing much better than what we had anticipated, and we'll give you another update at Q1. We'll sit with Sage sometime in March to look at the data and say, what do we see as some of the trends. But so far, so good.

Charles Triano Executive

Thanks, Chris, and that will conclude our call. Appreciate you all joining us today.

Operator Operator

That concludes today's call. We appreciate your participation. You may now disconnect.