Biogen Inc.

Biogen Inc. - Q4 2024 Earnings Call

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Event Participants

Executives 4
Tim Power, Christopher Viehbacher, Priya Singhal, Michael McDonnell

Analysts 10
Salveen Richter, Michael Yee, Timothy Anderson, Brian Abrahams, Marc Goodman, Paul Matteis, Umer Raffat, Christopher Schott, Evan Seigerman, Philip Nadeau

Operator Operator

Good morning. My name is Jennifer, 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 2024 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. Tim Power, Head of Investor Relations. Mr. Power, you may begin your conference.

Tim Power Executive

Thanks, Jennifer, and good morning, and welcome to Biogen's Fourth Quarter and Full Year 2024 Earnings Call. During this call, we'll make forward-looking statements, which involve risks and uncertainties that may cause actual results to differ materially from our forward-looking statements. We provide a comprehensive list of risk factors in our SEC filings, which I encourage you to review. Our earnings release and other documents related to our results as well as reconciliations between GAAP and non-GAAP results discussed on this call can be found in the Investors section of biogen.com. We've also posted slides on our website that we will be using during the call.

On today's call, I'm joined by our President and Chief Executive Officer, Christopher Viehbacher, Dr. Priya Singhal, Head of Development; and Mike McDonnell, Chief Financial Officer. We'll make some opening comments and then move to Q&A and to allow us to get through as many questions as possible, we'll kindly ask that you limit yourself to just 1 question. And with that, I'll hand over to Chris.

Christopher Viehbacher Executive

Thank you, Tim. Good morning, everybody. Perhaps before we get started, I'd just like to note

that this is Mike McDonnell's last quarterly presentation as CFO of Biogen. Mike, I believe this is your 97th quarter as a publicly quoted CFO. So congratulations on that amazing career and I'll just take the opportunity to thank you.

You've been a terrific partner and team member, and it's been great working with you, and we will miss you. And we, of course, are joined here also by Robin Kramer. I'm also proud to say that we've been able to promote from within, and it's a great source of pride that we have that level of talent within the organization.

So let's turn to Q4. As you all know, we have been faced with increased competition for our multiple sclerosis franchise. And really, all of our priorities are thinking about how do we now build a new Biogen, how do we build a new phase of growth. And we are focused really around 3 core priorities. The first are clearly the 4 products that we launched last year in Alzheimer's, Friedreich's ataxia, depression and ALS.

Each of those products is not only first-in-class, but first disease-modifying agent in each of these diseases. Now that's a source of pride in the level of innovation that Biogen is capable of. But equally, from a commercial point of view, this is a significant challenge since the level of education when you're a pioneer in an area is so much greater, and we'll come back and talk a little bit more about that. The next is we have really reprioritized the pipeline. It's certainly been my experience over the years that focusing on a number of key projects is core to business success.

And I'm pretty grateful to both Priya Singhal and Jane Grogan because they have both really, I think, cleaned out the pipeline for development in Priya's cases, in research in Jane's case, and we're actually excited now by the products that are in there. We've got a number of key developments that will start reading out in 2026. We think this is a multibillion-dollar portfolio. And we're probably one of the few companies that can look at a pipeline that could be more than -- it could be more than our current biopharmaceutical business when it gets to peak sales if it all, obviously, comes to market.

So if we can go to the -- and the third point, of course, is we have redesigned the company with a reduction of operating expenses, not just saving costs for the sake of cost but the ability to release resources for investing in growth, and that's what we're continuing to do. We're excited about our pipeline, but we've also freed up an awful lot of cash flow, as you'll see later. And that cash flow, we're investing for more substrate in growth. So yes, now, Dan, please next slide. So the race really that we are faced with is seeing the erosion of our multiple sclerosis product revenue, but I'm particularly happy to see in 2024 that the revenue from our launch products really offset the -- more than offset the decline in our multiple sclerosis product revenue.

And indeed, when you actually look at total revenue declined by $160 million, and you note that contract manufacturing declined by $247 million, it meant that really our core pharma business actually grew, and that's for the first time in 4 years. And that's really what we're all about in the near term is trying to make sure that the revenue can exceed the multiple sclerosis product decline.

Multiple sclerosis product decline is obviously driven by a number of factors going forward,

including the timing of it Tysabri, biosimilar in the U.S. and timing of TECFIDERA generics in Europe. So as I said, we've got actually 4 very innovative pioneering products. LEQEMBI, we'll come on and talk about it in some detail. SKYCLARYS in Friedreich's ataxia, again, very first treatment for Friedreich's ataxia.

We have been able to determine from basically medical claims data that there are approximately 4,800 patients in the U.S. That's about what we thought. One of the complexities is that it's harder to find these patients because you could have a primary care physician in a rural setting that has 1 single patient and you have to go find them. And we're talking to primary care physicians, talking to cardiologists, talking to pediatricians. So it's quite a large prescriber base for a very narrow patient population.

But that, of course, is the core of what rare diseases does. I remember years ago, when we acquired Genzyme when I was at Sanofi and the marketing folks are saying, our marketing strategy is looking for needles in haystacks. And that is exactly what rare disease is all about, and it's what Biogen is also very good at. And of course, today, we've got a lot more technology. We can use tools such as AI and genetic testing to help find those patients, but by its very nature, it is unfortunately not going to be the nice smooth progression quarter-on-quarter.

That said, we are particularly proud to say that we have been able to double the number of patients on treatment in the past year. Not all of those are yet being reimbursed. We are able to get a lot of patients on drug and then negotiate with governments, particularly in Europe to get the reimbursement and once we do that, the patients flip from being free goods patients to actually revenue-generating treatments. There's always a bit of a -- in each country, a number of patients who are diagnosed who have been waiting for treatment and you can get those quite easily. There are a number of older patients who actually have lived with this disease for 30, 40 years.

And they are the ones we actually have to go hunt for.

We will see another growth driver this year and that we expect to get approval for SKYCLARYS in Latin America. I was in Brazil last year and there are quite a number of patients in Latin America. So as we started with the U.S., we moved to Europe and then we're moving to South America and indeed areas of the Middle East. We expect to see continued steady growth out of SKYCLARYS. But again, I of appreciate that it's going to be hard for some of you to model on a quarterly basis.

ZURZUVAE was a very nice launch last year and certainly exceeded our expectations. One of the things that was different from our expectations was that the main prescribers actually OBG and OB/GYN. We had actually been targeting originally high-prescribing psychiatrists. We still see some of those, but as you can see, 80% of the prescriptions are driven by OB/GYNs. This is also an area where you could have potentially more people who have ever prescribed for PPD than you actually have patients.

And again, targeting and thinking about multichannel marketing and commercial approaches are extremely important. We have filed in Europe and would hope to see an approval sometime later this year.

QALSODY is not necessarily a big revenue generator, but this is really a breakthrough treatment in ALS. This is the first time we've been able to demonstrate that neurofilament can really help predict drugs early in development as to whether or not they are likely to work or not. And that allows just the whole research and development in ALS to be accelerated. So we're particularly proud of that. The impact on patients is absolutely extraordinary.

And so -- while we may not be making a big impact on revenue, we're certainly making a big impact on patients' lives. Go to the next slide, please. Dan?

Now I showed this slide at JPMorgan. And there were several investors who looked at that chart and said, this is not the chart of a small product. And we've all been in this business and looked at a lot of launch curves, and we all know that we like to see an acceleration in the curve. But any curve that goes from bottom left to upper right is in my books good unless we talk about operating expenses. And this is good, steady quarter-on-quarter progress.

We have seen some questions on the ex U.S. launch. Clearly, the ex U.S. launch is contributing more than we have seen in prior launches in other areas. I think part of that is -- first, I think Eisai is extremely strong in Asia and they are leading that launch there.

But second, I think the single-payer system removes a lot of the obstacles that we're dealing with in the U.S. When you have a single payer, you're not having to negotiate quite so much in terms of PET scans and MRIs and infusion beds, and that has facilitated the progress. And it's as strong in China as it is in Japan, not necessarily patient numbers, but we're seeing very strong growth in China, and that is that is a cash pay market. And it goes to really a demonstration of how people value the importance of LEQEMBI. So we'll go to the next chart, please.

Now, I talked about some of those obstacles and we certainly see that making this easier for both patients and physicians is going to accelerate the launch. And we have a number of these catalysts. The first one has already been achieved. So we have the LEQEMBI IV maintenance, that's now FDA-approved. We now have the first patients who are hitting that 18-month mark.

They've cleared their plaque. But as the data have demonstrated, you've got to stay on treatment, otherwise, some forms of the plaque actually come back. And we have demonstrated 3-year data to show that actually staying on treatment, patients do better than those who stop treatment. And that's an important message because our competition is actually not able to say that. And so this is also important for the education of the disease.

It's not just about plaque clearance, it's about maintaining that clearance. The second is really the introduction of blood-based diagnostics. Certainly, LabCorp and Quest continue to see rising sales of these diagnostics. What I think will really make a difference is getting FDA approval for some of these diagnostics with an evidence base that will give physicians the confidence to be able to confirm diagnosis without the need for a PET scan or a lumbar puncture. And so again, this is something that could not only facilitate the work of the neurologist, but we might also be able to see this being used increasingly to triage patients.

Something like 50% of patients who actually managed to get into a neurologist are actually not eligible for treatment because they're too far advanced in their disease. So if we could

actually triage some of these patients, particularly at the primary care level, then we can actually get a higher quotient of patients who visit neurologists actually being eligible for treatment. The subcutaneous form for maintenance, we would expect now. We have a PDUFA date on August 31. That, again, will really facilitate the journey, both for the patient as well as for the physician, no longer needing the infusion beds and patients can actually take the drug from the comfort of their own home.

A major game changer we see as the subcutaneous for initiation, which we expect to have in the first half of next year. And that obviously would also facilitate that for the same reasons of not having to deal with infusion beds and patients can have that in the comfort of their own home. The AHEAD 345 study is fully recruited. We expect to read out in 2028. This is a landmark study because this is where we could see the promise of potentially prevention of Alzheimer's.

We know that before patients actually exhibit symptoms, they've been accumulating plaques in their brains for many, many years. And unfortunately, a lot of damage is done already by the time patients actually exhibit symptoms. So if we can get patients earlier, we think that we can actually have even better efficacy. And in fact, Priya is going to show shortly, again, the low tau patients, which is a marker for earlier-stage patients. And there, we see dramatically improved efficacy versus just the 27% on the CDR sum of box that was demonstrated in the CLARITY study.

So next slide, please.

So those are the 4 products. Clearly, we're also looking at our pipeline. And I think there are 3 key areas in this to look at. The first is continued investment and commitment to Alzheimer's. We gather some of the top leading experts in Alzheimer's from around the world.

They're the ones who are telling us, one, that nobody is really doing so much research in a broad area of modalities as Biogen, but the other is they are extremely excited about the opportunity to reduce tau and the impact that, that could have on Alzheimer's. So Alzheimer's is going to be a core franchise for Biogen for decades to come. We had very positive data on dapirolizumab back in September. And we've already initiated the second Phase III. But we also have litifilimab in both CLE and SLE so we got a nice lupus portfolio of assets coming along.

I'd remind everybody, yes, people are looking at a lot of potential competitors in Phase I, Phase II, but out of the dozens and dozens and dozens of molecules that entered the clinic, only 3 molecules have ever demonstrated a positive Phase III result, 2 are already in the market and the dapirolizumab is the third.

So we know that you can get excited about a lot of things, but it's not until you actually see Phase III results that you can really have conviction. But that's a potentially significant market and fits nicely with Biogen because we can take a lot of the learnings from MS and apply that to lupus. And of course, the third area are really these auto antibodies. We have our anti-CD38. We are expected to enter into 3 Phase III trials in 3 separate indications with auto antibody-mediated resistance, IgAN, the PMN.

And we have very compelling Phase II results here. There are no guarantees any time in

research and development, but I think we feel particularly excited about felzartamab and the potential this could have in rare kidney disease. And of course, then we have a whole phase of readouts coming along and I think that will become the story of Biogen as we get increasingly more data and people can gain increasing confidence and excitement -- share our excitement in our pipeline. And so with that, I think I'm going to -- let's continue the story on R&D. Priya, I'll turn it over to you.

Priya Singhal Executive

Thank you, Chris. Biogen's development organization had another very productive quarter. We achieved several important milestones across key strategic areas for the company. I would like to begin with immunology, where in collaboration with UCB, as Chris mentioned, we initiated the second Phase III study for dapi pegol in SLE. This follows the positive readout of the first Phase III study and sharing of detailed study results as a late breaker at the ACR Annual Meeting last year.

Dapi pegol, as Chris mentioned, is only the third agent with a positive global Phase III study in SLE.

Additionally, felzartamab was granted orphan drug designation in the EU for both solid organ transplantation and IgA nephropathy. We believe this designation, which is intended to support development of treatments with significant unmet medical need, underscores the potential for felzartamab to become a meaningful new therapy for serious immune-mediated diseases like AMR, IgAN and PMN globally. In rare disease, we continued unlocking new geographies for SKYCLARYS. In Friedreich's ataxia and QALSODY in SOD1 ALS. Leveraging the results of the SKYCLARYS-positive MOXIe trial, we obtained approval in Chile and currently have 13 additional regulatory filings under review.

This includes additional filings in Latin America, where we expect regulatory decisions this year in countries such as Brazil and Argentina as we continue our global rollout. Importantly, we also took significant steps towards expanding the value of key portfolio products for patients. In SMA, regulatory filings for high-dose nusinersen have now been accepted in the U.S. and EU, and we expect an FDA decision in September of this year. And in Alzheimer's disease, we recently received FDA approval for LEQEMBI less frequent IV maintenance dosing.

This is both a significant step for LEQEMBI and a meaningful advancement in the evolution of Alzheimer's treatment more broadly. I would like to briefly review why there is an urgency to treat now and why maintenance is important based on LEQEMBI data that we have obtained to date, based upon tau brain pathology. Therefore, we have placebo-controlled clinical trial data across the full early Alzheimer's disease population, including individuals with no and low tau, which represents the earlier stages of AD. In this population, 76% of patients showed no decline and 60% showed clinical improvement at 18 months as assessed by CDR Sum of Boxes. What this means is that in over 3/4 of early AD patients, their disease was stabilized and more than half the patients showed improved symptoms when treated with LEQEMBI.

The reason why this is important is that this data suggests that patients treated early in their disease can see a profound benefit, which underscores the importance of initiating treatment

early. Furthermore, this data also supports the potential of our ongoing presymptomatic AHEAD 345 trial. And now that I've shown you why early treatment initiation is important, let me remind you why the new maintenance IV approval is also very critical. And that is because data shows that Alzheimer's does not stop after plaque removal. Importantly, prior data from the LEQEMBI Phase II study and its open-label extension show that discontinuation of treatment is associated with reaccumulation of Alzheimer's biomarkers, including amyloid plaques and importantly, a reversion back to the placebo rate of clinical decline.

With its differentiated mechanism of action, we believe LEQEMBI's uniquely positioned as it is the only disease-modifying therapy in Alzheimer's today to show additional benefit with continued treatment after plaque reduction.

As you can see from this slide, the 3-year data from the Clarity AD study and its open-label extension support the potential for long-term benefit to patients by showing that continued LEQEMBI treatment resulted in a doubling of the clinical benefit observed at 18 months as compared to a matched natural history cohort. With these findings in mind, we are working with Eisai to deliver additional options for patients with the aim of maximizing both the convenience and the clinical benefit of the LEQEMBI. This includes a subcutaneous formulation with the potential for at-home administration to further add to patient optionality and convenience. For subcutaneous maintenance dosing, we now have a PDUFA date of August 2025. Next year, in 2026, we aim to introduce subcutaneous dosing for treatment initiation, which we believe will allow even more patients to get started on therapy.

And building upon the encouraging results we obtained in the no or low tau population in Clarity AD, we continue to advance evaluating AHEAD 345, evaluating LEQEMBI in individuals who have amyloid plaque pathology in the brain, but before the onset of symptoms, which has the potential to further expand the use of LEQEMBI. Turning now to the pipeline. We have previously discussed our efforts to augment our pipeline with the objective of rebalancing the risk profile and investing to win in key areas of expected future growth. As a result, we have focused our development efforts on a smaller set of clinical stage programs that we believe are high conviction and well positioned to deliver a regular cadence of pivotal readouts and potential launches. This includes key late-stage programs that have the potential, as you see on this slide, to deliver innovation to benefit patients across Alzheimer's and immunology.

We will continue to remain disciplined in our approach as we continue to assess inflection points for our internal development pipeline but also as we evaluate potential external innovation opportunities that we believe can help support Biogen's goal of sustainable growth. With that, I would now like to hand the call over to Mike for a financial update.

Michael McDonnell Executive

Thank you, Priya. Good morning to everyone. I'd like to begin by providing some highlights from the reported results. Total revenue for the quarter was $2.5 billion, which represents 3% growth from the fourth quarter of 2023. Fourth quarter non-GAAP diluted EPS was $3.44 and that's 17% higher than the fourth quarter of 2023.

For the full year of 2024, total revenue of $9.7 billion represents a decline of 2% from the --

from 2023, consistent with our most recent guidance of a low single-digit decline. And full year 2024 non-GAAP diluted EPS was $16.47 and that's 12% higher than the full year 2023, also consistent with our most recent guidance range of $6.10 to -- $16.10 to $16.60. EPS. Growth and operating income expansion in both the fourth quarter and full year was supported by our Fit for Growth and R&D prioritization initiatives. We are pleased that this performance allowed us to generate $722 million of free cash flow in the quarter, which brought us to $2.7 billion for the full year and that's an improvement of $1.4 billion from $1.3 billion generated in 2023.

Now I'll turn to a few comments on revenue and commercial dynamics from the fourth quarter. Our MS product revenue declined roughly 8% at actual currency and 9% at constant currency as compared to the fourth quarter of 2023. And that was driven primarily by competition in the space, partially offset by some seasonal channel dynamics. Interferons continued to be impacted by competition as patients transition to higher efficacy therapies, and TECFIDERA continued to be impacted by generic competition globally. Tysabri has seen some impacts from a biosimilar entrant in Europe.

And although a biosimilar has not yet launched in the U.S., we continue to see competition increasing in the high-efficacy class. VUMERITY saw an increase in demand in the quarter and also benefited from some seasonal channel dynamics.

Next, our rare disease franchise produced revenue of $535 million in the fourth quarter and that represented a growth of 13% at actual currency and 15% at constant currency from the fourth quarter of 2023. Global SKYCLARYS revenue in the fourth quarter was $102 million, an increase of 83% versus the fourth quarter of 2023 with nearly double the number of patients on therapy. U.S. SKYCLARYS revenue in the fourth quarter was $71 million. We continued to add patients in the quarter, but revenue was sequentially impacted by an inventory build in the third quarter that was drawn down in the fourth quarter as well as some Medicare discount dynamics.

Global SPINRAZA revenue of $421 million in the fourth quarter grew 2% year-over-year, including growth in the U.S. of 6% year-over-year. We are encouraged by the performance here and look forward to a potential future launch of the high-dose option. ZURZUVAE delivered approximately $23 million of revenue in the quarter, and that was driven by an increase in demand, partially offset by channel dynamics. And we again saw steady sequential growth for LEQEMBI with fourth quarter global in-market sales booked by Eisai of approximately $87 million and that's up approximately 30% sequentially from the third quarter of 2024.

LEQEMBI fourth quarter end market sales in the U.S. were $50 million and that's up roughly 28% sequentially from the third quarter of 2024. I'll now turn to a few comments on dynamics from a few key expense lines. Non-GAAP cost of sales as a percentage of revenue improved 300 basis points in the fourth quarter as compared to the fourth quarter of 2023, and that was driven primarily by lower idle capacity charges. Fourth quarter non-GAAP core operating expense or R&D plus SG&A expense increased 4% year-over-year as the benefits from our R&D prioritization and Fit for Growth initiatives allowed us to mostly absorb incremental spend associated with our launches.

Non-GAAP other expense was $72 million in the quarter, and that was driven primarily by net interest expense. Non-GAAP diluted EPS was $3.44 in the fourth quarter, representing growth of 17% versus the fourth quarter of 2023.

Now a brief update on our balance sheet. We generated $2.7 billion of free cash flow in 2024 due to strong operating income. Please note that the timing of certain cash tax payments in 2024 also benefited free cash flow. We ended 2024 with $2.4 billion of cash and roughly $3.9 billion of net debt and continue to believe that our balance sheet remains strong and allows us to continue to invest in both internal and external growth opportunities. Turning now to our full year 2025 guidance ranges and assumptions.

We expect full year 2025 non-GAAP diluted earnings per share of between $15.25 and $16.25. This guidance range, which is based upon FX rates on February 7 of 2025, includes a $0.35 EPS headwind from foreign exchange when compared to average exchange rates in 2024. Total revenue for 2025 is expected to decline by a mid-single-digit percentage. This is driven primarily by an increased decline in our MS business as compared to 2024. The pressure on our MS business is expected to be driven by potential biosimilar entry for TYSABRI in the U.S.

this year and potential generic entry for TECFIDERA in certain European markets. We expect this decline to be partially offset by continued strong and increasing revenue growth from our new product launches. Please note, this revenue range also includes a roughly 1% headwind from foreign exchange. In 2025, we expect an impact from Medicare Part D redesign at the total company level to be limited approximately $50 million to $100 million. We expect approximately 1/3 of this impact to be related to SKYCLARYS with the remainder coming from MS.

On operating expenses, we remain on track to deliver the $1 billion of gross and $800 million of net savings from our Fit for Growth initiative by the end of this year. With this in mind, we expect full year 2025 combined non-GAAP R&D and SG&A expense to total approximately $3.9 billion. And as it will take time for the savings to crystallize, we expect to see higher OpEx in the beginning of the year. We expect non-GAAP operating margin percentage to remain relatively flat in 2025 as compared to 2024. And on the nonoperating side of expenses, I would highlight the components of our non-GAAP other income and expense line.

This line includes interest expense on our debt and some other expenses, partially offset by interest income on our cash balances. For full year 2025, we expect other income and expense to be a net expense of approximately $180 million to $220 million.

And finally, some additional considerations as you think about your models. As has been the case in previous years, we expect the first quarter to be pressured due to seasonality, driven by higher discounts and allowances as well as channel dynamics in the U.S., and that will mostly impact our MS business. I would also note with regard to FAMPYRA that we terminated the license and collaboration agreement effective January 1, 2025. And as I just mentioned, our current year guidance takes account of the stronger dollar today compared with the same time last year. For modeling purposes, each cent change in the euro versus the U.S.

dollar impacts revenue by approximately $15 million. I would also refer you to the current slide as well as our press release for other important guidance assumptions.

And in closing, we welcome Robin Kramer, as Biogen's CFO, following my retirement later this quarter. This orderly transition plan has been in process for some time now, and I have full confidence that Robin will be a great CFO. I'm excited about Biogen's future and will remain a supporter and shareholder of Biogen in the years to come. And with that, we will now open the call up for questions.

Tim Power Executive

Mike. Jennifer, can we go to the first question, please?

Operator Operator

[Operator Instructions] Your first question comes from the line of Salveen Richter with Goldman Sachs.

Salveen Richter Analyst

What is your latest thinking on the capacity preference and potential time lines for external BD? And in terms of your growth outlook, just help us understand the balance between the existing pipeline and the assets you could bring in?

Christopher Viehbacher Executive

Thanks, Salveen. I mean I think I'll get Mike to give you an update on capacity. As I said, we are very excited about the pipeline that we have. But I think one of the things that we'd like to do is continue to reinforce that pipeline. Over the years, I've come to the conclusion that you can never have enough pipeline.

First element is we've done a major restructuring of research because I think as companies in our industry, it's very expensive to bring in late-stage assets. And we would like to have research be our primary source of innovation, obviously, internally, but also externally. And so I think we have completely restructured research to create the financial capacity as well as the talent capacity to do more collaborations and bring assets in, particularly pre-GLP tox. Beyond that, we are looking at virtually every phase, the early phase development. Right now, I would say Priya would probably agree with me that our early-stage development pipeline is still relatively thin.

But even if we can find things in Phase III, if it's got a really solid Phase II, I'm not big on taking a lot of risk on Phase III clinical trials because that gets expensive. And in terms of acquisitions, we have been migrating in new areas such as immunology and rare diseases. And if we can find acquisitions that can bolster our positions in that, we will do so. We don't have a particular size that we're looking for. It could be late stage development.

It could be early stage commercial. The one thing it has to do is make financial sense. I think where we are as a company, we don't need to be taking a huge amount of risk on acquisitions. That said, we are always looking. We always have about at least 15 to 20 different projects that we're looking at, at any one time.

But as you know, you kind of have to look at 100 things before you find something that is of interest. And Mike, maybe you want to talk about capacity?

Michael McDonnell Executive

Yes. And Salveen, on capacity, the balance sheet remains in excellent shape. As we mentioned in the prepared remarks, we ended the year with $2.4 billion of cash on hand. The EBITDA run rate is north of $3 billion a year. So with $6.3 billion of gross debt and $3.9 billion of net debt, you're in the ZIP code of maybe 2 turns gross and 1.5 turns net.

And we were very pleased with the free cash flow results this year or last year, I should say, 2024, $2.7 billion. So that cash balance will continue to grow. So when you look at the modest amount of leverage, the $2.4 billion of cash on hand the growing free cash flow, the balance sheet is in an excellent position. As Chris said, the plan will be to stay very disciplined and only do things that make good financial sense, but we've got significant capacity to do a series of smaller things or perhaps a larger thing if it does make good financial sense.

Operator Operator

We'll take our next question from Michael Yee with Jefferies.

Michael Yee Analyst

Priya, you mentioned that on the LEQEMBI slide, one of the important developments is the potential for blood-based diagnostics. And my understanding is that, that's coming this year. Can you walk through how important that is in terms of any bottlenecks and specifically whether that totally would be able to replace PET or how that actually works since diagnostics are a little bit complicated.

Priya Singhal Executive

Yes. Thanks, Mike. So overall, I think that accurate diagnosis of Alzheimer's disease and confirmation of amyloid remains very important. And it is the entry point for the kind of care pathway here. So it's important.

I think with the advent of the anti-amyloid therapy, we've seen amazing momentum there. And as Chris mentioned, we have tests available today that are at triage sort of level. The question here is what is the -- what is going to be the availability in the near term for an in vitro diagnostic approved by the FDA that can be used widely and can also be reimbursed and give physicians and neurologists confidence that they can actually trust that outcome and that result versus a PET. And we think that this is likely going to happen in the near term. Fujirebio has already filed.

We know there are a couple of others like C2N and Roche that are sort of working on these IVDs or in vitro diagnostics. And one was already filed -- Fujirebio filed last year. We believe that usually the time frame is about 6 months. I think the next stage will be generating data so that payers and others are confident that it can adequately represent the Medicare population, which tends to be the broader population. So I think concordance is important as is reimbursement.

But we think this is moving really fast, and we think we'll see quite a few milestones occur in the near term.

Operator Operator

The next question comes from Tim Anderson with Bank of America.

Timothy Anderson Analyst

On your spend guidance, you're saying $3.9 billion combined R&D and SG&A which is about $200 million lower than consensus. Revenues are also a little bit lower than consensus. So it offsets each other. My question is how much does the Royalty Pharma deal take out of the R&D line in 2025, specifically? I know it's $250 million in aggregate that they'll fund, but what's that relief to 2025 R&D?

And then on Royalty Pharma, can we expect Biogen to do more of these off-balance sheet types of transactions with pipeline programs over the next 1 to 2 years.

Michael McDonnell Executive

So Tim, Mike speaking. On the Royalty Pharma transaction, our current expectation is that the $200 million that we would receive in 2025 from Royalty Pharma would be accounted for as a reduction to R&D expense. So that would be a dollar-for-dollar reduction that's in the mix of our guidance.

Christopher Viehbacher Executive

Well, just in terms of other deals, the remuneration to those provided financing is usually through royalties. And it's not easy to make work for every product. So I think at the moment, we look at this as a one-off transaction. But it is a useful model to take risk off the table and be able to spread the investment across more assets. I mean it's essentially a way of getting more shots on goal.

Operator Operator

Go next to Brian Abrahams with RBC Capital Markets.

Brian Abrahams Analyst

On SKYCLARYS, can you elaborate a little bit more on the dynamics you're seeing in the U.S.? Like are there ways to accelerate patient identification to meaningfully grow revenue there? Should we be expecting this to more be an ex U.S. international growth product? And how are the hurdles in terms of reimbursement outside the U.S.

Christopher Viehbacher Executive

In the U.S., I think there have been already a number of creative approaches. One is using AI and looking across social media to be able to identify where patients are. As I said before, there's quite a large number of potential prescribers you could go to.

So the question is how do you zero that down to a geography and a type of physician that makes the visit efficient. And so say, we've used the AI. Obviously, as -- whenever you

develop a treatment for a disease, there's a greater interest in diagnosing it. And so I think one of the things that we're seeing is a much greater use of genetic testing. Genetic testing does have a cost and physicians have not always been interested in using it if it wasn't going to lead to a treatment.

But now that SKYCLARYS is there, we are seeing that increased utilization. The final thing is using multi omnichannel marketing to be able to reach physicians just to educate them about what is Friedreich's ataxia. There are also multiple ataxias out there. And so that's where the genetic testing can become important. But when you listen to the patient journeys, it can take often 3, 4 years before a patient gets a definitive diagnosis.

A lot of particularly younger people are just kind of thought to be clumsy for a period of time and then progressively lose mobility and it takes a while because there are a lot of physicians who've never even heard of Friedreich's ataxia, and so that's where the education is needed. I would say today with the technology we have, we have a lot of tools that we didn't have even 15 years ago. But it is still finding patient by patient. We look at how many patients we found every week. And then it's -- the reimbursement isn't really an issue in the U.S.

There are hurdles to it. This is where Biogen is particularly good. We have a very adept group that can help patients navigate the reimbursement system.

In Europe, I don't think we're necessarily seeing any -- going to find any issues of reimbursement. It's mostly getting through the whole process, presenting the cost-effectiveness data but we are very encouraged by the uptake. And once you have uptake, then that's a good demonstration of the value of the medicine when it comes to discussing things with reimbursing countries. So it will be progressive. I think there are 10 countries today in Europe, which we reimburse, and every quarter, we'll be adding more countries.

And the same will be true ex Europe, in Latin America, for example.

Operator Operator

We'll go next to Marc Goodman with Leerink Partners.

Marc Goodman Analyst

Could you give us a little more flavor on what's happening with SPINRAZA in the U.S. and OUS, just dynamics and how much inventory is mattering and what's happening with pricing? Just a little more color there.

Christopher Viehbacher Executive

I'll let Mike take the inventory question. SPINRAZA, so this is a very competitive market with a very limited number of patients. So you've got a gene therapy, an oral therapy and an intrathecal therapy, all competing for a relatively small patient number. There are actually quite a number of patients who have not been diagnosed or treated. So we tend to be in younger patients, but there is actually a much larger adult patient population.

And getting at those is a lot like the same process that I just described for Friedreich's ataxia. So we are doing that. So the interesting thing is how do you compete in a market like that?

And we've all grown up in this business and we say, okay, one pill a day beats 2 pills a day, a pill beats an injection. But the actual reality is in a lot of these devastating diseases, it's efficacy that matters.

And that's really the story of SPINRAZA.

The high dose, I think, will be important because you can get to the therapeutic levels of drug that you need much faster, and in a neurodegenerative disease, that's extremely important. So we will be able to cut the number of loading doses, if you like, from 4 to 2 and then you go to 3 injections per year. One of the things that I think will be important is we are developing a device that hopefully will hit the market about, I think, 2026, Priya. And it's a port that you can insert under the skin pretty much anywhere on the body, but certainly around the abdomen as an example and has tiny catheters that lead to the spinal column. And that means that you can actually just do the injection directly under the skin.

That has had huge patient positive response and that could actually make intrathecal injections a whole lot more patient friendly, not just in SMA, but pretty much for all of the intrathecal products that we're developing. So I think that one will also be a game changer going forward. And Mike, do you want to talk about the inventory dynamic?

Michael McDonnell Executive

Yes. And Mark, nothing to call out on inventory. We did see some lumpiness in SPINRAZA revenue throughout 2024 due to some shipment timing and so forth outside of the U.S. But the fourth quarter, the global 2% growth and the 6% in the U.S., nothing material to call out in terms of inventory or channel dynamics.

Operator Operator

We'll go next to Paul Matteis with Stifel.

Paul Matteis Analyst

Chris, if you take a step back now, you got to be at a point, I would think, with ZURZUVAE, SKYCLARYS, lecanemab to some degree, although maybe the variance of outcomes there is a little bit wider. Or at least for the next couple of years, you probably have a pretty good window into the range of outcomes for these products. So I guess taking a step back, do you feel like you can get back to sustainable revenue growth based on what you have internally and what you have high visibility into? Or how important, I guess, is getting a big upside win from the pipeline or buying growth externally via BD.

Christopher Viehbacher Executive

Right. Well, we've got about -- if you add in the everything, there's probably about $4.5 billion of revenue in MS left and probably about $3 billion of profit. So that's going to be the headwind over the next 5 to 10 years because actually, some of these products are actually quite sticky with patients because patients do well on these products and tend to stay on them. So it's a slower decline. So that's the problem we're solving for.

When you look at it, the #1 product that has the most potential to offset is that is clearly

LEQEMBI. And there, I think we are encouraged by the more recent results, and I think we feel pretty confident that these catalysts could offer the potential to see some acceleration of growth. So we do believe that there's a tremendous unmet need in Alzheimer's. People forget that this is a fatal disease. And when you look at the data that Priya showed, if you could get 76% of patients stabilized on this, this is -- this is data that I think we really need to do more of in demonstrating the value proposition of LEQEMBI.

So we have a number of different approaches. We've, I think, had extremely productive discussions with our partner, Eisai, on the commercial approach. And there was an awful lot of effort at the start, just to explain care pathways and the side effects and the reimbursement. And I think now we can actually focus a lot more on the value proposition and why treating patients. I think there's a huge opportunity in expanding the prescriber base.

We have focused on a smaller number just because of the effort involved by the neurologist. But I think with things like the subcutaneous formulations and the maintenance, we have an opportunity to go broader, there's about 13,000 physicians who are targets, and we have a small fraction of those today who are actually prescribing. So there's a lot there, and SKYCLARYS will continue to grow, as we said. ZURZUVAE is certainly an interesting, I'd call it kind of a 2-base hit in baseball terms in the U.S. Europe will probably be a more limited set of markets that will actually be able to reimburse this product.

I think we've got a lot that we can be doing. I think the real growth story is when you start to see the pipeline coming through because as the MS portfolio declines and the new products become a bigger part of the equation, then suddenly you add a pipeline product on top of that. And the nice thing about Biogen is that $1 billion really moves the needle. So we don't need a lot here to really have a meaningful impact on our growth. And so I think it's a combination of all of the above, Paul.

We will see an increasing percentage of our business coming from these new products and the pipeline can only augment that.

Operator Operator

We'll go next to Umer Raffat with Evercore.

Umer Raffat Analyst

I want to say thank you to Mike for all your help over time, and welcome to Tim. I have 2 questions today, if I may. First, maybe for Priya. In a scenario where Lilly hits TRAILBLAZER Alzheimer's 3 in preclinical on the progression endpoint, how does that factor into your thinking around how you could accelerate time lines for AHEAD 345? And also your comfort with the endpoint being used there.

And secondly, Chris, maybe a big picture question. It seems like with where the valuation stands today around $20 billion in market cap relative to the amount paid for Reata as well as the amount of balance sheet available for an additional deal coming up. I guess, market is almost reflecting somewhat of a view that the M&A choices in the last couple of years may not have been what market was expecting or perhaps the expectations were higher. I guess how do you think about all of that? And what learnings are you taking from that into additional

capital deployment?

Because it will be a very significant move if there were to be a $10 billion deal again.

Priya Singhal Executive

I can get started. Thanks, Umer. So I think, overall, we remain excited, as I shared in my prepared remarks about the potential for AHEAD 345. Just a reminder is that we completed enrollment last year. It's a 4-year therapy.

And so we expect -- and Eisai has recently actually reiterated the outcome expected in 2028. Now that said, we always retain and we always continue to evaluate optionality for earlier readouts and earlier cuts, and we continue to engage with regulators like the FDA very closely on this, and all of that is progressing well. Now the most -- so that's kind of the acceleration piece. I think the important piece here is the way we've designed the trial. It is quite specific for amyloid load.

And as you know, it's 2 sister trials, one with a lower amyloid load that's AHEAD 3 and then 4, 5, which is a higher amyloid load. Now in the AHEAD 3, we have a biomarker outcome, which is amyloid clearance essentially. But in the 4, 5, where patients have a higher load of amyloid, we are looking at a very important endpoint that's called the PACV, which is the preclinical Alzheimer's cognition composite. This comprises elements of memory, the intelligence test, MMSE and other components. And it is supposed to be quite sensitive and specific for preclinical AD.

TRAILBLAIZER III has different outcomes like CDR -- CDR global score and is also doing a time to event. So I think we'll wait to see more on how that unfolds. But I think we feel very confident about the design of this trial and what it can actually tell us about preventing or slowing down onset of Alzheimer's disease. Over to you, Chris.

Christopher Viehbacher Executive

Yes. I mean, Umer, look, there's a human factor here, right? One of the things I have seen over the years is that your interest in doing significant acquisitions is kind of inversely proportional to your level of confidence in what you've already got in your pipeline. So if you don't think you have a lot in your pipeline, you're more likely to be interested in spending more externally. And whether that's logical or not, it is tended to be where you are.

And I have to say coming into Biogen, we tended to go after the hardest problems to solve, where we didn't understand the underlying disease biology, where we didn't really have Phase II data that could really predict where we were in Phase III. And at that point, you sort of say, well, if you don't know what you've got, you're more interested in looking at things. I would say where we are now 2 years down the road is I think [Reata], with the [steely eye] has really taken a lot of the stuff out of our pipeline that either was never going to make it to market or if it did make it to market, it was never going to have much impact. And what we do have, and we've got more data now, gives us a whole lot more confidence. I mean, when you got a dapirolizumab now with a Phase III, I mean, litifilimab has advanced.

The HI-Bio acquisition, we see as pretty transformative for our pipeline because that is

exactly what we would like to see more of is data in Phase II that really gives you a sense of some level of conviction into Phase III recognizing that there are never any guarantees in R&D. So I think where we are is we could continue to do more of the HI-Bio type transactions. We actually like the Reata transaction. Maybe TheStreet had a different view, but I don't think theStreet really completely understand how some of these rare diseases really work. For us, over time, we believe that SKYCLARYS is going to be a significant product.

I think it is already a significant product. If we found another Reata where we -- you've got a product that is about to be launched on the market, and you could buy it for a price that generates a return for our shareholders then we would do it. But I think part of the problem is I don't think the people who are selling companies have quite integrated a lot of the pressures that are on this industry. The IRA is a de facto reduction in patent life for our industry, and there's a lot of pricing pressure from around the world. So the total commercial return for any one molecule today is not what it was even 5 years ago.

And yet, I don't see really any shift in the premiums being paid or the price being paid. And there's always an asymmetry between the products that you know and the products that you're going to buy. And so I think right now, we say we will look, if we could find another Reata, we would probably do it. We don't particularly want to do one deal that takes all of our cash flow because I think there is an interest in building the pipeline with multiple assets. If we could do more HI-Bios, that's probably a nice sweet spot for us.

We've kind of concluded that actually, we can probably manage quite nicely until the pipeline matures even further. So we don't feel any particular pressure to do things but I do think it's a job of every leadership person in this business to constantly look outside if we can find other sources of innovation. But I'm actually feeling very good about where Biogen is. Our share price may or may not reflect it, but I'm certainly not alone in this interest in thinking that the share price doesn't reflect where we are. And I think that's -- it's a function of a lot of the uncertainty around our industry.

But we are just keeping our heads down and executing on our launches and making sure these products get to market. And finding if there are shareholder value-enhancing transactions that can be done at pretty much any stage of the value chain.

Operator Operator

We'll go next to Chris Schott with JPMorgan.

Christopher Schott Analyst

I want to come back to the OpEx space. I know the company is wrapping up its Fit for Growth program and there's some moving pieces here with the Royalty Pharma deal. But as we think about the P&L going forward, is this kind of $3.9 billion or so OpEx space a good rough number to think about for Biogen going forward? Or is there any other color about how to think about margin progression as we think about the next few years?

Michael McDonnell Executive

Yes, Chris, I think that's right. The Fit for Growth program was designed to take our OpEx to a

level that supports our revenue expectations. And I think that as we exit 2025 and go into future years. Obviously, if we have launches to support and other things, we'll need to invest in those appropriately. But I think the way that you described it is correct.

And the program will be completed at the end of this year and the $3.9 billion base rate is a good a good number to use as your baseline model.

Christopher Viehbacher Executive

Yes. And clearly, business development, every time you do a deal, you bring in potentially new R&D expense. But I think what you've seen us do is prioritize. We've actually stopped a number of internal programs, which actually creates the financial capacity to bring other assets in.

One of the biggest problems of business development typically has been is that the R&D budget is full, and there isn't any room to bring in new things. Well, we are actually making some of those difficult choices and the same is true on research. We have dramatically reduced our research budget but the idea was not necessarily to just save cost. The idea was that we wanted a different mix in there. And by prioritizing, we can actually do business development without having to increase our overall expenditure, at least that's what we've been able to do so far.

Tim Power Executive

And then we're running short on time. Maybe to squeeze 1 or 2 last ones and let's go to the next one.

Operator Operator

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

Evan Seigerman Analyst

Mike, congrats on your retirement. You will be missed. Robin. I'm really looking forward to working with you. And Tim, congrats on your first Biogen earnings call, I got that all in.

I want to touch very briefly on the use of GLP-1s in Alzheimer's disease. Novo Nordisk has talked a lot about the EVOKE trial, high risk, high reward. What happens if that hits, and this could evolve the standard of care for the kind of prevention of Alzheimer's disease. Priya, would love your thoughts there.

Priya Singhal Executive

Yes. Thank you, Evan. It's a very interesting hypothesis. And it's supported by some preclinical data as well as meta analysis that was looking at all-cause dementia and then some subsets, which also had Alzheimer's disease. And really, the scientific hypothesis behind it is thinking through about how glucose metabolism or regulation of that can impact neuro inflammation, vascular health, all of that and contribute to kind of more brain health situation.

And I think that, that is a -- it's worthy of exploring. I mean -- I think we need to remember that some randomized controlled trials have failed in the space, Takeda with pioglitazone and then

actually Novo with liraglutide, small trial, 72 subjects, the ELAD trial, they didn't meet their primary endpoints. That said, I think we look forward to seeing the outcomes. What I think is really important to continue to remember is that when you're tackling something like Alzheimer's disease, you need to tackle the central pathology. We also note that the central pathology is not an overnight buildup, but build up over years.

So for that reason, we continue to believe that an anti-amyloid agent like LEQEMBI that really addresses plaque, but continues to address soluble toxic species after plaque clearance will have an important role to play. So I think we're looking forward to the results of EVOKE and EVOKE+ just like everybody. But I think we continue to believe that this is going to be -- LEQEMBI is going to play and continue to play an important role.

Operator Operator

Our last question comes from Phil Nadeau with TD Cowen.

Philip Nadeau Analyst

Let me add our congratulations to Mike, Robin and Tim on their transitions. Just to drill down on the LEQEMBI short-term trajectory a little bit more closely. In Q4, revenue was up 30%, but the revenue recognized was only up $1 million. Can you talk about the dynamics behind that? Were there onetime issues?

Or is there an increase in spend that we should project into 2025? And looking at 2025 trends, growth in 2024 was largely driven -- not entirely driven, but largely driven by ex U.S. Is that replicable in 2025? Or are the low-hanging fruit of those markets already picked?

Christopher Viehbacher Executive

Well, I think LEQEMBI in the U.S. was certainly up 200% Q4 on Q1. And so we are seeing significant growth in the U.S. Yes, the ex U.S. has certainly been strong as well.

But I think it's both. So I think for 2025, in the absence of anything else, we see pretty much continuing trends would be our best guess at this. There may be some acceleration with the IV maintenance but we're not going to get the subcutaneous for maintenance until really in the last part of the year. Blood-based diagnostics could play a role, but we all know that it takes a while to get diagnostics to be actually accepted and reimbursed. So I think we're going to just see good, steady progress quarter-on-quarter.

There hasn't been that much impact of yet on donanemab. That could have a role at some point, but I think they're dealing with the same issues that we are. I think the big thing is really to, as I say, to expand the prescriber base. I think really focus on the benefit of treatment and roll out these new formulations. So I think it's going to be continued progress.

We obviously continue to believe that Alzheimer's can be a significant market, and that's why we're investing not only in tau, but in other modalities. The unmet need is incredible, 500,000 new patients every year. It's one of the leading causes of death. Certainly amongst over 65 year olds, but it's even a top 10 cause of death just in the general population. So not to mention the devastation that this causes to family.

So the unmet need is huge. It is clear that in the short term, we have a lot of capacity constraints, but I think we've made a lot of progress in relieving some of those. And so I think now with these new formulations such as subcu and with the blood-based diagnosis, we have an opportunity to accelerate our growth, I would say, over the next 2 to 3 years.

Michael McDonnell Executive

Yes. And Phil, on the numbers, just to reiterate something we said in the prepared remarks, the LEQEMBI fourth quarter end market revenue was $87 million globally. That's up about 30% sequentially from the third quarter of 2024. In the U.S., it was, of the $87 million, $50 million in the U.S., and that's up about 28% sequentially.

Tim Power Executive

Thanks, Mike, and thanks, everybody, for your time today. The IR team is available if you've got questions later today. Thank you.

Operator Operator

This does conclude today's conference. We thank you for your participation.