Biogen Inc.

Biogen Inc. - Q3 2024 Earnings Call

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Event Participants

Executives 5

Stephen Amato, Christopher Viehbacher, Priya Singhal, Michael McDonnell, Alisha Alaimo

Analysts 10

Brian Abrahams, Philip Nadeau, Marc Goodman, Salveen Richter, Michael Yee, Umer Raffat, Jay Olson, Evan Seigerman, Paul Matteis, Terence Flynn

Operator Operator

Good morning. My name is Cynthia, and I will be your conference operator today. At this time, I would like to welcome everyone to the Biogen Third Quarter 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 Dr. Stephen Amato, Senior Director of Investor Relations. Dr. Amato, you may begin your conference.

Stephen Amato Executive

Thank you. Good morning, and welcome to Biogen's Third Quarter 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 have also posted the slides on our website that will be used during this call. On today's call, I'm joined by our President and Chief Executive Officer, Chris Viehbacher, Dr. Priya Singhal, Head of Development; Mike McDonnell, Chief Financial Officer; as well as our Head and President of North America, Alisha Alaimo who will be available for Q&A. We will make some opening comments, and then we'll move to the Q&A session. To allow us to get through as many questions as possible, we kindly ask that you limit yourself to 1 question.

I will now turn the call over to Chris.

Christopher Viehbacher Executive

Thank you, Steve. Good morning, everyone. I'll start first by thanking you, Steve for stepping up as interim Head of IR and done a great job of preparing us for this quarter. Also earlier this week, we announced the retirement plans of our CFO, Mike McDonnell, and also the appointment of his successor, Robin Kramer. But Mike is still very firmly in the saddle as CFO, and we will be recognizing his significant contribution to Biogen with the fourth quarter earnings call later.

So I think Biogen has made significant and very strong progress over the last 2 years. And I do think the company is well positioned for the future. Our launches are progressing well with good sequential quarter-over-quarter growth. Our cost base has been significantly reduced, but more importantly, a value-for-money approach to spending, I think, has been embedded in our culture. The acquisitions we've done to date have been well received and are already creating value.

And I think we have a strong late-stage pipeline emerging. So if we turn first to the launches, let's start talking about LEQEMBI. Now although LEQEMBI revenue in the U.S. continues to be below the expectations of our collaboration and the prescriber base is not expanded to the extent that we had anticipated, global revenue still grew by 66% in the third quarter as compared to the second quarter. And we've got continued uptake outside the U.S.

and new prescriber growth of nearly 40% in the U.S. The collaboration continues to refine the commercial strategy, and we are seeing benefits from an increase in our sales force, really who started out there in the field from first of September. And we continue to evaluate opportunities to potentially accelerate our business. Now we've continued to see some health care systems who are treating expand and extend and extending their treatment sites in the U.S. And more recently, we're starting to see large infusion networks activating in high-population geographies to help absorb patient demand.

We've been encouraged by the rate of uptake outside the U.S., including Japan, where revenue nearly doubled from the previous quarter. And I think there's been terrific launch activities in particular, Japan and China. It does seem like a single payer system has also enabled that kind of growth. And overall, we expect continued sequential growth quarter-on-quarter for LEQEMBI over the near term. We believe there are a few future potential catalysts that could accelerate uptake, including the potential availability of IV maintenance as soon as next year, a subcutaneous formulation for maintenance and eventually induction and more widespread utilization of blood-based diagnostics.

Just to underline how much of a lift this is for physicians, some of you may have noted an opinion piece in JAMA Neurology, dated October 14, that was written by Katherine Possin of UCSF, Jeff Burns at University of Kansas and Brent Forester at Tufts. They talk about the unprecedented time of advances. But equally, they say the challenge and the importance of translating scientific advances in diagnostics, treatment and care into practice in a timely and equitable manner cannot be overemphasized. Innovation at the clinic health care system and policy levels is necessary to equitably translate advances at scale. So we continue to believe that this is going to be an important market.

But again, we don't believe that we have a demand issue. It is just taking the health care system time to actually adapt to treating this number of patients. Turning to SKYCLARYS. We

saw increased demand globally as we broadened our footprint, particularly in Europe. SKYCLARYS is now generating revenue from both commercial and other paid mechanisms in 15 markets outside the U.S.

This includes a number of countries in the EU, where we are seeing increased demand quarter-over-quarter. Now at this point, I'd like to say there is a difference between how we generate revenue in the U.S. and how we're seeing demand develop in Europe. In the U.S., our revenue is rising at the rate we find patients. In Europe, we are actually already out there commercializing the product.

And we have a number of early access programs in place. But the strategy for a lot of products in Europe is to get patients on board while you're negotiating with governments to get reimbursement. And at some point, then the governments reimburse those patients and you have an immediate population of patients ready to go because they are already on treatment. So when you're looking at the progression quarter-on-quarter, the ex-U.S. piece is not going to be a reflection of growing demand, but it's going to be a reflection of at what point in time do we get reimbursement for governments.

But I can tell you that we are adding patients every day, every week in Europe at a pace that has exceeded our expectations. Now we are looking to expand access to more patients, and there are now 11 regulatory filings that have been submitted globally. So we're looking now beyond the U.S. and Europe, and they could start generating revenue as soon as next year. ZURZUVAE continues to outperform our expectations commercially in the U.S.

where we saw $22 million of revenue in the third quarter, and that's an increase of 49% over the second quarter, driven in part by a 40% increase in patients this quarter. I think the team has done an outstanding job with this launch. In all of the cases we've been talking about, LEQEMBI, SKYCLARYS and ZURZUVAE. I'd just remind everybody that these are not pre-existing markets. We are building these markets in each case.

And that always takes longer than having incremental innovation where you go in and you just are looking to take some market share from a pre-existing market. So if we could change the slide, Steve. Our goal is really for sustainable growth. And the short-term and there's medium-term growth. When I came to the company, I had really 3 major objectives.

One is to put Biogen back onto a sustainable growth pattern for revenue to build a pipeline that can sustain that growth for Biogen well into the 2030s and also to build a pipeline of leaders who will take this company to even more success in the 2030s. So as we look at the pipeline, I have to say, I think we are very excited about what we see emerging. Again, we are Biogen, we don't do incremental innovation. But I think there are some really interesting products that we feel very good about because unlike a lot of products in the past with Biogen, where we go into Phase III and we don't really know whether they're going to work. I think we've seen an awful lot in biomarkers, in data and other indications that suggest there's a -- we have a growing conviction in these assets.

So BIIB080, one of the things that excites me is that although this is an intrathecal as Priya will say, we recruited early on this one and were finished recruiting. And to me, as someone who's had commercial experience over 35 years, when I see a clinical trial recruiting early,

particularly in a competitive space where they're existing therapies, that augurs well for the product downstream. Dapirolizumab, we saw positive Phase III results, and I'd like to congratulate Priya because Priya had already thought about this and it's worked with UCB and there's actually a Phase III protocol ready to go. And so we'll be starting Phase III very soon. Lupus is an area of huge unmet need, and we have not only dapi, but we have litifilimab in 2 indications.

And behind that, we have also felzartamab actually in lupus nephritis. In felza, we had some very encouraging data at San Diego in IgAN, and we've had breakthrough status on AMR. This is a game changer for us in terms of our pipeline because, again, here, we've got Phase II data that look very compelling. We all know that there are no guarantees in pipeline development. But at least we have, I think, reason to believe that these products could come to market and make a big difference.

And as we start to look at the peak revenue for each of these products, the cumulative of all of these, if they all actually made it to market and got approved, have peak sales cumulatively of about $14 billion. And when you consider that our pharma business today is about $7.5 billion, this late-stage pipeline could really transform Biogen over the longer term. But I shouldn't really be talking about pipeline. The real expert is Priya. So with that, I'm going to turn it over to Dr.

Singhal.

Priya Singhal Executive

Thank you, Chris. Over the last 2 years, we have focused heavily on augmenting our pipeline, as Chris noted, with an eye towards transforming innovation into novel and impactful medicines. As a result, I believe our current pipeline has several programs that are both supported by encouraging clinical data and have the potential to deliver meaningful value to patients. This includes dapi in SLE, litafilimab in both SLE and CLE, felzartamab in multiple immune-mediated diseases, and our tau ASO BIIB080 in Alzheimer's, as Chris suggested. While advancing these programs remains our top priority, we are also working to implement acceleration strategies across the broader portfolio to expedite decision-making while continuing to focus on execution.

An important example of this is BIIB080, where we recently completed enrollment in the amended Phase II trial design and now expect a readout in 2026. Additionally, with the positive Phase III results last month, we are moving very quickly with our collaboration partner, UCB, to initiate a second Phase III study for dapi in SLE this year. We are also implementing innovative new clinical development strategies to enhance clinical execution and accelerate cycle times. This includes initiatives like using AI to help optimize clinical trial participation and site selection. In parallel to these efforts and aligned with our ambition of continuing to build the pipeline, we are working also with our research and corporate development colleagues to evaluate external innovation opportunities across the development stage and several indications.

Overall, we believe that through these objectives, we have the opportunity to execute on a meaningful opportunity that Chris has laid out for Biogen. Turning to the quarter. I would like

to begin with Alzheimer's, where we are working with Eisai to continue generating important insights on LEQEMBI in early AD. This includes areas like long-term treatment effect and real-world evidence, such as that presented at CTAD, but importantly, we are also working to provide optionality for patients. Encouraged by data showing expanded benefit with continued LEQEMBI treatment and beyond just the removal of plaques, we continue to pursue maintenance storing options.

We expect regulatory decisions on maintenance dosing for both the IV and the subcutaneous auto-injector next year in 2025. Furthermore, the AHEAD 3-45 study, evaluating the ability of LEQEMBI to prevent or delay Alzheimer's in preclinical or presymptomatic AD enrolled well, and we just completed enrollment this month in October. I look forward to us providing updates as this trial advances. We are also working to expand our leadership by advancing novel treatment approaches, including shuttles across different disease states and targets such as tau with BIIB080. Moving to immunology.

We believe we are building an industry-leading late-stage pipeline comprised of programs with established proof of concept. These programs cover a range of immune-mediated diseases that are characterized by significant unmet need. This includes our recent acquisition of felzartamab, where we expect to initiate 3 Phase III studies next year in AMR, IgAN and PMN while continuing to evaluate other indications where this mechanism of action may be relevant. Additionally, we have multiple programs in SLE where it is estimated that over 3 million individuals worldwide are affected and current standard of care are associated with suboptimal efficacy and various treatment-related toxicities, leading to lasting negative consequences such as organ damage. SLE is also the #1 cause of death in women aged 15 to 24 in the U.S.

and treatment options for before, during and after pregnancy are limited due to safety concerns and contraindications for most common therapies. Underscoring the potential of our immunology pipeline, we are pleased to report that the Phase III study of dapi plus standard of care met the primary endpoint, showing a statistically significant greater improvement in disease activity as assessed by the BICLA endpoint at 48 weeks versus placebo plus standard of care. Importantly, we also saw clinical improvements on key secondary endpoints assessing disease activity and flare prevention, 2 areas that represent key treatment goals for the management of SLE. Following the prior Phase II study, Biogen, along with our collaboration partner, UCB, spent time analyzing the results in an attempt to design and derisk a Phase III study and demonstrate a potential treatment effect. These learnings, combined with our understanding of the underlying disease biology inform the design of the Phase III study which included updated screening criteria to ensure patients had active disease in need of a biologic therapy on top of standard of care.

The success of this approach is punctuated by the fact that dapi is only the third molecule to show positive Phase III results in a global study in SLE over the last 20 years. We look forward to presenting detailed results from this Phase III study as a late breaker at the ACR annual meeting next month, and together with UCB, expect to initiate the second Phase III study this year. Turning to SMA. Our priority has always been on continuing to improve outcomes for patients. We were pleased to present detailed results from the DEVOTE study evaluating the investigational higher-dose regimen of nusinersen at the World Muscle Society meeting

earlier this month.

The higher dose regimen consists of 2 50 milligram loading doses followed by 28 milligrams maintenance doses every 4 months. This regimen of high dose delivers more drug in the first administration than the entire 2-month loading phase of the approved SPINRAZA 12-milligram regimen. Consistent with the more rapid loading regimen, higher-dose nusinersen, slowed neurodegeneration faster than SPINRAZA 12 milligrams as measured by neurofilament at day 64, an objective biomarker. The pivotal infantile onset cohort in Part B of DEVOTE, met the primary endpoint of change from baseline to 6 months in the CHOP INTEND compared to the pre-specified matched sham group, demonstrating a clinically and statistically significant improvement. We also observed trends in reduced risk of death or permanent ventilation versus both sham control and the currently approved regimen.

In addition, we shared initial results from the open-label Part C portion of the study with participants aged 4 to 65, transitioning from SPINRAZA 12 milligrams after an average of nearly 4 years on treatment. This group showed improvement in motor function after transitioning to higher dose. These are exciting results as we seek to help patients currently on disease-modifying therapies. Importantly, the high dose regimen was generally well tolerated and showed a safety profile similar to the approved 12-milligram regimen. We believe these results highlight the unique potential of SPINRAZA to help address remaining unmet need in individuals with SMA, and we aim to submit global regulatory filings later this year.

In conclusion, this past quarter, I believe we continue to execute well and achieved several important development milestones that highlight the potential of our pipeline to deliver meaningful new therapies to patients. In addition to late-stage readouts in lupus and SMA, we also submitted ex U.S. filings for zuranolone and PPD and obtained approvals for SKYCLARYS and QALSODY in Switzerland and China, respectively. We also presented new data insights across multiple disease areas, at multiple medical meetings, including Alzheimer's, neuromuscular and renal disease. Today, we believe that the pipeline is well positioned to deliver a regular cadence of pivotal readouts and potential launches.

We continue to aspire to bring transformative medicines to patients' lives while we deliver on Biogen's objective of achieving sustainable growth. Furthermore, I believe that the same core capabilities and deep disease area expertise that enabled us to reshape our current pipeline and establish leadership foothold in areas like Alzheimer's, immunology and rare disease also uniquely position us to evaluate external innovation as we look for opportunities to augment our pipeline. With that, I would now like to hand the call over to Mike for a financial update.

Michael McDonnell Executive

Thank you, Priya, and good morning to everyone. I'd like to provide some color on our third quarter results and all the comparisons that you'll hear me make are versus the third quarter of 2023, unless you hear me note otherwise. Total revenue for the quarter was $2.5 billion. Both total revenue and core pharmaceutical revenue were down 3%. Non-GAAP diluted EPS was $4.08 and that's down 6%.

In just a moment, I'll provide some additional detail on some key dynamics to note from the

third quarter. Non-GAAP operating income increased 4% versus the third quarter of 2023 as we continue to benefit from our R&D prioritization and Fit for Growth initiatives. We are pleased to again be raising our full year 2024 guidance range. And in just a few moments, I'll provide some additional color on our raised guidance range for 2024. Few comments on revenue for the third quarter.

Our MS product revenue declined by approximately 9%, and that was driven primarily by competitive dynamics in the space, along with some channel dynamics. Importantly, we announced last week that the European Patent Office upheld the validity of Biogen's TECFIDERA-related patent covering DMF dosing, which expires in February of 2028. We are pleased with the decision. However, generics are challenging this patent, and we do anticipate further challenges. TYSABRI has seen impacts from a biosimilar entrant in Europe, and although a biosimilar is not yet launched in the U.S., we continue to see increasing competition in the high-efficacy class.

Next, our rare disease franchise produced revenue of $495 million, and that represents growth of 10%. The SKYCLARYS launch continues to progress in the U.S., where revenue of $82 million increased 8% from the second quarter, and that was driven by increased demand. SKYCLARYS is now generating revenue in 15 countries outside the U.S. with third quarter global revenue of $102 million. This was up modestly from the second quarter, driven by an increase in demand, and that was partially offset by some pricing and reimbursement dynamics in some newly launched markets.

Global SPINRAZA revenue of $381 million declined $67 million or 15% and that was impacted by the loss of an annual tender in Russia, which resulted in an unfavorable impact of approximately $45 million in the third quarter. It is important to note that this tender which occurs and contributes to revenue only once each year affected Q3 2024 results, but we do not expect further revenue impact for the rest of this year. The global decrease was also impacted by the timing of shipments and some foreign currency. SPINRAZA U.S. revenue was up 2% to $153 million, and we remain encouraged by the performance here.

ZURZUVAE delivered $22 million of revenue in the quarter, and that's up 49% from the second quarter, and we continue to be encouraged by an increase in demand. We again saw sequential growth for LEQEMBI with third quarter global in-market sales booked by Eisai of approximately $67 million, and that's up 66% versus the second quarter. LEQEMBI in-market sales in the U.S. were $39 million, that's up 33% versus the second quarter. And finally, contract manufacturing, royalty and other revenue was $250 million.

That was notably lower year-over-year as expected due to the completion of certain batch commitments in 2023. Now I'll turn to a few comments on third quarter expenses. Non-GAAP cost of sales as a percentage of revenue decreased 2 percentage points, and that was driven primarily by product mix, particularly the year-over-year increase in revenue from new product launches and the decrease in contract manufacturing revenue as well as lower idle capacity charges. Non-GAAP R&D expense decreased $48 million as we continue to see benefits from our R&D prioritization initiatives. Non-GAAP SG&A expense increased 1% in the third quarter as benefits from our Fit for Growth initiative allowed us to absorb most of the $45 million of incremental costs in the third quarter associated with our launches.

We continue to believe we can garner $1 billion of gross and $800 million of net savings associated with our Fit for Growth initiative by the end of 2025. Non-GAAP EPS was $4.08 in the third quarter. EPS was unfavorably impacted by certain non-operating items, including a decline of approximately $80 million of net interest income on lower cash balances as a result of the Reata and HI-Bio-acquisitions. This was partially offset by some favorable tax items in the quarter, which added about $16 million to our net income. Now a brief update on our balance sheet.

We ended the quarter with $1.7 billion of cash and marketable securities and approximately $4.6 billion of net debt. We were able to generate approximately $901 million of free cash flow, and that was our highest free cash flow since the second quarter of 2021. Third quarter 2024 free cash flow benefited in part from some favorable working capital dynamics. We continue to believe that our balance sheet remains strong and provides us the capacity to continue to invest in both internal and external growth opportunities. Turning now to guidance.

We're pleased that the business performance year-to-date, again supports raising our full year 2024 non-GAAP diluted EPS guidance range from between $15.75 and $16.25 to a new range of between $16.10 and $16.60. This new range reflects expected growth of approximately 11% at the midpoint of the range compared to full year 2023. I'd like to highlight a few of the key assumptions relevant to this guidance. First, on the top line, we continue to expect that our total revenue will decline by a low single-digit percentage. And as we've communicated throughout the year, we expect to continue to ramp investment behind our new product launches and key R&D programs which includes felzartamab following our acquisition of HI-Bio.

And lastly, as is typically the case with our business, we expect seasonally higher SG&A spend in the fourth quarter as compared to the rest of the year. I would refer you to this slide as well as our press release for other important guidance assumptions. In closing, we remain focused on advancing our ongoing product launches and key areas of our late-stage pipeline. We believe our efforts in these areas will help position Biogen for long-term sustainable growth, which continues to be our #1 goal. And with that, we will open up the call for questions.

Operator Operator

[Operator Instructions] Your first question comes from the line of Brian Abrahams with RBC Capital Markets.

Brian Abrahams Analyst

I'm curious on LEQEMBI, when you might expect to see more pull-through from the expanded commercial efforts, whether you're starting to see any of those signals in October. And you mentioned as well the potential for some other commercial acceleration strategies in your prepared remarks. Can you maybe expand on that a little bit more and characterize your overall alignment with Eisai on the commercial plans?

Christopher Viehbacher Executive

Yes. I'll take the second part of the question, Brian, and then pass it over to Alisha who can give a little more color on the expanded field force. I think we have learned an awful lot really in the year since we launched the product. I mean, the product launch really started really last fall, I mean we had to get all of the commercial team in place, but we also needed clarity around things like reimbursement of the PET scans. So for us, I think this is about the anniversary really of the launch.

And there are a lot of things that we are now understanding the time it can take for IDNs to really get their protocols in place and the care pathways. But there are also a number of things like who's the right patient? And we have also an awful lot more data coming along. We're going to have the subcutaneous formulation, hopefully, next year for maintenance, the IV for maintenance sometime next year. And so it seems opportune for the 2 partners now to come together and just review what's working well and what could we be doing more?

So we'd probably be able to give you some more color on that. I would say the teams are working very well together. We both understand that this is a very complicated launch. I think more complicated than most that I've certainly seen, I think, most people have seen. And yet, we do see a lot of physicians, again, who are really putting an awful lot of work in to make all of this happen.

To triage the patients as to who's really the right patient, a high percentage of patients coming into the neurologists are not eligible for treatment. Then organizing the PET scans and the lumbar punctures, the MRIs and the infusion beds. So we've seen an awful lot of real effort out there in the marketplace, and we add prescribers every week and we see more sales every week. And so I think that's the way it's going to progress probably until we get the subcutaneous for induction. I think that could be quite a game changer.

And again, more use of the blood-based diagnostics in place of the PET scan. Both of those would, I think, dramatically reduce the workload of physicians.

But Alisha, maybe you can talk about the expanded field force and anything else you think might be helpful.

Alisha Alaimo Executive

Thank you, Chris, and thank you for the question, Brian. As all of you have seen in Q3, we did have steady launch progress as we've seen in prior quarters. And that's including in the new number of patients. Also encouraging what you don't see in the trends that we're able to see is the total prescribers writing and actually in Q3 the new number of writers increased by 40% versus Q2. So you are seeing these physicians come on every single week, IDNs expanding every single week as well.

However, at the end of the day, just like in the beginning of the launch and even today, fast forward after we've been out in the field for a while, what shows up in market research is the key barrier is still these infrastructure challenges, as Chris alluded to. However, now with the new Biogen team on Board, we're also able to confirm that, especially with physicians who haven't written yet, that is really one of their main concerns. Our second concern, of course, is still ARIA, even though it's not as big of a concern as it was prior. However, once they work through some patients and they work out their protocols, you do see that alleviate. However,

we now have our full field force out there.

And as a reminder, we were very intentional as an organization as to who to hire. We were in a little bit of a luxury situation at the time. When we posted these roles, we had over 1,000 applicants and we only had a little over 25 roles that we had posted. So we were really able to pick those individuals who either had history in Alzheimer's disease or a history in these territories and already had built in relationships. And so now the teams have been out there for several weeks.

We are starting to see in the offices specifically where Biogen has overlaid with Eisai, where we are engaging, we do see a little bit more accelerated growth than what you do see in the rest of the nation. We're able to reach more targets and also, doors are opening up a little more easily for us because, again, those representatives did have prior relationships with physicians. And so in the longer term, we obviously are going to continue with doing frequency in depth. But at the end of the day, for example, we can say in the Pacific Northwest, we had a rep that's been had a relationship that actually prior with MS for 17 years, they're able to help the physician right away. Another physician in the Southeast, they had a relationship over 20 years, they were able to unlock over 30 patients, I think, in less than a 2-week time period.

So the relationships we've seen has mattered. Also the history has mattered, and we are starting to see some acceleration, even though they've only been out there fully for about a month or so.

Operator Operator

Your next question comes from the line of Phil Nadeau with TD Cowen.

Philip Nadeau Analyst

Chris, you've referenced the subcutaneous formulation a couple of times already this morning. Could you give us a bit more of an update on the status of the subcu filings both for maintenance as well as for induction?

Christopher Viehbacher Executive

Sure. I'll turn that over to Priya.

Priya Singhal Executive

So we remain on top to really complete our subcutaneous maintenance filing as Eisai has indicated, and we expect that to be imminent. And then moving on to the initiation, we are working to generate the data, analyze the data. This is part of the Clarity open-label extension study in the subcutaneous sub-study. And as Eisai has indicated, we remain on track to expect a regulatory outcome on subcutaneous initiation therapy by Q1 of 2026 calendar year.

Operator Operator

Your next question comes from Marc Goodman with Leerink.

Marc Goodman Analyst

Could you comment a little bit more on SKYCLARYS o U.S. There was a comment in the opening remarks about pricing and reimbursement dynamics. And if you could just give us a little more color there to the challenges.

Christopher Viehbacher Executive

So as you know, you get approval in Europe, but then you have to go country by country to negotiate for reimbursement. And basically, what we are already doing is seeing physicians, and we're getting patients on treatment. But the actual revenue generation of those patients varies by countries. So there are some countries, for instance, where you can charge for an early access program. There are countries where you can't, there are some countries where you can get reimbursement much earlier than other European countries.

So we are in that process. What we have not done is really started the revenue generation -- sorry, the patient demand generation with reimbursement. We are active in all countries and signing up patients. And so we're tracking patient numbers, which are growing considerably every month. What you will see in the quarterly revenue numbers is when those patients convert to revenue-generating patients.

And that is, by definition, going to be a little lumpy because the patient demand is actually in advance of when we generate revenue. And on the -- on those programs where you have early access that you can pay for, you have to establish a price. But in some cases, there is a clawback if the reimbursed price is going to be lower than what the prices you're charging. And obviously, as we go into countries and have a better idea where the price point is, we've had to make some adjustments on revenue that we have booked and those programs where we can charge for an EAP. And that's just really a normal process in most launches in Europe.

Operator Operator

Your next question comes from the line of Salveen Richter with Goldman Sachs.

Salveen Richter Analyst

Chris, you spoke to the efforts with regard to the late-stage pipeline in R&D, but you've also noted the lever with regard to business development. Any updated thoughts here as to the strategy for the latter on the forward?

Christopher Viehbacher Executive

I mean we're in one of those classic situations in our industry where we've had a legacy portfolio of assets that is facing increased competition. And on the horizon, we see an extremely promising pipeline and how do you bridge across that. And some companies choose to simply wait that out and wait for the arrival of the pipeline. And our business is likely to grow between now and 2028, but I would say that the growth is not necessarily satisfactory for us. So we are looking and continue to look, I spent personally quite a lot of time on this.

Are there assets that we could bring in that could enhance our revenue growth in the near

term but also that still create value for shareholders. We're not really interested in just buying revenue. If we can buy growth, and we can make a very good return on investment, then we'll do so. But as you know, assets get pretty highly priced as they get close to the market. So you have to do an awful lot of digging and an awful lot of looking, and that's what we are doing.

We have a whole team of people that look at both public and private companies. And I think we still have considerable financial capacity. And Mike, you may want to comment on that. But we are active in that, but we are also disciplined fiduciaries of shareholder money. I've always said we get paid to make our shareholders wealthy, not somebody else's shareholders.

Michael McDonnell Executive

Yes. So Salveen, just on capacity, just to give you a frame of reference. We ended the quarter with about $1.7 billion of cash on hand. And when you think about our capital structure, about $6.3 billion in total debt on an EBITDA run rate of about $3.3 billion to $3.4 billion. So it's below 2x gross, that's a very modest amount.

And when you think about capacity, we're pleased with about $2 billion of free cash flow year-to-date, $901 million in the quarter. So with a couple of billion dollars plus of free cash flow per year and less than 2 turns of gross leverage, you can see over the next couple of years, if you added a reasonable amount of incremental debt at some point in time plus the free cash flow and the cash on hand, there's comfortably $8 billion to $10 billion of capacity that you've got over the next year or 2 in order to collaborate and transact and look at acquisitions and other things that we can do to help supplement our growth.

Operator Operator

Your next question comes from the line of Michael Yee with Jefferies.

Michael Yee Analyst

We noticed that you completed the enrollment of the AHEAD 3-45 study. And I just wanted to ask Priya,if you could remind us what the timeline would look for that, more specifically, if there is a potential for an interim analysis and/or what that would be based on? My understanding is that these are pretty early presymptomatic patients. Is there an enrichment of the population? And why would you be expecting that this can be positive?

Priya Singhal Executive

Thank you, Michael. Yes, we're excited about the fact that AHEAD 3-45 has completed enrollment in October. Just to remind everyone, it's 2 trials, and 1 is really looking at early intermediate stages -- patients with early intermediate stages of amyloid and the other is with higher load amyloid. And these are very large trials, so it's about 400 patients in the AHEAD 3, which is the earliest intermediate stage and about 1,000 patients in AHEAD 45 and the timeline, the trials have a 216-week time point. Having said that, we are continuing in parallel to engage with regulators and look at all options of when these might be ready to read out.

So we'll continue to provide more updates, but we're very excited about having completed

enrollment, specifically because the data that we've shared from the Clarity study shows that treating early and with patients with low tau or no tau, really, you see a lot of benefits in terms of stabilization and actually even clinical improvement. So it continues to really be a very exciting space for patients to have therapies, and that's why we're very excited about where we are today.

Operator Operator

Your next question comes from the line of Umer Raffat with Evercore ISI.

Umer Raffat Analyst

I thought I'll focus on a slightly different topic for a quick second. It does look like there's a very significant amount of R&D investment going into lupus between your dapirolizumab as well as your BDCA molecule and possibly the CD38 as well. And I guess my broader question is this. You hit a Phase III, which is obviously good news. But separately, we're seeing incredible remission data from some CD19 CAR-Ts, which might even possibly manifest in some CD19 bispecifics as well.

So it seems like you have a lot of exposure, not on that area, which is CD19 bispecific. And I guess, how should we weigh by the time you guys do get to this market relative to some of the emerging data from potentially CD19 bispecific or the T cell engagers?

Priya Singhal Executive

Yes, we continue to watch the innovation in the space, and it's exciting for patients. But I think when you step back and you think about the potential that dapi can offer, and with the data that we shared and we'll be sharing more data at ACR in a few weeks here, and it is embargoed, we're very excited by what we've seen in this moderate-to-severe population. So just stepping back, when you look at SLE, it is really a chronic disease, very heterogeneous, high global burden of disease, specifically in women and underserved population. And we believe that many options will be required. So I think while the bispecifics and the CAR-Ts may show efficacy in small population, we've got to keep in mind that these are very small data sets and likely may not be relevant to the entire population.

And I think that here is where the scientific hypothesis and continuing to generate data sort of in Phase II that makes us believe that we could have a high probability of success in Phase III becomes really important. And with dapi, we're really addressing and inhibiting the CD40 ligand, which has the ability to reduce B and T cell activation, downregulating interferon pathways. And then with litifilimab, we're going after the type 1 interferon signature and really looking at inhibiting BDCA2 in the plasma delta itself. So we believe that this is going to be really important and probably many options are required, but we remain really optimistic about the data that we've seen so far and the momentum that we have with our trials. So we continue to be believers in these pathways and these programs.

With litifilumab, as you know, we're also addressing cutaneous lupus where really there has been no innovation in 70 years. So again, we have high scientific conviction, as Chris mentioned, and we'll continue to prosecute these.

Christopher Viehbacher Executive

And I'll just add, Umer, I was at GSK when we were developing BENLYSTA over 15 years ago, and we almost killed that program because of modest efficacy until we realize that everything else was failing, and this was the last product standing. And to date, only 2 products have been approved. Dapi would be the third. And I can tell you, over the years, we've seen an awful lot of data in small populations as Priya has said. And so I think we have to wait and see who actually gets to the finish line.

On CAR-T, some interesting data, but the logistics of CAR-T are not yet such that you're going to be seeing significant numbers of patients being treated, in my personal opinion. So I think as Priya said, there's a need there today. We have a product that has demonstrated results, we're going full speed ahead. And just given the nature of this disease, I think you're going to find that there's not going to be any 1 product that ultimately is a winner. It's going to take different approaches.

Operator Operator

Your next question comes from the line of Jay Olson with Oppenheimer.

Jay Olson Analyst

Congrats on the quarter. We're curious about the $14 billion of peak revenue potential from your 4 key pipeline programs. Can you talk about the relative contribution and timing of the 4 products in terms of which ones are the largest and nearest term?

Christopher Viehbacher Executive

Well, I don't want to get into giving individual revenue forecast. I think the idea was to give a sense of what's the magnitude of the pipeline. We all know that not everything can always succeed. But I do think if you look at where are there going to be significant programs. If you look at BIIB080 in Alzheimer's, we do believe, and I think Biogen is not the only one.

I see Lilly and Roche continue to invest significantly. You've seen AbbVie lay out quite an awful lot of money for a very early-stage asset in Alzheimer's. So I think we all believe that as the health care system is ultimately able to adapt to the significant demand for treatment that this becomes an important market. And what we can see, and I was just at a major world-class medical school last week, spent a day there with a lot of researchers in Alzheimer's. They are excited about tau in a way that we have not seen always at Abeta.

Alzheimer's severity really varies with the level of tau and people really believe -- a lot of people in the field really believe that going after tau will really have a significant benefit for patients. So we do think that BIIB080 is certainly a product with a tremendous amount of potential. And as Priya said, we have dapi, but we also have litifilimab and also felza in lupus nephritis. So we do see that lupus is going to be a significant market. And again, you look at you look at BENLYSTA that is selling at about $3 billion a year.

And then there's an AstraZeneca product that hasn't done as well, but you look at the numbers of patients, this is still a market where there's considerable room for expansion. In felza, we have 3 Phase III programs going in, and we see all of those 3 indications as being a

significant opportunity. So again, you add them up. $14 billion is kind of like the top number, but somewhere between $9 billion and $14 billion is what our teams have estimated. Again, we have to wait and see what the clinical trial data looks like in the actual profile.

But if you look at the potential of these markets and the unmet need and the potential for differentiation, we're becoming increasingly excited about this emerging pipeline.

Operator Operator

Your next question comes from the line of Evan Seigerman with BMO Capital Markets.

Evan Seigerman Analyst

I know in the past, we've talked about the potential for SPINRAZA returning to growth. Given the softer numbers this quarter, can you just talk about how you think that this is achieved. Is it predicated on high-dose nusinersen? Or are there other factors and levers that you can pull to accelerate -- reaccelerate the growth of this product?

Christopher Viehbacher Executive

Well, so globally, actually, if we take out some of the onetime effects of -- or sort of the exceptional effects of the ex U.S., ex European markets, actually, we did see a growth for SPINRAZA. It's clearly a very competitive marketplace. And -- but it turns out that even though we have an intrathecal administration, that efficacy is really what matters in really severe diseases. And that's what we compete on. We had a study that has demonstrated, for example, the benefit of adding SPINRAZA on to Zolgensma as gene therapy.

And we know that the oral therapies have limitations in terms of which patients can be treated. I think that our teams believe that DEVOTE is extremely important because we can get to the -- through the loading doses and get to the right level of therapeutic benefit faster than we could previously. And that actually reduces the number of intrathecal injections at least for the loading phase. So I think this is really an efficacy gain, but I'll ask Alisha, at least from a U.S. perspective.

How you see that?

Alisha Alaimo Executive

SPINRAZA has really been a very strong contributor, especially in the U.S. business. So when you look at rare disease, we believe that SPINRAZA has really set that benchmark for what really excellent efficacy looks like and that it translates down to a patient. And so growth year-over-year, which my team has seen, and even that's during a time we've had 2 very strong competitors. We had an oral launch during stay-at-home orders and the team is still really leading the way with SPINRAZA.

And we do believe it's for a few reasons. One, the efficacy of the product is obviously very strong. And a lot of our growth also comes from switchback. There's a lot of patients that are returning back to SPINRAZA once they've switched away to a competitor, and they realize that maybe the efficacy isn't there. And so we do see quite a bit of that in the U.S.

And secondly, you fast forward 8 years, we are still finding new patients in this space, and

that's with 3 major biopharma companies putting money into this rare disease. And so you do see new patients still coming online. And we believe at least on the Biogen side, we are very good at patient finding. We're able to find them quite quickly. We have an excellent AI sort of machine that we use along with the field force.

We're able to locate them in centers of excellence and physicians are able to reach out and find these patients. And so with high dose coming, one of the pieces of feedback you do get from physicians and patients is, we just wish we had more. And so with that, we're preparing right now for that, obviously, the filing and the potential approval going into label, and we do believe that high dose will also support growth quarter-over-quarter, year-on-year for at least the U.S. organization.

Operator Operator

Your next question comes from the line of Paul Matteis with Stifel.

Paul Matteis Analyst

In connecting some of the dots here, Chris, as it relates to the hires you've made and some of your portfolio decisions around certain legacy high-risk assets, it feels like more and more Biogen is bolstering its expertise in neurology and maybe shifting away from neurology. Is that the right way we should think about things going forward? In other words, when you look at business development, do you have any appetite any more to take on risk in neuroscience? Or do you feel like immunology, rare areas that you have a lot of experience with historically are going to be the sweet spot going forward?

Christopher Viehbacher Executive

I would say, first, we're already long in neurology and neuroscience. I mean we have very significant investments, obviously, with the BIIB080 program, continued significant investment in LEQEMBI. We're still spending hundreds of millions of dollars every year on the LEQEMBI R&D. And we have actually a number of programs coming behind that in early-stage development. We're working on brain shuttle technology, but looking at other modalities in Alzheimer's, we still have earlier-stage programs in MS and ALS, a significant program in Parkinson's in partnership with Denali.

So I think we see neuroscience as somewhere where we already have a significant commitment. But to me, I think it's not a good idea to just be in 1 therapeutic area. And in addition, I think we actually already have capabilities beyond neuroscience, the whole MS franchise is really an immunology franchise. You treat MS through the immune system. And I do believe we have an awful lot of immunology capability and that certainly gave us the confidence to do the HI-Bio acquisition.

I&I, I go to a number of biotech conferences and venture conferences. I&I has now become the second most important area in R&D after oncology. And so you're going to have an awful lot of emerging opportunities for BD in this space. Biogen has a tremendous capability in small volumes and high-value products, highly differentiated scientific cell. And I think immunology fits that build.

Rare disease is really more of a commercial description than a scientific one, but we do have a commercial model in rare diseases that has an awful lot of capability that not everybody does. And so expanding into that area with that commercial model almost being, I would say, indication agnostic is an area that we can go. And I don't think we're stretching our capabilities. There are some capabilities that we have to build. And in some ways, Fit for Growth was as much shifting some of the focus away from a traditional heavy focus on MS and being able to adopt some of these other capabilities.

But I wouldn't -- we don't really want to get into those areas where we'd have to go up against really large pharma companies in the commercial model. We're not really into incremental innovation in Biogen. So I feel pretty comfortable that we can expand our horizons in certain areas of immunology, probably more related to rare diseases and neurological conditions in immunology, not necessarily things like RA or atopic dermatitis. But we have a legitimacy to play there, and we have the capability and we can really take advantage of a lot of the really smart people within Biogen.

Operator Operator

Your next question comes from the line of Terence Flynn with Morgan Stanley.

Terence Flynn Analyst

Mike, I was just wondering if you can help us think directionally about margins for 2025 and some of the puts and takes.

Michael McDonnell Executive

Sure. And I'm going to assume, Terence, that you're referring primarily to our operating income margin. But I think we've made really good progress. The improvement in the third quarter, it was a little bit less than what you've seen. There's a little bit of lumpiness to it.

And I think it's probably -- and some of that was driven by the revenue dynamics that we talked about in the quarter and some of the higher margin revenue like SPINRAZA and SKYCLARYS. But I think if you look at it on a year-to-date basis, that's probably the best way. We're 7% up year-to-date on the operating income line, a 7 percentage point improvement, I should say, it's 23% growth year-on-year. In our guidance, we talk about mid-single-digit improvement for the full year and high-teens growth for full year. And I think that we feel good about the improvement that we've made.

We still feel confident that we can garner the $1 billion gross and $800 million net savings, which will continue to help our margins. And we're not guiding beyond this year, but as we exit 2024 and head into 2025, I think it's important to remember that we've said that the $800 million of savings we expected to get half of that by the end of this year and the other half next year. So that will continue to improve our margin profile as we go.

Stephen Amato Executive

Thank you, Mike, and thank you, everyone, for joining us today. Of course, the IR team will be available to answer any additional questions. Thank you.

Operator Operator

This concludes today's call. Thank you for your participation. You may now disconnect.