Novartis AG

Shareholder/Analyst Call - Novartis AG

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Event Participants

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Sloan Simpson Executive

All right. Good morning, everyone, and welcome to the 2024 Meet Novartis Management Event. Thank you so much for your time, your engagement, your interest, as always. This is a special event for us, which we've actually been doing since 2014, someone reminded me of that at dinner last night, because it gives investors and analysts the opportunity to really engage with management across the company in an open Q&A format. Today, we'll have a presentation by Vas, followed by breakout sessions with Corporate and our 4 core therapeutic areas.

Before we get started, I'll read the safe harbor statement. The information presented today contains forward-looking statements that involve known and unknown risks, uncertainties and other factors. These may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. For a description of some of these factors, please refer to the company's Form 20-F and its most recent quarterly results on Form 6-K that respectively were filed with and furnished to the U.S. Securities and Exchange Commission.

And with that, I will hand across to Vas.

Vasant Narasimhan Executive

Thank you, Sloan, and thank you as well for everyone joining here live in London, and also joining on the webcast. This is a special event for us. It's a great opportunity to exchange openly with our investors about where the company is and where we're going in the future. I'd like to take a few moments to give you an overview that I think hopefully will inform the

conversations over the rest of the day, including our financial outlook, but as well as going into quite a bit more depth in each of our therapeutic areas, because we hope to focus today's conversation very much on our mid-stage pipeline, emerging technologies, so all of you can get a better sense of how we'll continue to grow Novartis into the next decade.

So first, starting with a little bit of history. As you all know, we've had quite a transformation over the recent years. Beginning in 2018, actually even before that with the exits of a few other businesses, but in 2018, we divested our GSK -- consumer stake (sic) [health] JV stake to GSK. A year later, we did our tax-free spin of Alcon to all of you, and Alcon continues to perform extremely well. We exited our Roche stake at a very attractive valuation and bought back our own shares.

We announced a new simplified organizational structure, which is really helping us drive our commercial performance. And then we had the successful spin of Sandoz, and we're very happy to see how well Sandoz is doing as a stand-alone entity.

Taken together, that allowed us to become a pure-play innovative medicines company. And despite the market pullback over the recent weeks, this number was a little bit bigger a few weeks ago, but we see a significant value creation and market capitalization increase of the combined entities. And with Novartis as a stand-alone company, we're already larger than where we were when we had 4 businesses back in 2018. I think that shows that the strategy is working, but also we've been able to unlock value for our shareholders in creating 4 companies from what was once one.

Now when you restate our financials back to 2018 as a pure-play innovative medicines company, I think we've demonstrated the consistent performance that I'm sure all of you would like to see from us. When you look at our sales on an innovative medicines company, 7% CAGR and the low double-digit growth that we've guided to in 2024. When you look at our core operating income, 14% CAGR, and again, high teens growth we've guided to for this year. And then from a margin progression standpoint, 990 basis points up on that core Innovative Medicines business. Now we've guided, of course, to the high 30s.

And as you all well know, we're well on track and continue to commit to getting to the 40% plus range by 2027. Now importantly as well, one of the things we've been wanting to improve is our cash flow generation, which enables us to, of course, both grow our dividend, buy back our shares, and invest in the business, but also our return on invested capital. Now here, you see our free cash flow going back to 2018. This is including the full business, excluding Alcon, which was just a few hundred million dollars back in those 2018, 2019 period. And you can see already in 2023, as a pure-play innovative medicines company, we're generating more cash than we did as a combined business.

And you can see the cash flow generation power now of the organization. 9 months in, we're at $12.6 billion. Our cash flow as a percent of sales now is at 34%. So the engine is really working to generate cash and then, of course, deploying that cash either to the business or to all of you as our shareholders. Importantly, as well, as a stand-alone pure play, and as we continue to drive up that core margin and stay disciplined on the balance sheet, you can see that the return on invested capital is at 12%.

We expect that to continue to go up. And based on what we can see and the visible consensus, we think we can get into the top quartile of our peers in terms of return on invested capital over time.

Now when you think about our strategy, we remain committed to the focused strategy that we outlined a few years back at our Meet the Management Day. We continue to believe it's the right thing for us as an organization to focus on 4 core therapeutic areas, the 2 plus 3 technology platforms, 4 priority geographies, which I'll talk more about, and then continue to think about accelerating growth, high-value medicines, continue to strengthen our foundations. We have a big focus on culture in the organization. We think that's paid off over time.

We make strategic bets on data science and AI, and I'll cover that from R&D in a little bit. We're a real sector leader now in ESG. You saw just yesterday, we were the #1 company in the Access to Medicines Index. And then we want to keep driving that productivity. We think low 40s is a reasonable place for us to be from a margin standpoint, but that doesn't mean we won't keep driving productivity and keep looking to be as efficient as possible as an organization.

Now briefly touching on capital allocation, and this is something we've been trying to be as consistent about as possible. We continue to make our investments in the organic business. But importantly, there's no change to our M&A strategy. We stay very consistent in our belief that we can generate the most value when we acquire assets primarily in the sub-$5 billion space. When you look at our recent deal track record, it's primarily in the sub-$1 billion space.

We think deals in this area where we're mostly betting on preclinical Phase I and Phase II assets, where we have a differentiated view versus the market based on our understanding of the science, that's where we have the opportunity to create value. We look at the $5 billion to $10 billion, selectively look at the larger deals. But if you think about the last 8 years, only 1 or 2 -- really 2 deals that we've done in that larger space. And then we're going to stay consistent with that in the future.

We also remain committed and we've continued to grow that dividend in Swiss francs independent of the spin-offs that we've made. And we also stay committed to share buybacks. When you look at that cash flow generation, we have the ongoing share buyback right now, $7 billion still to be executed through next year. And we have the firepower to continue to not only do M&A, but also maintain the dividend and do share buybacks where appropriate. And I think that's very unique for us to be able to have that ability to do all 3 and not have to make trade-offs.

As you know, we are unchallenged from a balance sheet standpoint and have very good discipline on maintaining a strong balance sheet.

Now looking at the profile of the company more broadly. When you look at our in-market and pipeline portfolio, you can see we have 13 in-market large blockbuster plus medicines. You can see also that we have 8 in-market brands now with over $3 billion peak potential. I'll go over each of our peak sales guidance in a bit more detail in a moment. One important element of our story often, of course, there is a desire to have very large medicines in a

portfolio.

But part of the reason Novartis has consistently managed through expiries, LOEs, and we'll do so again next year with Entresto, is only 13% of our sales are tied to a single product. We're a low binary risk organization. We're able to manage through these patent expiries given the diverse portfolio that we have.

We have 15-plus submission-enabling readouts, which I'll go through in a moment, 30-plus high-value medicines, which you'll learn more about over the course of today. You know well our 5 platform technologies. And when you look at our geographic profile as a business, we have increased our U.S. share of our global sales, now 40% U.S., 60% ex U.S. We remain the #1 company outside of the United States and continuing to move up in the U.S.

with very strong performance from our U.S. organization, but still time and work to do to get to the top 5. But very good growth in each of our core markets, Japan now back to growth, and we believe our Japan organization has the opportunity to double its business in the coming years. Strong performance in the U.S. and China.

I also wanted to say a word about our R&D transformation and how that's actually having an impact on how we invest in the business. Over the last 3 years, we've done a lot of work to focus the R&D organization. You all know well that the historical data shows that Novartis has been pretty consistent as a leader in the number of drugs that are approved, but rarely in the top quartile or top half in the value of those medicines. We took that data to heart and really wanted to rethink how we approach our pipeline. So we've made a significant reduction, nearly 40% reduction in the number of projects, clinical stage projects in the portfolio.

That is also the case in research, where our research teams have been much more disciplined about which projects they want to focus on, focusing on high-value medicines.

That's allowed us to increase our research resources per project. What that means is more chemists, more biologists, more expertise on each one of those assets to hopefully get them to move much quicker to the clinic. At the same time, we continue to grow our development spend on fewer clinical assets. That allows us to do more life cycle management, really maximize the medicines, and you've seen that with some of our recent launches like iptacopan. And overall, we continue to believe we're making the right investments in the development organization.

We've committed to over $400 million in technical development. This is primarily new capabilities in radioligand therapies, RNA therapeutics, cell and gene therapeutics, and novel format biologics, so bispecifics, trispecifics or biologics tied to another agent, so a biologic tied to an ASO or an siRNA. We'll talk a bit more about the investments we've made in AI and data science.

And the other thing we've worked on is to really optimize the global footprint to say how can we go faster on the clinical trials, especially given the arms race we're in with our peers to really get these trials fully enrolled. We also continue to believe we have the right game board that we use with RLT cell and gene on top of our core platforms of chemistry and biotherapeutics. We do reevaluate this. We do want to make sure with emerging technologies that are out there. Certainly, we have a position in ADCs.

We're thinking about gene editing and some of the other newer technologies that are coming out. But given the global scale we have and the opportunity to apply these technologies in our core therapeutic areas, we think it's the right approach. We continue to invest. And we also know it takes consistency. We know in the past, when we've gone in and out of technology platforms, you haven't fully realized them.

So the hope is to stay consistent over time and really get the benefits of these technology platforms.

So I did want to now come to our outlook and guidance before going into a bit more detail. You've seen in this morning, I hope that building off that 7% sales CAGR in Innovative Medicines, we've upgraded the '23 to '28 guidance to 6%. That's on the back of the launches, which I'll go through in a bit more detail. 5%, '24 to '29. So even with the Cosentyx LOE, expected LOE in that '29 time frame, we expect to continue to be able to grow given the momentum we're seeing in the business and the mid-single digit beyond that.

And what really underpins our confidence is derisked in-market brands that give us that '24 to '29 CAGR. Many of those brands with LOE going into the next decade, which gives us, again, confidence we can drive those brands to higher and higher levels. And then a reasonably broad and I think broadening late-stage asset portfolio. And that's what we hope to highlight to you all today.

So now going into all of that into a bit more detail. Now just to formalize the guidance. And here, you can see what I just said, 5% constant currency growth, 40% core margin. I do often get the question about the core margin and where do we think that might go. Certainly, we see in the productivity programs that we have and with the sales growth we're seeing, the margin will, I think, continue to go up from that 40% plus.

One thing we want to, of course, make sure of is that we're fully invested in R&D, fully invested in marketing and sales.

And if the trade-off is to push the margin even higher versus making those investments, we're prioritizing now making those investments to drive more top line growth. And I think once we get to that 40% plus, that's going to be the mindset that we take. Of course, we don't want to waste money. If we have the opportunity through productivity to go higher, we certainly will. But the focus will get much more now into investing for longer-run growth commercially and from a pipeline perspective.

When you think about how the dynamics will work in this 5-year period, we do know, as always, in our sector, we do have some important LOEs coming up, up through 2029. Entresto in the U.S. being most notable. I think a few things to note on that. One, uncertainties continue to guide to the mid-2025; 3 different cases that are unfolding.

We'll see how each of those cases unfold and understand better then as we go as to when exactly the Entresto might come in, in the United States. Promacta and Tasigna, we feel reasonably confident in our mid next year guidance, but it will depend on approvals. And of course, we can't predict exactly when the competitors will come in. And then what we would characterize as relatively smaller LOEs. So I think a manageable LOE portfolio for a company of our size.

And then the large in-market growth drivers in the base business, which I'll go through each in a bit more detail in a moment. And then a probabilized pipeline. I think it's important to note that we have the opportunity to outperform if our pipeline delivers. And right now, we continue to probabilize remibrutinib, Zolgensma in IT, atrasentan in renal diseases, ianalumab in a range of diseases, and pelacarsen. So we don't count on that to deliver the 5%.

And I think that's important to note and it gives us the opportunity to overdeliver. And you can see the power of the company when we do have pipeline assets hit with the 10% and 11% growth we've seen in the recent years.

Now one of the things that gives us a lot of confidence in making the guidance upgrade and seeing the momentum in the business and the improvement we've seen in commercial execution at Novartis. I think one of the big reasons for that has been the changes we've made with the Transforming for Growth program, where we dramatically simplified the organization, focused on 4 TAs, really differentially invested in our key markets, and then really improved our launch execution. And that's what this chart is really about.

Today, with Kisqali in the U.S., we're at 47% NBRx, a leader in the metastatic breast cancer. But in the first 3 weeks of the early breast cancer launch -- first 2 weeks, we reached 27% NBRx. And I can say that, from the preliminary data we see exiting in October, we're already approaching market leadership in NBRx 1 month in on the early breast cancer indication. So that gives you the sense of how well we're actually seeing the trajectory right now for Kisqali in early breast cancer. We'll, of course, have to see how that holds up.

But if we're already now approaching 50%, 51% plus in these early days, that hopefully bodes well for that brand.

When you look at Cosentyx in hidradenitis, 62% NBRx share against a very established adalimumab competition. We believe we have the right profile even with the competitor approval yesterday. We think when you look at our overall data set, our safety, our pain profile, our ability to manage flares, we can maintain a really healthy market share in a very large and growing market. Scemblix, a leader already in third-line CML. Now with the first-line indication, an opportunity hopefully to drive to even higher share over time.

Fabhalta, we're now the market leader in NBRx and for PNH. That's less than 1 year since launch and against some very, very entrenched competition. So I think our U.S. organization has done a terrific job launching that brand. Now Pluvicto, well, of course, we would like to see the sales trajectory continue in the post-taxane setting.

We are at 35% market share now. And I think against some pretty tough competition actively working against us and have the opportunity to reaccelerate that brand with the upcoming approvals.

And then outside of the United States, we continue to make steady progress, #1 player in Europe, #4 in China, #4 in Japan. Opportunities now with some of our portfolio launches in Japan and China to build out those businesses to be even larger over time. So I think this shows that our commercial execution is really very strong right now in the organization. And that's what gives us confidence to upgrade many of our peak sales guidance. Now Entresto, we are annualizing right now at $7.5 billion.

We're leaving our peak sales there at $7 billion plus given the uncertainty we currently have on exactly when the LOE might happen. With Cosentyx, we upgrade to $8 billion plus, annualizing this year right now at $6.8 billion, 28% growth. Importantly, we'll have 2 more readouts for Cosentyx in 2025. So assuming an LOE in 2029, we feel comfortable with an $8 billion plus guidance now on Cosentyx.

With Kesimpta, we're already annualizing at $3.4 billion. We currently don't see any biosimilars in the clinic. So depending on how things work out, we may not see competition for this brand from biosimilars until the early 2030s, we believe perhaps beyond the 2031, 2032 time frame. So we upgrade our guidance there to $6 billion plus on Kesimpta. Also noting that the BTK inhibitor class, we'll see how our data and Roche's data bear out, but may not be the same competitive threat that we originally thought when we gave our first guidance.

Kisqali, we upgraded to $8 billion plus. This is on the back of already seeing NBRx share leadership in metastatic in many parts of the world. And now with the early breast cancer trajectory, we're seeing the strong data we have in the node-negative patients and the node 1 patients with lower risk factors and the strong uptake we're already seeing in the United States. We feel confident in that upgrade. Pluvicto, we didn't give, I think, formal guidance, but we give $5 billion plus at the moment.

We always thought that the VISION population, where we already have approval, would be in the $2 billion range. We think with PSMA4, PSMA addition, the oligometastatic setting, we could at least get to that $5 billion. And we'll see over time how we can reevaluate that.

Leqvio, we're giving now our first peak sales guidance on Leqvio, and we do believe we can get now to a $4 billion plus over the life cycle of this brand. We do have LOE protection into 2036 to 2038. We are more confident than perhaps in the past that we might be able to get IRA relief at least for this segment or also the 9 to 13 fix more broadly given the current constellation in the U.S. And then Scemblix and Fabhalta, we maintain our $3 billion-plus guidance that we've given historically. But I think this gives us a nice portfolio of brands with exclusivity in the 2030-plus time frame.

And then when we go beyond that, we feel confident as well that we have some interesting assets that we are going to read out in the near term. Remibrutinib, we're on track to file. This is our BTK inhibitor for CSU, and then hopefully to expand into additional indications over time. We do think the CSU market might be undercalled and that if we can get an oral agent out for patients who have really a symptomatic disease, and this oral agent can address those symptoms in a relatively rapid time frame, that could be really attractive. When you look at the biologics taking 16 weeks or beyond, within 2 weeks, you get the itch relief with remibrutinib.

Pelacarsen, our IT with SMA with Zolgensma and ianalumab, and I'll come back to these in a moment as well. But I think 4 more assets that we think can drive significant multibillion-dollar potential as well over time.

So when you look at our upcoming submission-enabling readouts, I think there's a lot of commentary, does Novartis have enough catalysts? We, of course, don't design our pipeline around generating catalysts. But we are thinking about how we can consistently get to

important readouts over time. And you can see we do expect the SMA readout before -- in this year. Important there is we use the gold standard Hammersmith score, and we think we can be one of the first agents, hopefully, to show gold standard Hammersmith improvement versus placebo for these patients.

And even as a late entrant in the 2-year-old plus category, hopefully compete with the 2 other competitors in adult and childhood SMA.

The IgAN portfolio continues to progress with atrasentan and zigakibart. We do expect the atrasentan approval in 2025. And we do currently think, based on the earliest reads that we have, that we can manage this label to not have a liver REMS, which would give us an opportunity to really enable atrasentan to become a significant medicine. Fabhalta, as I mentioned, doing extremely well. We do expect -- we do have confirmation of a priority review for C3G for Fabhalta.

And I think that demonstrates the power of this brand. That would be its third indication, and then 2 additional readouts in 2026.

Remibrutinib, I mentioned CSU and CINDU. MS also on track. We'll see. I think, of course, with the failures in the space, we are more muted on this, but we'll see how it goes. Ianalumab, multiple readouts in 2025 and 2026.

Importantly, the Sjogren's readout would give us an opportunity, we think, to have one of the better medicines to treat Sjogren's disease. Pelacarsen, I think of high interest, and I hope many of you got tested last night, and I hope all of your scores are very low. But I think it's an opportunity again to be the first-in-class agent. And so we'll see how that reads out, but everything is on track from an event -- it is an event-driven study, so we'll have to see how the events accrue in 2025, but it's a great opportunity for us.

Cosentyx, 2 additional readouts, GCA and polymyalgia rheumatica, could give us additional energy behind that brand. Pluvicto, I mentioned. And then lastly, and I think importantly, what's often missed with Leqvio is we do have the first readout in 2026 of our outcome study. And as a reminder, it has probably been lost. Our outcome study is designed differently than the monoclonal antibody outcome studies.

Those were done over a 2- to 3-year time frame. We followed these patients for 5 years. And that gives us the opportunity to hopefully differentiate with a more significant cardiovascular risk reduction. If that bears out, that, of course, would give us the opportunity to differentiate, particularly in outside the U.S. markets, where for Leqvio right now, it's a pretty much 50-50 split between U.S.

and ex U.S. in terms of our sales base.

So now turning to beyond 2029, which I know is of high interest, because I think that's one of the key questions, and understandably on investors' mind, is you have all of these opportunities through the end of the decade. What is going to refill the pipeline of such a large biopharmaceuticals organization for the next decade? And that's where we're hoping to focus a lot of the conversation over the course of today.

So we went through the pipeline and really asked ourselves, where do we have significant opportunities, knowing, of course, there's risk. Many of these things, more than 50% of the things on this slide will not work, just to set expectations. But we do have many, I think, really interesting shots on goal. And so what we tried to highlight here is over 30 assets or categories of assets, which I'll go through in a bit more detail in the next few slides, that are assets that are either in Phase II or Phase III or entering Phase I with interesting data. And what we'd like to give is more clarity on when we see the next derisking event or the next informative data set in many of these pipeline assets, so all of you can get a better sense of how we're progressing in each of our core therapeutic areas.

So starting with immunology. So in immunology, as you'll have an opportunity to talk to talk to our team later, we have a very clear focus, of course, on some very large areas like psoriasis, psoriatic arthritis as well as emerging programs in atopic dermatitis. But the other shift we make in immunology is to focus much more on specialty immunology, areas where we think there's less rebating pressure, less payer pressure, opportunity for us to differentiate. You know well our anchor assets, we are very focused on immune reset, as I'll go through in a moment, and our bispecific and trispecific antibodies.

So the Cosentyx 2 readouts I've mentioned. One additional point on remibrutinib is we do have a hidradenitis suppurativa program. The notion here is as we build out the capacity in Cosentyx to address this disease, could we come up with a safe oral medicine that would be able to be used for the broader population of HS patients and then, of course, graduate to a biologic. You know that dermatologists prefer to use oral medicines when they can. So that's an important program.

And then we also continue to progress food allergy. On each one of these slides, you have the next milestone status. I won't comment on each one. But hopefully, that gives you a sense of when you could expect to see additional data that can support.

On ianalumab, in addition to Sjogren's disease, as I mentioned, we do have lupus nephritis and SLE, both with readouts in 2027. That gives us 3 readouts within the immunology space. We also expect this has the opportunity, as I'll show in oncology, to also address ITP. But also here as well, we do hidradenitis suppurativa in Phase IIb. So that will give us another biologic.

So the idea is we do think HS is a large and growing opportunity. And having, in addition to Cosentyx, 2 additional assets in the pipeline could be very attractive. And then systemic sclerosis, a more rare condition, but again, an opportunity to build out the portfolio for ianalumab.

Now on the immune reset portfolio, we continue to advance YTB, which is our rapid CAR-T, in a range of indications to hopefully capitalize on the opportunity to reset severe patients' immune systems and eventually become one of the leaders in tackling immunological conditions for these patients. Our SLE and lupus nephritis first study is actually fully rolled. We've got the initial data. We will plan to present that in the first part of next year. And then the full readout -- so that's the Phase I study, we do expect the readout of the pivotal Phase II study for that in 2026.

I think for each one of these, the question will be what is the evidence base FDA will require

for an approval? Will they want a large Phase III or will a randomized Phase II be enough if the data is compelling. And I think it will be very much data-driven. In parallel to that, we are actively recruiting Phase II studies now in systemic sclerosis, in myositis, and in ANCA-associated vasculitis. So that gives us, I think, a pretty good coverage.

There's a few other indications in the early stage in Phase I, not listed here, that we're looking at, really with the goal to say how broad can we go with YTB. One of the other things you probably want to discuss with our team is where can we go in terms of less onerous myeloablation or bone marrow ablation protocols to make the medicine more accessible. And then lastly, some emerging programs in IL-15 monoclonal antibody. This was recently acquired, which we're taking into a range of different indications. We have a big T-cell engager program to look at can we reset the immune system through bispecifics and trispecifics.

And then a bispecific antibody program looking at can we do better than the very high bar that dupilumab has set in AD and related conditions.

So moving to cardiovascular disease. I mentioned Leqvio, you all know well pelacarsen, maybe a few other assets in the mid-stage, which, again, high reward, high risk. One is our LTP001 SMURF1 inhibitor for pulmonary arterial hypertension. We know there is an approved asset right now, but the idea is can we have a better profile with this medicine. So that's currently advancing in a Phase II study.

We do have an siRNA in hypertension that is now also advancing into later-stage studies, QCZ. Multiple assets in arrhythmia. So we continue to think that arrhythmia is a broad area, undertreated at the moment with an opportunity for hopefully better medicines.

And then we also have our inflammasome portfolio. You know well with the CANTOS study, we have a lot of expertise in understanding how the NLRP3 inhibitors and related mechanisms can impact cardiovascular disease, something we're looking at. We have a broad portfolio of siRNA assets, I think worth discussing, trying to cover the full range. And the idea with these siRNA assets is can we life cycle manage Leqvio, can we life cycle manage pelacarsen, and can we get to deeper and better cholesterol control and cardiovascular risk management with that siRNA portfolio.

And then I think one of the important things to note here is our big commitment to renal disease and how we're really trying to build out a renal portfolio, given now we have a field force targeting nephrologists in the U.S. and now over time around the world. So atrasentan, I mentioned; iptacopan, I mentioned; zigakibart, which I think while not having the optimized profile overall versus -- from a dosing standpoint, we hope we can show very robust efficacy and safety. And then as a company that's then bringing the full portfolio to nephrologists to really maximize this brand.

We do explore iptacopan in additional indications in the Phase II setting. We do have an ATP modulator TIN816 in severe kidney -- acute kidney injury, which would be an interesting opportunity. And then a really broad early renal portfolio, both in-house as well as through a spinout we recently created in the Pacific Northwest. But the idea is, can we cover the target space within renal disease to ensure we own this space as best we can in the future.

So moving to neuroscience, neurodegeneration. I think the areas we've worked on, we've

worked on for many years, multiple sclerosis, neuromuscular disease, neurodegeneration. We are now, I think, at a place where we think our gene therapy capabilities and the capabilities we brought in-house with the various vectors from REGENXBIO and other partners will allow us to solve the biology that we did solve with Zolgensma, but then struggle to solve for other monogenic or polygenic neuromuscular diseases. We continue to also look at xRNA. We think targeting siRNAs into neural tissue is a really attractive opportunity.

We acquired a company, DTx, which has a lipid-based approach to targeting siRNAs.

We continue to look at transferrin and other approaches to also try to make sure we're at the cutting edge of hitting these targets in the brain. And then, of course, immune reset. So remibrutinib, we discussed; iptacopan, we also take into myasthenia gravis, so that is in a Phase III study. So I mean, that now is, I think, the seventh or eighth indication for Fabhalta, demonstrating the approach we have now as a company to fully maximize the assets in the pipeline.

We do have YTB as well now moving forward in 3 neuroscience indications. So relapsing MS, PPMS, so also very severe patients, and also severe patients with refractory myasthenia gravis. So again, that brings us, I think, to 7 or 8 different trials now for YTB to really maximize the immune reset portfolio.

SMA IT, we discussed. We are very interested in FSHD, DM1 and the other muscular dystrophies, but really thinking about how can we learn from the experiences of the first wave of companies that have had failures and perhaps some success with targeting these diseases. So we announced this morning, we have acquired Kate Therapeutics. This is a gene therapy company that we think has really solved some of the challenges of delivering the right targets or the right genes for patients with FSHD and DM1, and we'll see how we can also broaden that capability to help our own pipeline also advance in the neuromuscular space. We also have EDK060, that's the DTx asset I mentioned earlier, which we're also now advancing into the clinic.

And then we have the portfolio of high-risk, high-reward assets in neurodegeneration, our partnership on Parkinson's disease, our tau ASO, which is also targeted with an antibody into the CNS, our TREM2 inhibitor, which we take into ALS as well into Alzheimer's. So that gives you kind of a sense of where we are in neuroscience, and I think also an opportunity to discuss with our team future directions that we are looking at in this space.

And then lastly, importantly, oncology, where here on this slide, we've divided it by therapeutic area. There was a lot of questions last night about radioligand therapy. And of course, our goal is to own radioligand therapy for the long run. I'll talk more about our scale in that space in a moment. But you can see on the upper right, the cancers we're targeting, our anchor assets.

Most of our technology platforms, RLT, CAR-T, bispecifics, ADCs can be applied to oncology. But a few points I wanted to highlight on the oncology portfolio.

First, there's often questions about what are we doing to ensure Kisqali is ready for potential combination partner assets. And we do have an ongoing collaboration with an oral SERD for Kisqali to generate that data. And many other companies are using Kisqali as well as their

partner agent. So we feel confident that the oral SERDs will have data with Kisqali. And given where Kisqali is from a market share standpoint should put us in a good position to be the preferred partner agent.

We also have a partnership to look at Kisqali plus a mutant selective PI3K.

You do likely know we did test Kisqali with Piqray. Toxicities were a challenge. But we continue to want to be open and aware of where that space might head. And then importantly for us is that third line, which is our next-gen CDK asset portfolio. So we are working hard now to enter the clinic with CDK2 inhibitors as well as other assets in that same CDK2 line or combinations that will allow us to life cycle management of Kisqali.

We've, of course, scoured the biotech space as well, but we continue to believe our in-house assets right now have the best profile to take forward.

And then within the breast cancer space, 3 RLT programs, [indiscernible], FXX as well, which we'll talk about in a moment. That's our FAP, our fibroblast activation protein RLT, and then a number of emerging RLTs as well. Pluvicto, you know about the pre-taxane. We have the hormone sensitive. We're moving into the oligometastatic space.

Those trials are ongoing. But one of the things I think that often comes up is where is Novartis on actinium. We're actually quite advanced in actinium. We have actinium TRD capabilities. We have actinium clinical capabilities.

We have actinium supply, supply chain that's ongoing to be built out.

So we have 2 actinium PSMA assets to help us life cycle manage Pluvicto. One is called actinium-PSMA-617. Goal there is to be in the post-Pluvicto setting. We have actinium-PSMA-R2, where we think the profile might be a little more appropriate to take into earlier lines of prostate cancer. So that allows you to have, I think, a really nice portfolio in prostate cancer.

And then we had a partnership as well with an AR degrader, and we have from the MorphoSys acquisition also an EZH1/2 inhibitor.

And then in some of the other cancers, we are advancing now Lutathera and safety looks good. We'll see how the efficacy goes. But Lutathera in the small cell lung cancer space, our competitor continues to have challenges, I think, with some of the profile and supply issues there. And so the opportunity, hopefully, is to get Lutathera, if it works, the first entrant into small cell lung cancer. We are, with AAA-614, moving into additional non-small cell lung cancer, prostate cancer.

I mentioned FXX, which is the FAP. GIZ is our folate, which is also now in the clinic, folate-targeted RLT.

And then one thing we're really excited about is the HER2 RLT, the DLL3 RLT, which we recently acquired and our acquisition of Mariana and B7-H3, all of those we expect to get into the clinic next year. So then you have a portfolio of 7, 8 RLT assets in the clinic. We cover the target space we think that's relevant from ADCs and what ADCs have learned. And then we also have targets which are unique to the RLT space. And then we are always thinking about

lutetium versus actinium.

And I think it's worth having the discussion with our experts as to how to think about lutetium versus actinium in the RLT space.

So I think a pretty broad portfolio here. It doesn't cover everything we have. We also have a number of small molecule programs, bispecific programs, ADC programs. But the focus here very much is how we're using RLT plus some of our complementary programs to ensure we have long-term leadership in breast cancer, prostate cancer, and in certain other tumor types.

So moving towards the last few slides. I think important as well is we have to get faster. We know that. We need to get faster to IND. And so I think our research teams are working really hard to speed up how we get to IND.

We're working as well to speed up our clinical operations. We have a very systematic approach now that Shriram and the team are leading to ensure we close the gap in terms of either being at median or better than median over time in terms of our average clinical trial execution.

And then AI, which I think is obviously on many people's mind. And just to say a word about some of the things we're working on AI. Fiona and her team, and Fiona is a real expert actually in using AI in drug discovery. And I think the opportunity with our partnerships and what we're doing in-house is to hopefully, in a very targeted way, deliver real value from AI and not only participate in the hype cycle.

The deep target discovery is hard, but I think we are working hard looking at how to better work on target discovery. The chemistry area is quite advanced, I think, within Novartis. Our chemists all now use AI platforms. We recently announced a partnership with Schrodinger. We have the partnership with Isomorphic Labs, one of the 2 companies to work with the Nobel Prize winning team from Isomorphic Labs.

We've long worked with Microsoft, recent partnership with Generate Bio on biologics. So I think we have that opportunity here on the chemistry biologics space to hopefully speed up getting to the clinic.

And then a lot of work, maybe not as sexy, but the work to do optimizing our trial designs and trial enrollment. I think we have a really interesting case study in the case of VICTORION-PREVENT-1, where we sped up the enrollment time significantly, maybe 9 months to a year, by using AI to tell us which clinical sites to go to. I mean those are the kinds of stories that we hope to now systematically expand to really show we can speed up clinical trials over time. So a number of partnerships there, partnerships with companies like Deciphex. We are working very much on document generation, how do we optimize and automate, how we run our protocols.

So all things that I think can help us speed up over time.

And then when you think about those 3 platforms other companies are entering, but I wanted to highlight just the sheer scale Novartis has in each one of these platform areas. In xRNA, it's

now 7 clinical, 19 preclinical programs, 2 scaled manufacturing sites. Based on the external numbers, siRNA could be a $30 billion market, and we think we have one of -- and clearly, there are strong biotechs as well in this space, one of the leading capabilities within xRNA. In RLT, 17 clinical programs now, 18 research programs, 6 manufacturing sites.

We have capacity within our manufacturing sites, I think, now probably to support $8 billion to $10 billion plus of sales over time, and could go even higher if we needed, because our outstanding technical development team led by Stefan Lang, our manufacturing team has automated RLT production. So we continue to go further and further ahead of the field in how fast and broadly we can produce RLTs, actinium, lutetium, all possible within our portfolio. And here, I think the best estimate we could find was $29 billion in 2034. We'll see. I mean, obviously, the data will drive this, but a significant opportunity to own in the long run.

And then cell and gene therapy. As you know, we've been in the space a long time. We had our bumps with Kymriah, but we've done our best to learn from them and really ensure we have the right capacity as we move to Rapid Card. Rapid Card is significantly less time in the manufacturing site, a much shorter manufacturing time. So that allows us, I think, to hopefully expand really rapidly.

So it's 11 clinical, 16 preclinical programs, 3 manufacturing sites and, of course, depending on how many immunology patients you think will get treated by immune reset, a lot of opportunity.

So just in closing, I did want to highlight as well the activity we have in the deal space. It's not all visible, because so much of it is in the smaller side of things, but we've signed 30 strategic deals in the last 2 years. A lot of it in this exploratory to preclinical space, either getting new technologies or better covering targets that we need to cover. And then in the clinical space when we can find them. Of course, we want clinical stage assets.

Harder to find, valuations are tougher. But nonetheless, we think with this kind of portfolio approach, we will find a couple of really big hits like we did with RLT, which will then generate the next wave of growth for Novartis.

Now last point, I mean, ESG, of course, important for us as a company, sustainability. And I think now we're pretty consistently ranked as one of the #1 companies in our sector as well as across sectors. I mentioned ranked #1 in the Access to Medicines Index, industry leader now in Sustainalytics. We're in the leaders group of MSCI, leaders group of ISS ESG. So we really think now we're in a very solid foundation here, and we want to maintain that over time, ensuring it's important for our associates to know that we do the right things for the world, but also, I think, for key stakeholders in the world to know that Novartis is a responsible company, does things in the right way, does not want to deliver sales by ever compromising on our ethics, because in the long run, it's the trust with our stakeholders that will enable us to succeed over the decades to come.

So in closing, look, I think our strategy is delivering. You've seen the results over the recent years. But if you look back over the last 7 years, it's been pretty consistent. We think we have the right strategy, and we've delivered. When you look at our profile going forward, the 6% through '28, 5% through '29, also confident we can continue to deliver the margin.

I've tried to give you an overview of what you can see in our pipeline, but I think that's really the opportunity for today. You have, in every one of these sessions, our research and development leader as well as key commercial leaders. So you can go as deep as you want in these pipelines, because they know far more than I do about each one of these areas. And then ESG will continue to work to be a leader over time.

So that concludes the session here in the main room. This will be the session over the room over the course of the day that we broadcast on the webcast. And after, I think, a brief break, we'll then move to the next room. So I'll hand it back to Sloan. Thank you all very much.

[Break]

Patrick Horber Executive

Okay. Good morning, everyone. Thanks for joining us. Please don't fall from the tier. I'm Patrick Horber, and I'm the President of International.

I'm taking care of the business all outside of the U.S. I'm more than 20 years in the pharmaceutical industry and very passionate about immunology, big part of my career I have spent in immunology. And I'm really looking forward to the discussions which we'll have today on immunology together here with my team. And let me start to introduce them.

So we have Angelika Jahreis, who is our Development Unit Head in Immunology. More than 25 years of experience in development and a certified board dermatologist. Then we have Richard Siegel, our Head of Biomedical Research. Great track record, especially in research in rheumatology and as well work in the NIH. And then finally, Rob Rubinsky, who is the Chief Market Access Officer of the U.S.

and member of the leadership team there and will represent the U.S. business today if there are any specific U.S. questions.

To frame a little bit discussion which we'll have afterwards, I would like to provide you some highlights on where we are excited on from a Novartis perspective and, of course, as well the 4 of us here. You know that we have a very strong foundation in immunology. We have 3 anchor brands with Cosentyx, Ilaris and Xolair. The 3 brands do an annual revenue of around $10 billion sales. We have a very strong and leading commercial organization in international, but as well in the U.S., and that in 3 areas, it's dermatology, it's rheumatology, and allergy.

If we look into our life cycle management, but as well our pipeline development, we focus really in areas of high unmet medical need. And if I look now into the next couple of years, what kind of data flow we'll have, we have 10 Phase II readouts and 6 Phase III readouts till 2029. So significant readouts in the immunology area, and we'll go a little bit more into details now.

If I look into Cosentyx itself, our core business is performing very well, and that's in psoriasis, psoriatic arthritis and as well axial SpA. Then we have great momentum, which we have created this year in addition with 2 areas. One is the HS indication, and that globally, we got the approvals last year. Very strong momentum in HS. And then in the U.S.

specific, we have the IV formulation, which is really driving the growth in the U.S. So we're

tracking now to peak sales of $8 billion. You have heard this morning that Vas has updated our peak sales from $7 billion to $8 billion, and we're very confident to be able to deliver on that. In addition, we will have 2 Phase III readouts next year in 2 indications. One is GCA.

The other one is PMR. In GCA, with very strong remission data in Phase II, and we're very confident to see good data mid of next year.

Now looking into other brands like remibrutinib, we're currently preparing the launch across the world, so U.S. and as well ex U.S., as we have seen Phase III data this year, which have given us confidence from an efficacy as well as from a safety perspective. I think what's really important to mention on CSU is that this is really a significant opportunity because there is a huge number of patients which are unserved. If we look at it from a U.S. perspective, it's around 400,000 patients.

And from an international perspective, focusing on our EU -- 5 EU, China, Japan, it's slightly below 4 million patients who would need treatment. The great thing on the molecule, on one hand, it's an oral. Secondly, it really has a fast uptake, very sustained efficacy, and has a favorable safety profile, which will give us the opportunity to really position it after antihistamine treatment, but before the biologic treatment. So really big opportunity which we see there.

If we look into remibrutinib or the BTKi MOA, we see other indications which will come up like CINDU, which is chronic induced urticaria or as well food allergy. What we looked into and we saw the Phase II data this year was in HS, and we'll start with the Phase III program in 2025, expecting then data readouts in '28, '29. And looking into the whole brand with all the indications, we believe that this is a brand who could deliver more than $3 billion revenues in dollars.

Another exciting brand is ianalumab, where we'll see next year a first data readout on SjÃ¶gren's disease. That's the first one. Then we'll have data readout in '27 on SLE and as well in lupus nephritis. And these are all diseases where there is a high unmet medical need. So really, really exciting.

And if I look into the Phase II data, which we have seen on SjÃ¶gren's and in SLE, it just confirms as well what we're expecting from this very special MOA. It's a dual MOA, which on one hand does B-cell depletion, and on the other hand is above receptor antagonism. As well here, we see a potential opportunity of more than $3 billion sales across the indications.

And then last, more from a long-term perspective, Vas mentioned before that we could become a leader in immune reset. We have strong expertise in cell therapy. And basically, we have started with Phase II programs in different indications, and we'll see first data readouts in 2026, and then over time additional ones in other indications than SLE.

Then we're exploring as well T-cell engagers for immune reset. We just started a program in Phase I. And then finally, what makes me as well, and I think us here excited, we just entered into Phase II with a bispecific in atopic dermatitis, which is, as you know, a pretty big market. And if we really are able to prove that it works, then it will give us some additional opportunity to grow in immunology.

So with that, I think I gave you a little bit of glimpse on what we see as the key topics and the key areas, and looking forward to the discussion and the questions which you have. So let's start with the questions.

Graham Parry Analyst

It's Graham Parry from Bank of America. Just wanted to kick off on remibrutinib in CSU, which doesn't actually get that much airtime, but obviously, very large patient population you're talking about with 400,000 in the U.S., 4 million in your kind of commercial markets. Just perhaps talk us through potential launch strategy and also just remind everybody the reason for the filing delay into 2025. But when you get into launch strategy, how do you look at commercializing this target patient population? And is it the existing patients on high doses of antihistamine above approved doses that's the core target market.

And so perhaps quantify how big that market is for the early easy win, if you like.

Patrick Horber Executive

Yes, sure. So I may start and then I hand over as well to Rob from a U.S. perspective. So the delay of the submission to H1 2025 has something to do with the CMC dossier, which we had to put together really for the submission, and that will be ready. So we know that we'll submit next year.

Then from a market perspective, yes, you're right. So what we'll see is patients who have cycled antihistamines or have been even just on one treatment to be the target for us. So clearly before the biologics.

And I think with an oral with that level of efficacy which we have seen, and I think what's extremely important as well is the safety profile which we have seen, which is favorable, we have a huge opportunity there to enter into it, which means from a target perspective, and if I look into international, it depends market by market. In some markets, it will be dermatologists who are specialized on CSU. If I take Germany, for example, we will need to have referrals from the GPs, and that's the way how we'll build up our organization to really get into a broader penetration of the CSU market. And if you look at the numbers which we have, I think it's a huge opportunity which we really can unveil here. But I'm sure as well that it will take a certain time to really move these patients in countries which are with GPs to the dermatologists and get them treated there.

Rob, from a U.S. perspective?

Rob Rubinsky Executive

We totally agree with you, Graham. We think this is a little bit underappreciated and exciting. And as we think about this slide and some of the beauty and the depth that we've built in the commercial organization, leveraging those relationships with the providers and the prescribers, and then thinking about access and how we stack indications and build out this portfolio is exciting from a launch trajectory perspective.

Richard Vosser Analyst

Richard Vosser from JPMorgan. Just to build on Graham's question. Just on that safety profile, maybe you could give us the latest update across the program. Obviously, CSU safety looks really good, but you've got higher doses, I think, in MS and some of the other indications. So just give us some reassurance there would be great.

Patrick Horber Executive

Yes, sure. Maybe I'm handing over to you, Angelika?

Angelika Jahreis Executive

Yes. Super happy to take that. So as you have said, in our CSU program, we have seen a very clean safety profile. We have also presented that at different congresses. And one of the safety events that certainly differentiates us from other BTK inhibitors is the clean liver safety profile.

And as you know, we've also looked in Phase IIb studies in CSU on doses of 100 milligrams, which is 4x the dose that we use in CSU, and we have not seen an increase of liver safety events.

In our MS studies, and I think that's what you're referring to, we are using that higher dose as well. I think we have enrolled more than 1,000 patients to date across these programs, and we have not seen any concerning liver safety events in that program either. So we are very confident on the liver safety that we see. We know it's not an on-target event, because BTK is not expressed in the liver cells. So very happy about our overall safety profile that we have seen, and we think that really opens up the avenue to a safe oral therapy in CSU, which is incredibly important.

Richard Vosser Analyst

And sorry, just -- and no liver monitoring in CSU is your expectation in terms of labeling...

Angelika Jahreis Executive

We have no scientific basis to assume that liver monitoring would be required in CSU. Yes.

Patrick Horber Executive

Maybe adding, I think it's extremely important from a commercial perspective. If we really want to get the broad market, we need a safe product and I think an oral product safe with the efficacy. And I think what's extremely important as well is the speed of action. So you really have an immediate efficacy and urticaria goes away and your itch goes away. So it's very, very effective, and that's what patients are looking for.

Matthew Weston Analyst

It's Matthew Weston from UBS. If we just stick with remi, I'm really just trying to follow on from Graham's question around the commercial scale, because if I think about the market, I think about broad antihistamine use and the size of CSU, it just screams primary care to me in terms of the potential opportunity. Clearly, we've not seen pharma really engage in primary care a lot in dermatology or certainly not Novartis broadly. So I'd just love to understand this

patient transition from the primary care doctor to derm. That's something that you hope to engage, or you will only engage with the dermatologists when they're being seen?

And then I'd also just love to understand the comments around U.S. market access. Is this something where we should anticipate you leverage the Cosentyx rebate to accelerate access for remi going forward as we've seen others do in immunology over time?

Patrick Horber Executive

Rob, you can start and then I bring international perspective.

Rob Rubinsky Executive

So I'll start with the access question first. I think having size and scale in a TA helps with payer negotiations. So you can imagine a world where that continues to happen in immunology, so excited about bringing more medicines in immunology.

From a commercial perspective, I think we're attacking kind of a lot of different angles, both in primary care and dermatology. And I think we've seen this happen in other immunology categories, where a safe, efficacious product comes as an oral and is able to be tapped into those multiple pieces. So we're excited about that value prop.

Patrick, I don't know if anything else to add globally?

Patrick Horber Executive

Yes. Sure. Going back to your GP referral or maybe nonreferral and where are we positioned as a specialty company. I think if I look into the international markets, I probably only have one major market where we have around 30%, 35% of the CSU patients which are with the GPs. The other 65%, if we take the German market, they're sitting with dermatologists, some of them with CSU specialists, and that's around -- of this 65%, it's around 50%, 60% with dermatologists and the other 40% with the CSU specialists.

We will target the dermatologists and then we'll look how can we really then afterwards get the referrals from the GP. So there is not an objective to go into the GP and have a GP line. That's very clear.

And I think the other piece which is extremely important, we have seen it as well in the past in atopic dermatitis, many patients were sitting as well in the GP office. But then they got referred when the treatment was available. Today, from a GP perspective, they don't really see what's currently available as the best option. And having then an oral treatment, I think that will be another incentive for them to really shift and refer the patients then to the dermatologists.

Simon Baker Analyst

Simon Baker from Redburn Atlantic. I'll stick with remibrutinib slightly towards HS. I just wonder if you could discuss what the ideal profile of remi in HS looks like, how it meshes with Cosentyx in HS. And also looking at Cosentyx in HS, 60-plus percent NBRx in very short order is a great achievement and is indicative of the unmet need there. There are and have been very recently additional therapies approved, most notably bimekizumab, how sticky is that

NBRx share?

In other words, how do you defend Cosentyx against [indiscernible] imminent launch?

Patrick Horber Executive

Sure. Let me start maybe with the profile of remibrutinib, the first question, what would be great to be successful in HS, then I take the second one and then maybe I'll ask you, Angelika to give in or you, Richard. Where do we see from a research and development perspective where the profile of remibrutinib would land. So if I look into an oral HS product, you could look into that very similar as what you have seen in psoriasis. In psoriasis, we have seen first entries of biologics, and then oral treatments came in.

We know that there is a significant amount of patients who don't like injectable products, who even don't want to take biologics. So that's a huge market and it would give us an opportunity to broaden the HS market. Current penetration with biologics depends on geographies, it's somewhere between 10% and 20%. So there's a lot of room on one hand to really get more patients treated with biologics. But at the same time, as there are lots of patients who don't want to get the biologic treatment injectable, there is a huge potential opportunity there.

So from an efficacy perspective, you probably don't need the efficacy, which you see on the biologics, as we have seen as well in psoriasis. If we get to that level, that would be even better for sure. I think there is no question mark on that. But what's extremely important is that it is safe. So going back to discussion which we had as well on CSU, dermatologies look very much to make their life easy, yes?

So they want to treat the patients, but give me a tool where it can treat patients well and then they don't come back to my office just based on any side effects, and then I have to manage that.

So I think profile-wise, favorable safety profile, efficacy could be below a biologic. It is an oral, I think that's great, and that will give us a huge opportunity to have like a pre-biologic market where we can enter, and then we have the biologic market with Cosentyx.

Now with regards to [indiscernible] entering into that market, and there is already another biologic on the market with adalimumab. Nevertheless, adalimumab is there. We got very quickly in the U.S. to 65% NBRx share. If I look into the European markets, Germany, it's 55%.

The U.K., it's 58%. So we're somewhere everywhere at the 50%. And we're very confident. I think with Cosentyx, the data is good. We have a great safety profile.

Doctors, dermatologists know the product very well. They have used it for many, many years in psoriasis. So there is a heritage as well. There's a certain loyalty and they know what they get.

So we feel confident. Does it not mean that we may get more competition, we'll get maybe a slightly lower dynamic here. Yes, of course. I think that's part of it. But I'm very confident that we'll see a lot of usage in first line.

That's what we're seeing now in international. And if I look in Germany, almost 60% of the

dynamic share is coming from first line. And then the others are switches from adalimumab. And I believe bimek, bimek cells get into the market, then you will see them after failures of Cosentyx or maybe after failure of adalimumab. So I believe we're in very strong position there.

Unknown Executive Executive

From an access perspective, too, just very, very important 70% first-line unrestricted access, which enables everything that Patrick said about our first-line position and unrestricted nature of the volume.

Angelika Jahreis Executive

I can maybe add a little bit on the outcomes of the HS studies for remibrutinib and then talk a little bit about both our data as well as the bimekizumab data. In HS, in our -- with remibrutinib, we have seen very interesting data with a greater than 30% reduction in high score, which is better than biologics to date. And so these data the fast onset of action that we've also seen in HS, which is really important to patients who come with these very painful accesses to us who have -- many of them who have regular players associated with their menses. So it is crucially important to have a fast-acting safe oral product, and that's exactly what we have seen in our Phase II study. So we are very excited to go into Phase III for HS early next year.

And coming to the Cosentyx program, Cosentyx, let me go first and talk a little bit about the patient population. These are typically young women with a very devastating disease, typically overweight. Many of them are smokers, with a devastating disease of these very painful abscesses and inflammatory nodules in the axilla and in their groins as well as anal [folds]. So a disease that is often prone to superinfection, a disease also that leads often to social stigmatization and isolation. And I believe that our data with a very clean safety profile and a very good efficacy profile is really important for these patients.

So we have a reduction of flares by 70%, right? And we met the primary endpoint for flares with the Cosentyx data. We have a reduction in pain by one year in those who had severe pain to by 65%. So really important for patients with a disease like hidradenitis suppurativa.

Importantly, we only saw 1% rate of, for example, oral candida infections that compares to up to 10% for bimekizumab. And in bimekizumab, there was up to 25% of fungal infections. And we know the -- these patients will also already have some psychiatric comorbidity right? They maybe not the best suited for a therapy like bimekizumab. So I think we can be very, very confident in the Cosentyx profile for patients with hidradenitis suppurativa.

And maybe, Richard, do you want to add a little bit more?

Richard Siegel Executive

Sure. Just from a research perspective, why are we even talking about remibrutinib, a drug that blocks the B-cell receptor and [indiscernible] receptors in HS. And this is part of a paradigm shift that was partly due to research done in our group where HS was thought as primarily an inflammatory disease, but we know there's actually B cell infiltrates in the lesions and the discovery that was made by our group of a specific autoantibody, anti-CEL,

autoantibodies that's unique to HS. And the remibrutinib results came out of what we call a platform trial where we actually tested five different MOAs including a remibrutinib BTK inhibition and with a really positive result, and that's part of this paradigm shift towards maybe a more autoimmune B-cell involvement. That's why it's also shown here that we're also investigating ianalumab a B-cell depleter in HS, and we'll get those results next year.

So I think really a different -- a very differentiated therapy remibrutinib, not only from its quick mechanism of action oral, but as an agent that's acting completely differently than secukinumab or bimekizumab or TNF.

Patrick Horber Executive

Thank you, Richard. Thank you, Angelika.

Eric Le Berrigaud Analyst

Eric Le Berrigaud, Stifel. In the past, you provided some peak sales estimates for HS and IV formulation for Cosentyx. Similarly, you're having two new indications coming. Could you give us a sense about how much GCA and PMR might represent going forward?

And the second question Cosentyx psoriasis could you give a sense of how much that represents into total sales and how much that could be impacted by upcoming oral IL-23 in the coming years?

Patrick Horber Executive

So I can start maybe with the GCA PMR indications, the new ones which are coming next year. There are both indications which are definitely smaller than the ones which are currently in, but there are a couple of hundreds of millions of dollars, which they will add on the top of what we're doing now with the current indications.

With regards to psoriasis, what's the split between psoriasis and the other indications. I think it differs significantly market by market, I have to say. If I take the overall number for international and ask for [indiscernible] in the U.S., it's around 65% psoriasis. But we have markets where psoriasis is around 75%, 80%, and then we have other markets where it's 55% where PSL and AxSpA is just much, much stronger, and we had a lower penetration of psoriasis. So it's really market dependent.

Rob any?

Rob Rubinsky Executive

In line, 50-50 in the U.S.

Patrick Horber Executive

Okay. And then your last question was about the IL-23 from a penetration perspective. I think you've seen the IL-23s are already now for a couple of years in the market, if it's in the U.S. or as well in international. And they have mainly eroded the TNF inhibitors that we wrote at the other IL-12/23.

So STELARA, which is becoming biosimilar next year.

There has been a certain erosion as well in the IL-17s, but it's pretty stable. If I look into the international markets overall, we are holding very well, holding share and at the same time as well dynamic share. If you're holding dynamic shares, so you have pretty good confidence as well that you can hold the share over the next years.

Eric Le Berrigaud Analyst

No change [indiscernible] oral?

Patrick Horber Executive

Oral -- sorry, I didn't get the oral piece. So you mean now the IL-23 from J&J. Personally, I don't think so, yes. And mainly because they are going to an oral market. I think it's a little bit of a discussion, which we had before.

There will be further market expansion. If you look into the oral business in psoriasis today, you have two players currently in the market, a TYK2 and then Otezla, which has launched already many, many years ago, and they have a pretty significant part of the market. And what I believe is that the IL-23 based on the profile, if it's from an efficacy perspective, but as well from a safety perspective, we'll definitely penetrate that market.

The IL-23 is even doing currently a head-to-head trial against the TYK2 of BMS. We'll see how the data will look like. But based on the data which has been shown yesterday, there is a chance that they will show superiority there. So I think that will be probably the oral to go in the future, but less an impact than on the biologic market because we didn't see any biologic impact when we saw Otezla launching or as well the TYK2.

Peter Welford Analyst

It's Peter Welford, Jefferies. I wanted to come back to something Vas said at the start, Vas said that immunology, you're increasingly focusing on specialty indications because there's less reimbursement pressure. But I want to sort of try and square that then with other comments we've heard from you talking about access, the bigger indications, some of the products they're obviously important for access. And is it for the sort of existing psoriasis sort of indications, you just don't think you can get above the ceiling of efficacy we've already seen? Or what is it that's driving from an R&D perspective while you're not pursuing those indications.

And equally, you've said for orals that you think there's room for oral study largely biologic dominated markets. So why when we look at your pipeline side, don't we see a potential oral looking at psoriasis, psoriatic arthritis or those sorts of indications, I guess coming back to the same question regarding is there something challenging about that? And perhaps, again, just related to this, -- just in terms of -- with the specialty indications more sort of as a portfolio, is it your intention because some of these products are going after multiple different indications. Do you believe with payers that going after many different specialty indications, you can still preserve that value? Or do you think that ultimately, if you pursue 4 or 5 specialty indications, you'll face the same challenges as if you were to go after psoriasis?

Patrick Horber Executive

Maybe let me start with the general -- less on the market access and let's call it the rebate wall, and then I will hand over to Rob so that he can give his perspective from the U.S. because we don't have let's say, revert wall in international. So totally different access situation there. I think one thing, if you look into the more specialty indications like SjÃ¶gren's disease or systemic lupus or lupus nephritis, these are diseases where today there are no treatments or there are only treatments, which really are not treating patients to a certain level of remission, which you would like to see that.

So -- these are indications if you have the right MOAs and you have the right molecules, gives you a huge opportunity to enter into these markets. And that on both sides, if it's from a U.S. perspective, but as well from international perspective because no competition. There is not a set price yet. There is not a biosimilar or any generic in that market.

So that's a great opportunity.

Now if you look into indications, as you were saying, psoriasis, why are you not going into an oral psoriasis. We don't have an oral in psoriasis. I would put it that way first. If there is the great oral, it's not that we will not follow that. And I think J&J, if you look into their IL-23 oral, I think they have a very nice molecule there, which will give them a huge opportunity to really broaden the oral market.

But if I look into psoriasis in general, biologics, there is a certain level of remission, which has been achieved with the IL-17s or many, many years ago and now with the IL-23s, which there is not a need for a better treatment. And even I would say, if you go -- we go into international markets but as well into the U.S. with maybe, I don't know, 5% or 6% higher PASI -- 90 PASI or 100, I don't think that there will be a huge adoption. So I think we're getting to a certain saturation if you look into psoriasis.

In HS, I think we're in a different level there. There is still space to really have better treatments if they are biologic treatments or all treatments in general biologic treatments are more efficacious. So there is an opportunity. So we are looking there where there is a potential opportunity. Psoriasis, clearly, I don't think that there is a need for another biologic.

Is there an opportunity for the oral segment, yes. I believe that with what currently is coming to the market will come to the market, it's very well served.

So I don't see it really for us psoriasis a big opportunity. That's why we're looking to HS. We're looking to the other more, let's say, severe indications where there are no treatments. And as I mentioned in the introduction, we're looking as well in atopic dermatitis, where you have certain treatments, but the current treatments are not, let's say, reaching a certain level of remission, which you would like to see. But [maybe erupt] from the rebate well perspective for access perspective in the U.S.

Rob Rubinsky Executive

So in the U.S., there's a triangle we consider. It's the speed of access, it's the quality of access and then the price that you could achieve in that position. And everything that Patrick had

mentioned about PSO with 10 entrenched competitors and then multiple MOAs. That triangle is very difficult to achieve at this point. So thinking about these other moderately sized TAs with limited innovation for the past several years, we find that a much more attractive triangle.

Richard Vosser Analyst

Richard Vosser, JPMorgan. Maybe moving to ianalumab in SjÃ¶gren's. Maybe you could contrast the data you've seen with the FcRns, how you think that stacks up in that in that area, but also not just on the main primary endpoints but on the functional endpoints, but just yes, how you see that panning out? .

Patrick Horber Executive

Sure. Angelika maybe and...

Angelika Jahreis Executive

Yes, I can address it, and then I'll pass it on to you. Very interesting data that have been shared, and I was just at the ACR last week where there was an oral presentation of these data as well. So I think our ianalumab data in SjÃ¶gren's disease, let me start out with that, right? They have shown a significant reduction in the STI score in those patients who have systematic involvement. And as you know, if you look at SjÃ¶gren's, there are -- it's a wide spectrum of disease from patients who have a more glandular disease with dry eyes, dry mouth as well as then these who really go on to 5% of patients having B-cell lymphoma.

And these patients are those patients with systematic involvement who have interstitial lung disease, who have, also arthritis right, and these patients who are severely sick. And that is the patient population we are studying in our trials.

So we have seen not only a significant reduction in the STI score at 24 weeks in our Phase II trial. We've also shown that about 30% of patients are responders to therapy based on what is the minimum clinically important difference. And we have shown that about 60% of patients who entered the trial with moderate to severe disease at week 24 only have mild disease. So really impactful data and that is associated with every 4-week subcu injection, right?

Now looking at the competition and for example, nipocalimab, I think we're -- it is an every 2-week IV injection infusion and, we have seen efficacy data that are about comparable to what we have. However, what is from my side, something that you really have to look at in the larger trial is how the safety will evolve with the just very unspecific reduction in immunoglobulin and that affects not only those immunoglobulins that are kind of the auto antibody profile for SjÃ¶gren's, but every immunoglobulin that is protective safety.

What we have shown at ACR is when you look at our data, that the immune response against is -- against regular antigens is intact, and we selectively reduce the immunoglobin levels of the autoantibodies. So a very different onset and a very different mechanistic profile we will see across the Phase III studies, how that evolves into a benefit risk profile overall. But we are very confident in what we have seen with respect to our data in SjÃ¶gren's in our Phase II studies and we wait for our phase III readout next year. Do you want to add anything?

Unknown Executive Executive

Not much of that, I think you really covered everything. It is -- we don't think of SjÃ¶gren's disease like myasthenia gravis, where the auto antibody alone is the pathogenic -- sole pathogenic Insider. And so it is a positive surprise that we have clinical response from FcRn, which would only modulate antibody levels. We think here by depleting B-cells, including a really important cell the plasmablast that's a producer of auto antibodies, we're getting more of the root cause of disease.

And we -- next year, we'll have data where we're actually biopsying salivary glands of patients treated with ianalumab to really see what we're doing in the tissue. We know that FcRn would not have any of those effects. So I think it's early days. We are very confident in the MOA and the robust Phase IIb results from a few years ago. And I think being also first to market, I'll let my commercial colleagues comment, but I think that's a big advantage for ianalumab.

Patrick Horber Executive

For sure. I think first to market, and it's subcut versus IV. I think that's another opportunity. And there is a huge unmet medical need. So if we really get the Phase III data looks good, I think it's a great potential for us from a commercial perspective.

Matthew Weston Analyst

Matthew Weston at UBS. Two, if I can. One is back to commercial in the U.S. and particularly a very near-term focus. So payers have had a great deal of success income from rebates from adalimumab over recent years.

And now if we look at the outcome for 2025, it's going to be the first year where they really don't have that income. So I'd be very interested on the near-term impact of payer pressure in the immunology market going into 2025? Are we seeing them much more aggressively look at molecules like Cosentyx in psoriasis. And is that something we should expect to see when we get to the early quarters of '25, where we normally see the majority of that access impact.

And then secondly, completely separate pivot, -- have you disclosed the targets of your bispecific antibodies in AD? And if so, what are they?

Unknown Executive Executive

I think [indiscernible] question first. So we're really happy with the 2025 commercial negotiation season, which is closed at this point. So I'd expect a very, very modest gross to net erosion over time, very analogous to the past few years for Cosentyx. So quite happy with how the teams navigated that.

Patrick Horber Executive

Maybe on the targets, Richard or Angelika?

Angelika Jahreis Executive

I can maybe start with our bispecific antibodies for atopic dermatitis. We will be starting a Phase IIb study with a bispecific antibody that is a dual IL-13 IL-18 inhibitor. So we are building

on the efficacy of the IL-13 molecules, and there have been data. They have been data published, for example, by GSK on IL-18 inhibition that show very interesting responses. We've also looked at that in-house.

We haven't published this data yet. But we think that this is a very interesting combination because this is at least additive. We expect at least additive efficacy from these both pathways. And maybe you can talk a little bit more, Richard, on why we are so excited about combining these 2 specific pathways.

Richard Vosser Analyst

Yes. So I think as it says, this is part of a larger strategy in atopic dermatitis, where unlike psoriasis, we've reached a certain plateau of efficacy with IL-13 or IL-4 receptor, 13 receptor, alpha dupilumab MOA. And so building on known MOAs that are successful like 13 and combining them with a very robust platform that we have now in-house for bispecific antibody generation. We have a set of bispecifics that we're developing behind the IL-13, 18 that we want to explore. We don't know what's the magic second arm that will really give us the transformative efficacy, but we're taking a very large investment in multiple bispecifics that we'll be developing over the next few years with the launch of the first Phase IIb trial next year.

Patrick Horber Executive

Okay. Thanks, Richard. Thanks, Angelika. It's almost last question when I see the timing.

Graham Parry Analyst

So I'll start and I'll finish as well. Graham Parry, Bank of America. So I'm just going to follow up on the AD actually. So just where do you see the unmet need there in atopic dermatitis. So -- or do you think that Dupixent will always be sort of the go-to first-line biologic just given safety, breadth of indications, rebate wall, et cetera.

And actually, what you're looking for is the DP failure market there. And then going back to ianalumab, just -- can you just help us understand the proportion of patients commercially that you think is that target population who don't just have the [moisture] issues that actually have all the systemic problems as well. And then last one on that one is if you look at the Phase II, you failed on the secondary endpoint of ESSPRI, just comparing contrast why is ESSDAI more important than ESSPRI in SjÃ¶gren's disease.

Patrick Horber Executive

Okay. Thanks for your question. I'll start with the AD piece. So I think if you look into the current treatments in atopic dermatitis, you have IL-13, you have Dupixent, you have some other IL-13s which got into the market. But you're still not from a remission perspective at a very, very high level.

And we know as well that around 40% of dupilumab patients, they feel of a certain time and they need another treatment. So there is still a significant unmet medical need.

Now where do we position our bispecific, I think it depends at the end on what the profile will

be. The aspiration would be to have I call it, dupilumab Plus, which means a product which could be superior to dupilumab. If that's the case, if it's from an access perspective, and I don't think there is a big difference the U.S. or international, then we have a significant opportunity to go into the first-line market. If that would not be the case, then we'll have to look what it means and it could be dupi failures or even JAK failures there are as well JAK inhibitors in the atopic dermatitis market.

But that's the way how we look into that. But we definitely have the aspiration with the bispecific in building on the IL-13 efficacy and adding an IL-18 to really get to the next level from an efficacy perspective.

Keeping, of course, and I think you mentioned that and I think that's extremely important in the dermatology market, keeping the safety profile -- the safety profile, which has been seen by the dermatologist with dupilumab. Maybe on ianamulab, I'm handing over to you, Angelika.

Angelika Jahreis Executive

Yes. Happy to take that. So we have 40% of the patients with SjÃ¶gren's disease have systemic manifestations of the disease. And these are the patients that we have included in our clinical trials in the 2 pivotal clinical trials. The ESSDAI is the score that is assessing the systemic manifestations.

So our patients have been enriched for having very severe systemic disease. And that is the outcome measure that looks at the 12 different components and the 12 different organ manifestation of systemic manifestations of SjÃ¶gren's disease.

The ESSPRI in contrast is an outcome measure that looks at dry eyes, dry mouth as well as pain, and as such, would be more an outcome measure to look at the other part of the SjÃ¶gren's patient population. So I think I'm very happy that we have reached the outcome measure that is really relevant for the patient population that we have involved.

Patrick Horber Executive

Thanks, Angelika. With that, I thank you for your attention and for joining us here and asking all these questions, and wish you a continuous good discussions and a Q&A with the other therapeutic area. Thanks a lot.

Victor Bulto Executive

Well, good morning, everyone, and thank you very much for joining us in this cardiorenal metabolic section. I'll do a brief introduction of our panelists today and go briefly through the slide, and then we'll get started with the Q&A.

So on our right, we have Shaun Coughlin. Shaun is our Global Head of Discovery of Research in the cardiometabolic space. He joined Novartis in 2017. He joined us from UCSF, where he was most recently the Director of the Cardiovascular Research Unit, and he is a cardiologist by training. So thank you, Shaun.

And then we have Dave Soergel as well with us, also joined us in 2017 at Novartis. He's also a cardiologist, and he leads our Global Development Efforts across cardiorenal and metabolic.

So thank you very much, Dave.

And Ingrid Zhang, who joins us as well today. She's the Chief Commercial Officer in the international markets. So all the markets across the globe, except for the U.S. And most recently, she served as the Country President for China, where she led our substantial growth there. And I'm Victor Bulto, I'll be hosting you today and lead the U.S.

business.

Now if we look at the slide here in the background, when we think about the cardiorenal metabolic strategy, not unlike every other therapeutic area, where we're looking at developing its depth, that is depth in the areas where we operate and just seeking to compound the research experience that we have over decades, the development experience in those spaces and of course, our commercial experience and footprint. So that's how you will see the [indiscernible] is shaping up.

And then we start, of course, with our first pillar, which is established leadership in what we call [indiscernible] cardiovascular risk factor management with a focus on our -- across RNA platforms. Of course, part of that is [indiscernible] with both secondary prevention trials ongoing and the primary prevention trial as well. We've expected readouts already in '26 and '27. Pelacarsen, the ASO looking at reducing lipoprotein A with the HORIZON trial ongoing. That's an event-driven trial that is looking for a readout sometime in 2025.

And QCZ484 also an sRNA targeting resistant hypertension. As you can see here, advancing into Phase II in next year.

And then the other part of the portfolio that you'll see is multiple sRNA assets that we're working on as a life cycle management for Leqvio for Pelacarsen and others just seeking to address again, cardiovascular risk factors. Then you will see as well that we're developing what we call a high risk, high-reward arrhythmia portfolio with several assets that should come into the clinic in 2025 with a substantial unmet need there when it comes to rhythm control. So Shaun is leading our efforts there, and we can go a little bit deeper into them.

And then, of course, advancing also an innovative inflammation portfolio as well across multiple modalities. And there, we expect the first asset in the clinic in 2025 as well.

And then last, but not least, our renal portfolio. That's our latest entry, but as you all know, we have been building breadth and depth across multiple assets and indications. They're all basically rare or ultrarare diseases, but they aggregate in total affecting about 2 million patients across the globe. [indiscernible] being particularly prevalent in some Asian countries.

With atrasentan, so we have FABHALTA already approved in IGA nephropathy with 3 months into the launch with good progression thus far ahead of our expectations. And we have atrasentan with an approval expected in 2025 to complement our IGA nephropathy portfolio.

Iptacopan just received the filing acceptance by the FDA with a priority review. So we will be preparing for a potential launch next year. And then, of course, other indications for iptacopan, Zigakibart and some other early renal portfolio that we're developing, again, with

the idea to building a synergistic portfolio there in the renal space.

So with that, we will welcome your questions. Thank you very much.

Richard Vosser Analyst

That's the plan. Sorry, Richard Vosser from JPMorgan. Maybe pelacarsen to start. Perhaps you could just talk about maybe the impacts of COVID on the trial. We've seen cardiovascular outcomes trials have impacts there from the COVID effects on cardiovascular disease.

So just thoughts on that. Maybe also one on the choice of patients in the trial in terms of the level of Lp(a) and the ability to reduce that with pelacarsen. Have you got high enough risk patients? Others suggest have gone higher in a different patient population. So just thoughts on those 2 dimensions to start with.

Victor Bulto Executive

Well, thank you very much, Richard. Dave, I'll pass that on to you.

David Soergel Executive

Yes. So the first question was about COVID the impact on Horizon. Indeed, we did see an effect on recruitment during the COVID period. That didn't -- that did cause a bit of a delay in terms of the study. We've seen events track in the way we expect.

I mean, obviously, everything is blinded right now. So that gives us comfort that we're not seeing anything like a blip in terms of poorer outcomes than we would have expected in this patient population. So as events continue to accrue, of course, we'll have a better understanding of when the final data will be coming out. But right now, we're projecting 2025.

So your second question had to do with the patient risk levels based on their Lp(a) levels. So as you're aware, Lp(a) is a -- what's happened recently, actually over the last couple of years is we've gotten a better understanding of how Lp(a) modulates cardiovascular risk. So back when we actually designed Horizon, there was a question about whether or not Lp(a) was a threshold effect risk factor versus a continuous risk factor. So continuous risk factors, for example, is like LDL-cholesterol or blood pressure, you have a kind of a linear increase in risk as you go up and level. So what we found out more recently through the work of Brian Ference and his colleagues, is that through valuation of Mendelian Randomization data and Epidemiologic data that Lp(a) does appear to be a linear risk like LDL-cholesterol.

So then the question is at what level do you really start to see the biggest risk accumulation? When you go to 70 milligrams per deciliter, which is where we are, which is equivalent to about 150 nanomoles per liter just to try to cross equate to other trials, you see about -- that's in the top quartile of the population, right? So that's the top sort of 20% of total patients in that upper risk quartile. And in that group, you expect about a 1.4 risk over time compared to. So -- and that's independent risk when you factor out LDL-cholesterol, you factor out other risks.

So we think we're in the right range to show a benefit of pelacarsen in this population. Pelacarsen, as you know, drops Lp(a) by about 80%. So you're going to get to very low levels

of Lp(a), whether you're at the 70-milligram per deciliter cutoff that we talked about as the total population or that second strata at 90 milligrams per deciliter. In either case, you're getting to very low levels to more normal levels of Lp(a).

Victor Bulto Executive

And maybe just to complement from a size perspective. Dave mentioned about 20% of patients above 70, about 10% of patients above 90 in our studies, right? So not in our studies in the prevalent population. Yes, Graham?

Matthew Weston Analyst

Sorry, I've stolen the microphone, Victor.

Victor Bulto Executive

Okay.

Matthew Weston Analyst

It's Matthew Weston from UBS. If I can stick with pelacarsen. I'd be really interested in how the commercial strategy maybe needs to flex depending on the outcome of law changes around IRA. So currently, I believe it's going to have a 9-year life within IRA. And if I think back to Diovan and Entresto and Leqvio, they all seem to follow a pattern of about 5 years to get to $1 billion and then $1 billion a year thereafter.

So you make all your money in year 6 and beyond. If you've only got a 9-year life, it's very difficult to make a real commercial success of an siRNA.

But if you are able to change the legislation, the industry is able to change the legislation and get to 13 years then you have a much bigger opportunity. So in Novartis at the moment, is there a debate about going very high only, making it a real specialty cardiology medicine, higher price, getting it to profitability much quicker, and then only thinking about lower risk patients over time if IRA is changeable or are you rolling the dice and going to go for the 5-year slow and steady launch make your money at the end?

Victor Bulto Executive

Yes, that's a great question. And look, I would say irrespective of IRA, what we've been learning launch after launch in cardiovascular is that actually when you go very broad, it -- as you mentioned, it takes longer for you to go and narrow down to the actual patients that you're going to treat. If you look at Entresto, even now after that many years in the market, we're treating about 30% to 35% of the overall population. So the key here that we're asking in the trial, but also in the work that we are doing is what's going to be that 20% -- 10%, 20%, 30% of the population that will see the highest benefit clinically. But also what are the factors that contribute to that faster identification and willingness of the patient and the HCP to get on the treatment for a chronic and a symptomatic disease, right?

Because that's the key to that uptake.

And yes, that's a debate we're having right now that we are going to look at that more

restricted population, understand also much more clearly than we did in the past who are the cardiologists that are way more motivated to treat these patients? And then focus our launch efforts in those subpopulations of both HCPs and patients to achieve faster uptake. And again, that's irrespective of IRA, right? We do believe that now that the Republican party has a broader control in the U.S., there's higher chances of us as an industry affecting that, but that would not change our launch strategy.

Matthew Weston Analyst

So just a quick follow-up. The only thing that's clear is if you set a primary endpoint that includes all of the higher-risk patients and demonstrate positivity, isn't it going to be very difficult for you to negotiate with payers and say we're only going to focus on the higher, higher risk patients in the early stages because you could easily drift down into essentially all comers? Or is there a potential that you have to change the endpoint and focus on the 90 cutoff?

Victor Bulto Executive

Yes. So I mean in terms of risk reduction, and Dave can comment to that. Of course, we'll have to see the results before we make those decisions, right? So that we will see the magnitude of the effect. But irrespectively of that, and I'll let Ingrid comment for the HTA markets.

One thing is price that will have to be incorporated. The other one that we can know with respectively of is who are we going to target and why, right? So these are different strategies that we will have to weave in. But Ingrid, I don't want to -- for the HTA markets where payers will look at this much more closely.

Ingrid Zhang Executive

Yes. So I would first say, based on Entresto like our experience, international contributes to about half of the global sales, yes. And secondarily, I mean, yes, U.S., we talked about IRA impact, but internationally, we're guiding towards more 2039. So we have a reasonably long trajectory. And the third point is building on what Victor said.

We're going to be taking a much more focused approach, right, which basically means is, we are going to essentially and leveraging the learning of Leqvio using the same field force, targeting the same physicians, but disproportionately go in where there's an urgency to treat. So that's like CCUs, that's like cardiac, rehabs, et cetera. And then HTA markets we're launching with actually outcomes data. So actually, that's a bit of different scenario from Leqvio, right? And of course, we have to do new testing.

But again, we're going in where the urgency to treat is significant and building into the lipid panel. So we're already making quite significant progress there.

Victor Bulto Executive

Yes, Rich? You have -- you guys decided. You pass on the mic.

Simon Baker Analyst

Simon Baker, Redburn Atlantic. I'll stick with pelacarsen and again, sort of related to

Matthew's question on the commercial launch strategy. The other element of this is testing. And clearly, in this hotel today, testing provision is phenomenal. But thinking more broadly, across the U.S.

and international markets? Where are we? And how will you drive that going forward because it's obviously part of the launch? And then a second quick question, we saw data from Lilly a few days ago with their oral muvalaplin. Just your thoughts on how that fits in within this market, we were talking about in an earlier session the relative merits of orals versus injectables in this particular setting.

Victor Bulto Executive

Yes. Absolutely. So why don't I ask you, Dave, to address that second question on the Lilly data and oral versus injectable, and then Ingrid and I will address the second one.

David Soergel Executive

Yes. Yes. I mean, look, the data look good. I mean, the drug seems to work. I mean I think the thing that we run into typically in these chronic diseases is people not taking their medicines.

And one of the reasons why we have injectable and long-acting strategies in chronic diseases because it improves adherence and improves population outcomes overall. So the reality is different patients are going to prefer different options. But I think ultimately, when you -- I was going to actually comment also from the previous question, our pipeline strategy also buttresses this whole -- the entire strategy, right? So we have other long-acting agents that we're developing as the fast followers. So we'll -- we have -- we'll be the first-in-class, first opportunity for Lp(a) reducing therapy.

We'll introduce that with great data we expect. And then we have -- we'll have the next generation of the next siRNA follow-ons to come as well.

Victor Bulto Executive

Great. Thank you, Dave. Do you want to start with -- there's quite some differences in lipoprotein (a) testing across the globe. So maybe we'll start with Ingrid.

Ingrid Zhang Executive

Absolutely. So again, international, we are spending across 80 different markets. So the situation is quite different. But having said that, testing is something that we're absolutely really focusing on prelaunch activities on. And as we're saying, we're learning from vallecular experience.

And this is going to be super going to be focused and targeting launch. So we're going in, targeting stakeholders with HCPs and patients who are at higher risk, premature at CV events in the last 12 months. And we're looking -- we're testing them where they are, so for example, as I was saying earlier, in the CCUs, cardiac lab, cardiac lab rehabs as well as lipid clinics, where there's essentially for us -- much easier for us to raise the awareness.

And the second point is we're going in building this into the lipid panel. So make it easier. So rather than the individual tests, but just part of lipid panel, such as LDL-C. And we're seeing

very good progress. For example, in the lower end, in Germany, we've actually gone from very single digit, we've tripled that testing rate in the last year.

Whereas in markets like China, we're actually in a very good place. The rate increased from 15% to 30% in the past year, which give us the confidence that, as we are waiting for the data readout, coupled with the fact that available therapy, encourage physicians patients to test and treat. I think an international guideline also is recommending patients to raise awareness of lp(a) through testing. So I am confident.

Victor Bulto Executive

Yes, the guidelines recommend now a once in a lifetime testing for lipoprotein (a). In the U.S., we have lower levels of testing right now than compared to China. But when you see a level of awareness amongst cardiologists, there's about 98% awareness on lipoprotein (a) testing amongst cardiologists, and about 1 in 2 cardiologists have at least tested 1 patient over the last 12 to 18 months, right? So that is increasing and the level of testing has increased by about 20% again in the last 12 to 18 months. We do believe that's an area where we'll have to spend quite some time and energy.

But at the same time, again, we'll do it in a targeted way rather than testing everyone. We know in LDL-C everyone's tested, not everyone's treated. So going back to who is most likely going to benefit, but also who is most likely be willing to take the medicine, again, linked to early events or premature events and others. Who has the mic now?

David Soergel Executive

You have it.

Unknown Analyst Analyst

So yes, just following up again on pelacarsen. So what do you see as would be a clinically meaningful profile at 70 and 90 in terms of MACE reduction in -- so is it 20%, is it 15%? And what sort of difference do you think you need to see between the 2 to go down a more targeted approach into the greater than 90 population. So does that need to be a 10% difference just kind of like rough numbers?

Secondly, just following on from the testing questions really what drives treatment in things like LDL is guidelines though. And as you pointed out, guidelines at the moment for a single lifetime test. So how long and how quickly do you think you can guidelines implemented for regular Lp(a) testing, aside from just getting it on the panel actually just that being embedded into guidelines?

And then the last question is, assuming this does take time to roll out, there are longer-acting agents with potentially some of them greater Lp(a) reductions that are coming through behind. So what is the risk that you sort of create a market for them? So how far behind do you think your next generation can actually be to avoid that happening?

Victor Bulto Executive

Great. So why don't we start with the first questions, right, on the outcomes that we would like

to see, particularly if there's a difference between 70 and 90.

David Soergel Executive

Well, so what -- so we have to think about what the unmet need is here first, right? So there are no agents currently that effectively reduce Lp(a) and reduce cardiovascular risk on that basis. So starting with that unmet medical need, what ends up being clinically meaningful is a drug that will reduce risk to the level of at least 15% and probably 15% to around 20% is what one would typically expect from these outcomes trials. And if you look back over the last few outcomes trials that have delivered, they've been in that relative risk reduction range.

When we think about -- you asked sort of a nuance question about what the cutoff levels are in terms of risk reduction. Because we believe Lp(a) is a continuous risk factor, we would actually expect relatively similar relative risk reduction, right? The difference would be an absolute risk reduction. You would assume that the higher risk stratum is going to have a higher absolute risk, and therefore, the relative risk reduction that you get is going to produce a larger absolute risk reduction. Long story to basically say we would expect a similar numerical result on relative risk reduction, but the absolute risk reduction should be a bit higher and that higher stratum.

Victor Bulto Executive

Ingrid, do you want to comment on treatment guidelines? And how do you expect them to evolve in the international markets?

Ingrid Zhang Executive

Sure. This is -- it's somewhat related to your third question, which is how we're going to leverage the first-mover advantage, right? So absolutely, I think guideline shaping, working with important stakeholders in terms of -- again, with the data readout. We're really looking forward to having that guideline changed as soon as possible. I think that's part of the prelaunch efforts, right?

The second point I want to make is we -- our effort is really being able to target the most relevant stakeholders, physicians, patients at high risk, as I was saying. I think the third thing is we're testing where it's relevant. And maybe I also wanted to just double-click on our prep effort is also focused on how do we expand the access that's needed for this group of patients, and especially in the international market. Having that early mover advantage whether in terms of setting the price for access, whether it's in terms of tendering business or even hospital listing, really drives the sizable differences. And we're really looking forward to using that opportunity.

So as soon as the therapy becomes available, we're going to be benefiting as many patients as possible in that targeted population. But of course, U.S., right, that matters a lot.

Victor Bulto Executive

Yes. No. And I would say from a commercial standpoint as well, just to raise there's a very high degree of synergy between the stakeholders we're addressing with Leqvio and the ones with pelacarsen. So we would take any day being first in market and do that effort in an area that

we know really well. And as you pointed out rightly particularly with a strong potential portfolio coming after that.

So Shaun, maybe you can comment on how soon you think we can start seeing some data on that future portfolio in life cycle management?

Shaun Coughlin Executive

Yes. Thanks, Victor. So we're very excited by the paradigm that Leqvio has established long-acting placebo-like safety, very effective new option for making prevention easy. And of course, we do have a suite of follow-on programs to address other risk factors in a similar way. We're unable to disclose the stage of specific programs, but I can say that we'll have multiple programs in the clinic next year.

Victor Bulto Executive

Right. So multiple programs next year. Yes, next question.

Unknown Analyst Analyst

Sorry, just one more on pelacarsen. Just the idea of a specialty launch because you've tried before, I think, with the PCSK9s. They put in 40,000, and it went absolutely nowhere. I know they were sort of bridging primary care and specialty and not really doing either. But just price is key here, isn't it?

Victor Bulto Executive

Yes. So price is key. When we say specialty launch, don't equate it necessarily to a high price right from the beginning. What we're saying is, from the perspective of how do we go to market, including price, including what access, but not limited to that, included to in the U.S., for example, who are we going to target with DTC to begin with, for example? How targeted are we going to be, and which physicians are we going to target?

So Ingrid had a great example here. What we are seeing with Leqvio is that we're seeing progress when we started down to patients with have higher risk, higher perceived risk as well and where we started targeting, for example, interventional cardiologists, right? There's a segment of physicians that are much more prone to identify and address risk factors in a certain population of patients.

So I'll be a little bit more specific when it comes to lipoprotein (a). We know that patients who had either themselves in a premature event or had premature events in their families are much more prone and eager to seek treatment and adhere to treatment, right? So that's, for example, how we're thinking of deploying DTC activation and HCP activation. Then price comes into that factor, but it's not set. It will depend on what we see in terms of cardiovascular outcomes.

And of course, we're learning from past experiences of what happens when you go above certain thresholds. So all of that will be taken into account.

David Soergel Executive

I'll just add -- can I add one thing?

Victor Bulto Executive

Yes.

David Soergel Executive

I mean I think the other thing that's really important to remember about Lp(a) versus LDL is that when LDL was first identified as a risk factor, we started getting effective therapies to manage it, the first statement was always, well, you should try to diet and exercise first, right? And then of course, that is completely unsuccessful. And so now we have effective medicines that actually do the job much more effectively. But we've wasted a long time, I think, as a field, talking about diet and exercise. With Lp(a), we know already that diet and exercise doesn't work.

This is a genetic disease. So it's a very different sort of medical paradigm when you think about it. And by the way, once -- I don't know, I'm not going to ask people to raise your hand about who eyes a LP(a), but I'll raise my hand, I have high LP(a), right? So I will get my family tested, right, because I want to be able to project and protect my family for the future. So it's a different dynamic than you think about for LDL.

Ingrid Zhang Executive

And I would just add internationally, right? Because Novartis, I mean, we are the leader -- one of the leaders in the international markets. And we have an incredible heritage in cardiovascular. And so maybe the comparison to the PCSK9 player is perhaps not as fair, right? Given our rich experience and legacy, today's portfolio synergy with Leqvio and Entresto, I remain confident in our launch.

Victor Bulto Executive

Great. Thank you.

Peter Welford Analyst

Peter Welford, Jefferies. Two questions. Firstly, just sticking with the pelacarsen topic, but thinking, I guess, internationally more, is it potential that on a country-by-country basis, you think you could actually end up with different large strategies? I guess I'm thinking some countries presumably in Europe or equally rest of the world could perhaps think this is worthwhile for a high population, whereas others on the other hand, maybe be more encouraged to do a broad launch? Or is that not something you want to pursue?

Because I guess that could then impact as well, pricing potentially on a country-by-country basis and reimbursement.

And I guess, countries like the U.K. were keen, although it was disaster to do inclisiran. This is obviously a very different dosing profile. Can you achieve anything like that? Do you think that you've done in places like the U.K., Middle East?

Or is it not really feasible yet until you get to that every-6-months sort of shot. And then I've

got to ask -- sorry, the second question got or maybe was already to. I've got to bring up a bit because it's obviously cardiovascular. Just curious here on your thinking, obviously, you've talked about long-acting siRNAs. We know most of the targets in obesity are pretty challenging here with that sort of idea.

Do you have any ideas top of mind as to what targets could be amenable to your dosing strategy?

Victor Bulto Executive

Great. So why don't we start with the question on pelacarsen across other countries?

Ingrid Zhang Executive

Absolutely. So of course, international is a very complex geography, right? So certainly, we'll have to look at -- I mean, we're going to price responsibly, but we also want to recognize the innovation that it brings the society in patients. We're going to look at this closely. When -- and at extreme, you're going to have Japan, which actually we're going to expect in pricing very similar to the, U.S..

But on the other hand, HTA markets where we have to look at how we value this. But it's a great thing that we're launching. We're going to be the first therapy into the market as well as we're going to launch with outcome study. So that actually puts us in a very, very good position.

Markets such as China, again, huge volume, and we have to get to the right price and volume ratio. And then, lastly, maybe I'll make a comment because again, we have large population, 7 billion people in the international region and looking at Novartis' commitment to access. And this is where we actually have a strategy of emerging market brands that how we serve the low to middle income countries. And that's something we're quite proud. So yes, it's going to be different.

You're right.

And I think you also have a point about U.K., yes, you were mentioning U.K. Now we're going to take the learnings of Leqvio? I mean, as you know, U.K. is a very special situation where how we are working with NHS. But that being said, this is going to be -- it's a bit different from Leqvio, yes, the lipid lowering versus LP(a) is a bit different market.

And there's no -- direct access don't work. There are no alternatives right now. So I'm hoping we're learning from this. But certainly, we are going to be also working with cities, provider groups to see how we can be helping a broader population where it's appropriate and where it's right. That gives us the right price and volume benefits.

Victor Bulto Executive

Great. Thank you. On the obesity side, before I pass it on to Shaun. I mean, we've been very clear about how we see the market. Clearly, a very attractive market, but one where we will have to see a differentiated profile to support the -- not only the investment but also the commercial efforts that will be taken -- will have to take once the 2 current players are well

established.

There's a number of future entrants as well. And Shaun, of course, has been working on this for a while. So Shaun, what is it that you'd like to share on the topic?

Shaun Coughlin Executive

Yes. Thanks, Victor. So we agree as the question implies that the field will evolve. Incretins are wonderful medicines, transformative in many ways, great for Type 2, not obviating the need for other medicines to address risk factors -- other risk factors specifically. And for obesity, the tolerability issue, the adherence issue is something that's top of mind to sustain the benefits that people are achieving with incretins.

They need to continue to take them. It's easy for some people, not for others. So we do believe that the field will evolve, that there's room for orthogonal approaches. We're studying a number including durables and energy-wasting and lean-mass-sparing mechanisms. We are exploring siRNA based approaches.

I can't disclose targets at present.

Victor Bulto Executive

Thank you very much. Yes.

Matthew Weston Analyst

Matthew Weston again from UBS. I want to pivot to renal. So on the slide above you, half the slide is renal. Of the questions you've had, none of the questions are renal. And I think that indicates a challenge of a therapeutic category that the audience probably has had very little exposure to over their time looking at the pharma industry.

But there's clearly a huge excitement at Novartis and a huge excitement probably in the drug industry.

You said yourself, victor, that all rare diseases, but they add up to a very large number of patients globally. It's going to be a slightly unusual question. How do you engage investors to make them understand what you see as the potential of renal when it's an extremely fragmented rare disease market that we just aren't familiar with because it's very clearly a big part of getting the revenue growth 2028 onwards? And quite frankly, if you look at consensus, market doesn't believe you.

Victor Bulto Executive

Yes. So that's a great question, Matthew, and thank you very much for it. Look, I'll separate the question in 2 parts. I'll ask Ingrid to first comment on what the prevalence numbers are in Asia, right? Because we do think about this as a rare and ultra-rare disease from Europe and the U.S.

perspective. But she'll share numbers about how those -- that population is substantially larger, for example, in China. So maybe we start with that, and then I'll comment on the rest of the strategy.

Ingrid Zhang Executive

Yes, sure. So yes, it is multiple diseases. Yes, it's rare renal overall. But I would just double-click on IgAN, which actually is a much higher problems in each agent population. You probably heard from Victor and David, when they shared in the previous conference, which the epidemiology is between 7 to 24 patients per million population, but number is orders of magnitude larger in Japan and China.

So for example, biopsy confirmed that patient cases in China alone is close to 1 million, yes, versus something like 20,000 for C3G. So it's a very, very different ball game. So that's the first point.

On average, a nephrologist sees a lot more, many, many more IgAN patients versus others. So that's the first point. The second point is that we also have a tremendous legacy in renal, starting from our transplant days, but also through our commitment to cardiovascular through hypertension, but also Leqvio.

So I will then turn it over to Victor.

Victor Bulto Executive

So that is one area. The other one and the reason why we're looking for a multi-asset, multi-indication precisely because what you see. I mean, these are rare and ultrarare diseases. But -- so if you go with one single asset and try to commercialize it, it's going to be a very inefficient and complex task. Here, we will be deploying singular teams that are actually relatively small in size, that actually will target all these assets that you see in here in a highly synergistic way, right?

And there's almost 70% to 80% overlap in all the prescriber bases in all these diseases that we can tackle quite effectively. And that's why we've also been working as well on the patient-finding capabilities. Once you develop those capabilities, they're replicable across all those different diseases.

It's also an interesting field from 2 other perspectives, right, and that's part of our strategy across many of the therapeutic areas that you will see. I mean we look for areas where, one, we have a unique right to win; and two, that are not heavily intense from a competition standpoint and from a payer control. I mean if I speak specifically for the U.S., these are relatively small areas under the radar of payers, less rebates in general, right, where we are going to realize over time higher net prices moving forward. So if you combine sizable populations in aggregate, small resources compared to other markets, lower rebates and higher prices, you end up compounding all these effects into what is a substantial business over time. Yes.

Eric Le Berrigaud Analyst

Eric Le Berrigaud, Stifel. Two questions on renal as well. You determine the peak sales for iptacopan quite a while ago was already CHF 3 billion way before you knew about all the data in C3G and IgAN. Since then, you know the data, you get the acceptance of filing and peak sales still is CHF 3 billion plus. So maybe plus, I can say a lot.

But just to understand what are the push and pulls, what could determine maybe higher potential than CHF 3 billion? Is it IgAN that carries most of the potential, and how you would split this potential across the different indications?

And maybe given an answer to this in the second question, in terms of the IgAN-specific indication, it looks like the drug will go first into third line, fourth line if only because of the price of it, and so after SGLT2s and all the therapies will have been used. But it looks like not all IgAN are identical, and it's very heterogeneous and some are complement mediated and some are not. And so it could potentially be used early in the disease as soon as you get a certainty that it's complement mediated. Do you have enough data to go in earlier lines in the specific population? And is everything in place to target those patients as early as needed to do it?

Or do you need more data to do this?

Victor Bulto Executive

Yes. So I'll ask Dave to comment first on the data and how we are thinking, and what we're hearing from the nephrology community and where they see iptacopan versus atrasentan, for example, or the anti-APROs and then I'll tackle the rest of the question.

David Soergel Executive

So you've probably seen the updated KDIGO guidelines around IgA nephropathy treatment. So what you just said about the heterogeneity population is basically recognized by the new KDIGO guidelines, right? So you tackle 2 pieces of the pathophysiology, you tackle the chronic kidney disease part, and there, you think about agents like ACE inhibitors or endothelium receptor antagonist like atrasentan. And then secondarily and at the same time, you target the immuno-inflammatory mechanisms. And there, you think about iptacopan, right, where it targets the inflammatory part of IgAN.

So I think the field has evolved from just IgAN being this singular disease into something where there's a much more refined approach. And this -- honestly, this is because the therapeutic options have evolved substantially over the last 5 years. It's been actually a remarkable progress that's been spurred by both the evolution of the science, the evolution of the regulatory environment and drug discovery and development in the space.

So I think where we see iptacopan fitting is really as a therapy for those patients who continue to have a very strong inflammatory signal despite the initial therapies. As you pointed out, I mean, everybody is going to start on a RAS inhibitor and they're likely going to start on SGLT2, right? I mean that's just what we would expect. But most patients, many patients will continue to have proteinuria despite those effects. And in fact, in our trials, we optimize RAS inhibition before you start -- before you start the randomized control part of the trial.

And we show, of course, substantial benefits of iptacopan, atrasentan and Zigakibart in these patients. So I think it's really exciting because the field is evolving and it's becoming much more specific. Your second question about earlier lines of therapy, we didn't study it so I can't say specifically. Our entry criteria were very specific to the 1 gram per gram UPCR entry

criteria and so these were patients who were already pretty far along in their disease who have significant proteinuria. Whether you would target patients with even lower levels of proteinuria, even more preserved renal function at an earlier stage when you first identify the disease process, I think the field will eventually start to get to that point.

Now that requires better diagnosis. It requires more biopsies, more refined approaches to finding these patients. But I think the field will go in that direction over time.

Victor Bulto Executive

Yes. And actually, we are now 3, 4 months in the launch of iptacopan in IgA nephropathy in the U.S. And actually, what we're hearing from nephrologists, rather than thinking from a line of therapy, they think in terms of that inflammation marker. So if they see persistent hematuria that comes along the persistent proteinuria and they had to use a couple of rounds of steroids with that particular patient, that's the kind of patient that they actually identify as a patient that may be mediated by the activation of the complement and therefore, they're more likely to actually put on a drug like Fabhalta on top, again, of the foundational therapies. So that's the whole positioning of the drug and actually matches well the pricing.

I mean, the pricing of Fabhalta, we've actually set up understanding that the majority of the indications that we will have are ultra rare. So we priced at that price point, understanding that for IgA nephropathy, we will not be treating the entire population as a foundational therapy, but rather that subsegment of inflamed, activated patients and that's how it's panning out today. To your question on the peak sales guidance, I mean, really, we will see how all the subsequent indications evolve, right? So right now, 2 indications approved for Fabhalta, vast share today across even neuroscience, we have a number of indications. So as we see those going on, you'll see compounding.

We haven't guided to specifically the different indications and the value, but I can tell you that it's actually pretty spread. It's not necessarily IgA nephropathy driving the majority of it, right? There's a component of that, but we see really as a pipeline appeal, which each one of the indications will incrementally contribute to the overall development of this molecule. Yes. I think we have time for one last question.

Graham Parry Analyst

Yes. Just one follow-up then actually on iptacopan and one of the other indications, so C3 glomerulopathy. The big unmet medical need. The Phase II data looked very promising. Phase III, you seem to see a bit of a drop off and efficacy went from sort of 50% proteinuria reduction to 30s.

And the EMPAVELI data seems to be at the higher end. I know it's a mixed trial with 2 indications, but I think most opinion is that, that looks like better data. So I guess the question is why did we see a drop off? And then how do you compare that with EMPAVELI? And if you're in the market first, do you think you'll be able to get stickiness of patients launch quickly?

Or is there a risk here that you're actually going to be a second-tier player in that market?

Victor Bulto Executive

So maybe, Dave, you take the data question, and I'll take the commercial.

David Soergel Executive

Yes. I think, look, the data going from Phase II to Phase III was pretty much as we would have expected. And I think there are a couple of really important pieces to the data that are sort of beyond the UPCR and stabilization of GFR effects that we see in the peer study. The biomarkers show that we fully inhibit the alternative pathway, which is the causative factor of C3G. A lot of times, we don't know exactly what causes a particular disease.

In this case, the disease cause is very specific to the alternative pathway, and we know that we shut that down with iptacopan and we show that in the trial. Second thing I'll say is you can't really do any better than GFR stabilization, right? That's the whole point. And what you see with iptacopan, as we showed on the call the other day, as patients went -- before they're randomized into a peer have a decline in their GFR that's quite precipitous, and you see that completely level off when patients start iptacopan. So the data are very compelling.

In addition, Of course, iptacopan is a pill, right? I mean you can -- it's a twice-a-day pill that's very easy to take. And the other thing that's important before I hand it back to Victor is that we monitor patients by looking at proteinuria, right? So it's an easy marker to track. So an individual when they start iptacopan, you're going to be able to see whether or not they respond.

You're going to see their UPCR go down, right? So it's a relatively straightforward approach. But I'll hand it back to you with respect to...

Victor Bulto Executive

What we keep hearing as well, if you look at the difference between IgA nephropathy and C3G when you talk to nephrologists, C3G is -- IgA nephropathy is heterogeneous disease depending on which one of the hits is most activated. But C3G is even considered a separate and distinct disease, a very high degree of volatility in the proteinuria and variability in the proteinuria, right? That's why they don't necessarily give that much emphasis into the proteinuria, but rather the eGFR. And then from a positioning standpoint, I mean, we expect to potentially be first in market, as you were saying, with an asset that nephrologists already will know that we will have established solid access by the time we launch as well and that is a pill, right? So we fully intend to leverage our commercial presence there to very quickly help these patients who today don't have any other therapy at their disposal.

So we do believe that we will have the right to win here in the first line. And potentially, patients can then move on to other therapies, if they see the need, right, with their HCPs. Anything to add on the international side, Ingrid?

Ingrid Zhang Executive

No, this is actually -- C3G will be our first entry into the rare disease area. So we're really looking forward to that.

Victor Bulto Executive

Great. Excellent. Well, with that, I think we conclude the CRM session. Thank you very much all for your questions and your time. Thank you.

Unknown Executive Executive

Okay. So welcome, everybody, to the neuroscience session. I'm very pleased to introduce you to our neuroscience leadership team, starting with Bob Balow, who heads up Neuroscience Research; Norman Putzki, who heads up development for Neuroscience; and Tracey Dawson, who's here representing Commercial and Tracey leads the U.S. Commercial Neuroscience team. So obviously, Vas has already given you an introduction to our neuroscience area, but really just to remind you that Novartis has been committed to the neuroscience field for many, many years, and it continues to be a very high priority for us, huge area of huge unmet need.

And what we really think is that we are at a really good inflection point, particularly with the types of technologies that we have invested in. So technologies like gene therapy, RNA. And this is being helped now by other advances in the field, including better understanding of disease mechanisms and better biomarkers for measuring target engagement of therapies that also helping us to predict disease outcomes. So really looking at our portfolio, these really are sort of strategy areas. First of all, maintaining our focus in multiple sclerosis, continuing to bring added benefit to patients.

You'll hear a bit more about remibrutinib from Norman. Also iptacopan that you've heard about, which is our oral complement inhibitor, we do know that complement is a component of neuroinflammatory diseases. So we are taking iptacopan forward in myasthenia gravis. You've also heard about our strategies for immune reset using a number of different approaches, but probably most importantly and the one that has a real opportunity to change outcomes for patients is YTB323, which is our CD19 CAR-T approach that can produce real profound depletion of B cells that generate the autoantibodies driving immune diseases. So as well as the other autoimmune diseases you've heard of, we are taking YTB forward into MS as well as myasthenia gravis.

And then building on our leadership with ZOLGENSMA, we continue to pave the way for taking gene therapies as well as RNA therapies into rare neuromuscular disorders. And we were excited to announce this morning the acquisition of Kate Therapeutics that takes us into a whole new generation of capsids that have been optimized to deliver to muscle and cardiac tissue but also detargeted from liver. And Bob can tell you about how we're going to sort of bring that technology together with our own internal capabilities. Also, EDK-060. So this came from our acquisition of DTX.

This is a different way of delivering a therapeutic modality, in this case RNA, using a lipid conjugation that allows really robust uptake into neuromuscular tissues. And the lead asset there is for what I think is quite an unrecognized disease given that it's actually not so rare as Charcot-Marie-Tooth disease. And again, many of these diseases, we do have a deep understanding of the biology given the sort of driven by human genetics. And then, of course, the biggest area of all is really the neurodegeneration space, and we're working across all the major neurodegenerative diseases, Alzheimer's, Parkinson's, ALS, Huntington's using a

number of different modalities and approaches. So low molecular weight oral therapies that may be disrupting the aggregated protein, splice modifiers as well as RNA therapeutics, including ASO and siRNA and antibody therapeutics.

And one we're particularly interested in is targeting microglia with a TREM2 activating antibody. So I think with that, I will throw open to questions from the audience.

Graham Parry Analyst

It's Graham Parry from Bank of America. Just start on remibrutinib in MS. Obviously, after what we've seen with the other BTK inhibitors using relapse rates as a primary endpoint, that's clearly challenging. I think Vas was alluding earlier this year, the potential to do sort of a hard stop futility with a high hurdle on remibrutinib. So I just wonder if that thought process would progress further and what the timing of that would be.

So when will we know if that's actually continuing or not? So that's the first question. Second question is on iptacopan. You got a program running in myasthenia gravis. Just interested why you didn't run a program in MS.

And then on YTB, just perhaps help us understand like commercial strategy. I know it's early days of Phase II, but given that most MS therapies are oral or, I guess, easily subcu injectable or infused so just talk us through distribution? How do you envisage that fitting into the marketplace?

Unknown Executive Executive

Okay. So quite a few questions there. Let's talk with Norman and [indiscernible].

Norman Putzki Executive

Yes. Well, we get a lot of questions around BTKi's for obvious reasons. So let me give you a bit of an update on where the program is. So that's the remodel program. We're running 2 identical trials against teriflunomide as a comparator.

You alluded to the methodological challenges, I think, and that's not really news. Over the past 10 years or so, we have seen a steady decline in relapse rates during the clinical trials on placebo and also on the comparator drug. So when we designed remodel, we knew about that, and we designed the trial in a way that we could address this by an event-driven design, for example, by powering the trial appropriately. And what we have designed in remodel is essentially a trial that is powered to demonstrate close to Kesimpta like efficacy against the comparator. We will be able to manage lower event rates in that setting, but it requires that the biology also pans out.

But methodological, we wouldn't run into issues to demonstrate that efficacy if the molecule does what it's supposed to do. So the trial is going really well at this point. We have, in one trial, 90% or so of patients have passed 3 months, and the other trial is sort of 70% plus. Also important in terms of the safety information that we have in the RMS population, we haven't seen anything. So we're really excited how it is progressing.

In the trial, we did a futility analysis early on based on MRI imaging, and that was unblinded to

our DMC and the trial passed that futility and we could continue as planned. Safety is also continuously monitored through the DMC. So the program is progressing as planned. Maybe last thought, if we see an event rate that is lower than anticipated, we will be able to manage it within the specifications of the protocol because as I said, we designed the trial in a way to accommodate for these methodological challenges that we see this way.

Unknown Executive Executive

Okay. Let's move on to the next question, which was around iptacopan and which indications we've chosen. Obviously, this is an oral complement pathway -- alternative pathway inhibitor. And we've already had approval in complement-driven renal diseases. So what we've tried to focus on here is disease areas where there's really clear evidence that complement is playing a role in the disease etiology.

So while you can see complement elevated in a number of different diseases, in some cases, that's more of a sequelae or consequence. What you really want to do is go to those indications where you think complement is driving the disease. And in myasthenia gravis, although you get the autoimmune antibodies at the neuromuscular junction, there's pretty compelling evidence that the complement is then causing a lot of damage that then contributes to the disease area. And I think the connection in MS is less clear, but I don't know if either Bob or Norman wants to add anything to that?

Unknown Executive Executive

No, we're certainly interested in the role of the innate immune system and complement in MS. I think for iptacopan, which is not something which we think we can access the central compartment with, that would not be an agent we would bring in. But we're really interested in a variety of ways to alter microglia in particular, and the negative effects they may have. So I think it's an interesting approach, but not perhaps for this molecule.

Norman Putzki Executive

Yes, agreed. I mean when you look at our portfolio, you will recognize that we are in a position to make choices how we want to tackle a particularly progressive disease, right? And I think at this point, complement is not on top of the list, but you see other opportunities within our immunoneurology portfolio that will allow us to make some choices.

Unknown Executive Executive

And then Tracey, on the commercial opportunity for YTB.

Tracey Dawson Executive

So I think the first thing to remember for YTB, if you look at the indications that we're looking at, we're really targeting refractory diseases. And so we're some ways yet from bringing it to market. We need to do the experiments first in those indications and understand that it's working well and safely. But in terms of actual commercial preparations, I mean, already today, we're leveraging some of the infrastructure that we have in place from our Kymriah experience. We're also building capabilities around what we term advanced technology platforms, whether that be RLT, whether that be gene therapy programs that allow us to really

sort of become very specialized in delivering these what often could be called just-in-time type medicines where it's very bespoke to the individual patient.

So it's probably -- today, to be honest, it's a little bit too soon to say exactly what that commercial model will look like. But I know we have time in hand to be able to really build out that infrastructure that we're going to need to expand the availability of a cell therapy to the populations that we believe we can serve.

Matthew Weston Analyst

It's Matthew Weston from UBS. Two questions, if I can. One, very near term on commercialization in MS. So your Basel competitor is extremely excited about subcu administration of ocrelizumab. You've just meaningfully raised your Kesimpta peak sales estimates.

I think we'd all be very interested not only to understand early experience from the field as to how Kesimpta versus subcu OCREVUS is going. But also, it's an opportunity for you to kind of lay out how you see Kesimpta in that market of what we see, I guess, as community neurologists where I think you've done well and understand how you are going to fight back and defend your share there? And then the second question, just quickly following up on YTB, I may be completely wrong. I think the trial in MS is in ex U.S. markets because the FDA hasn't yet or you haven't yet got permission to do CAR-T in MS in the U.S.

I might be completely wrong. If that is correct, what are the hurdles to actually get permission to run MS trials with CAR-T in the States?

Unknown Executive Executive

Okay. Thank you very much. Tracey, over to you to start with.

Tracey Dawson Executive

Yes. So as you heard this morning, we've raised our peak sales guidance to $6 billion globally for MS. And so first of all, I would say that we're very confident in doing that for multiple reasons. As Vas already alluded to a bit today, with the reduction in the BTKi competition, we believe there's more headroom for growth for the therapies that are on the market today, including Kesimpta. Specifically regarding the OCREVUS subcu formulation, first of all, I always pull it back to what is it that makes Kesimpta unique?

Because at the end of the day, if you really want a subcu formulation for a patient, this is why we have been very successful in that general neurology segment that you mentioned, it's because Kesimpta is purposely designed for 1 minute once a month, to be given at home or anywhere on the go. You can't do that with the current subcu formulation with OCREVUS. It still requires premedication. It still requires physician administration. It still requires to be in a hospital setting.

So, so far, we're only a few weeks into the launch in the U.S. and actually in the U.K. as well. We're not hearing any great experiences. We're not hearing any bad experiences.

We're generally not hearing much experience yet at all. So I think it's an area that rightfully so

we'll continue to watch. But my point, whenever I talk about this, is to bring it back if a patient really wants a subcu formulation, the best subcu formulation, the only true subcu formulation on the market today's Kesimpta.

Unknown Executive Executive

Thanks Tracey. And Norman, do you want to comment on the location of the YTB trials in MS?

Norman Putzki Executive

Yes. So this is almost hot off the press. So we just started these trials. We have talked to health authorities globally around how to do it. With the FDA, it's not binary.

It's not doing it or not doing it. The question is what -- like how do you do it? So questions like dose, safety requirements, monitoring and so forth are important. And certainly, we heard from the agency what they're -- where they set the bar. And at this point, we were able to accelerate the program by going ex U.S.

But clearly, going forward, we are working with the agency to provide the data that will allow us to expand into the U.S. But for the sake of acceleration, we're currently working outside the U.S.

Richard Vosser Analyst

Richard Vosser from JPMorgan. I just wanted to go back to remi. And I know you highlighted that it's event-driven and powering for Kesimpta like efficacy. But it's the control arm that has been performing better and the early-stage patients that just don't relapse. So just maybe you could drill down a little bit more because I don't see how tough the things you've described will guide against perhaps the biology actually isn't there on relapses and it's there on disability progression as we see from the data.

So why don't you change the endpoint and things like that, which others are thinking about?

Unknown Executive Executive

Okay. I will take that one. Let me start on the biology. So I think when you look at the class, I think you see some commonalities between the different molecules in development. Except for remibrutinib, the other assets that we are aware of had dose-limiting toxicity.

So they could maximize the dose. We can do that. We are going with 100-milligram BID. That's important for the selectivity that the molecule has for tissue penetration where we can maximize the efficacy with it. We haven't seen -- because of the selectivity of the asset of remibrutinib, we haven't seen liver toxicity neither in the CSU population nor in the MS trials going forward.

So that's also a differentiating factor.

When you look into the Phase II trials, you could already see that it was a dose response and then there was a decision made to pursue with a lower dose. And I think that has an impact on how you perform in the Phase III trials. And when you look into the recent data that one of our competitors has shown, plus the Phase II trials, I would say that there is actually a strong

indication that the class has an anti-inflammatory effect. I wouldn't dispute it. The question is in a Phase III trials, can you actually demonstrate that.

So at the end of the day, you need to have a molecule that is biologically active enough to actually differentiate from the comparator. So I -- like the way I look at it is not that Aubagio or teriflunomide is doing any better. It's just that we have a different population in these trials. These days that are somewhat earlier, somewhat less active.

It's interesting when you look at the inclusion criteria and when you look at the baseline demographics across those trials, you don't see any huge differences actually when you compare, for example, to the previous ofatumumab trials or even earlier trials. So there's not just one factor that is really striking where it's a like a totally different population.

What we need to keep in mind that over time, the diagnostic criteria have changed where you make a diagnosis of MS earlier. Also the armamentarium has changed, where I think these days, particularly in more sophisticated markets, you see that patients who are active, they are more likely to go on anti-CD20 like Kesimpta and you get active patients still in the trials, but it's a different kind of an activity. So I think there are methodological constraints. But if the biology pans out, and if I assume like a similar activity rate on teriflunomide that we've seen in the comparator trials, we will be able to show Kesimpta efficacy in the trial. But the biology has to work.

And I think when I look at the characteristics, what I would say is pharmacological superiority of remibrutinib. I think we are very confident that we have a differentiated molecule that has the ability to maximize the potency on efficacy and remain safe without liver toxicity.

Simon Baker Analyst

Simon Baker from Redburn Atlantic. Two, if I may, a big picture one first. It's good to see some discussion of your gene therapy activities because, say, for the occasional comment on Zolgensma IT, we've not really heard or seen much since it was approved.

So I just wonder if you could give us any idea, firstly, what's been going on in the background. Secondly, why we didn't get as a lot of people thought a fast followers once you'd established the first product on market? And then the second one, going back to YTB and the commercial angle. Two factors. I was wondering about scalability and reimbursement.

On scalability, you said you've learned and used your learnings from Kymriah. How does the manufacturing process and scalability of YTB as it's envisaged compared with where you were with Kymriah?

And secondly, in terms of reimbursement, this is -- I suppose in a sense this is a learning from gene therapy that you have a very, very expensive one-off therapy. So over time, the economics look fantastic, but the budgetary impact in year 1 looks to be obviously challenging for some payers, didn't seem to be much of an issue with Zolgensma. But how do you think about it in this setting? And I mean, this is almost a question of more sort of finance than science. How are you -- what are you thinking in terms of how YTB is priced and when it's paid for?

Unknown Executive Executive

Okay. So thank you very much, Simon. So let's go to the gene therapy. And things have gone quiet for a while, you might say. So Bob, maybe you could say, what actually has been going on over the last few years.

Rob Rubinsky Executive

Absolutely. Great question to sort of frame the same way we talk about it internally. I mean we look at the great success of Zolgensma and what drove that. And in part, it's that it targets the right cell types in the nervous system at the right time with a payload that can actually fix the problem that's there. And with the first generation of capsids, mostly naturally occurring capsids.

We see that most different indications that we would be interested in, don't match that tropism of the virus, either with the level of dose that one would need to give, which brings up safety concerns or for you could administer it surgically or other ways to administer it but it doesn't get to all the cell types you want. It's really about biodistribution.

And so we've chosen to approach this by innovating in capsid space. That's been our major focus. And we've done 2 deals, obviously, one you heard about today, previously one with Voyager Therapeutics for CNS tropic capsids, and we've enabled a whole series of internal programs to utilize those.

And then the second one is Kate. And Kate -- each of these uses a similar technology. They're really taking a naturally occurring capsid and evolving it in different species to try to define a tropism profile that matches the disease that you want to go after and then typically de-target safety tissues.

So Kate, we think, has a really best-in-class myotropic capsid. It's muscle extremely well, cardiac muscle as well and very low tropism for the liver. So we think for this cluster of neuromuscular diseases that we're interested in, somewhere on the chart there, FSHD myotonic dystrophy that this will match very well with able to -- with us being able to give a safe dose and effectively transduce all the muscle fibers that we'd like to for maximal efficacy.

So that's been our entire focus actually over these last period of years. And we did a lot of internal work. We've published a lot of work about where AAV9 goes in different administration profiles. Although it still is remarkably effective, in fact, for IT, right? So I don't know, maybe I'll pass it to Norman.

Norman Putzki Executive

Yes. I think -- I mean, you alluded to the challenge that we have seen. We're excited now about the IT readout that's still happening before the end of the year. It offers an opportunity across a really broad range of SMA patients. So we study kids between 2 and below 18.

They can sit, but they never walked. So if this onetime gene therapy, Zolgensma IT, it's going to work, it will really open up a new opportunity for many of these prevalent patients on the market, and you also talked about the business model there. I think it will play an important role to address those patients because in the U.S., we have like 100% newborn screening

these days. So that's for Zolgensma IV, as you know, I think that's the door opener that has happened over the past couple of years.

Maybe I would just only add that in addition to what you said, like we haven't been that silent on gene. Just a quick reminder, last year, we acquired cystinosis cell and gene therapy from AVROBIO that's now ready to go into the clinic early next year. So there will be much more visible activities to that end. And I think also from the perspective of the recent acquisition with Kate, these programs move really fast, right? We have a very supportive regulatory environment, I think, specifically in the U.S.

that will hopefully allow us. It's early days to give exact time lines, but that should allow us to move forward pretty quickly.

Unknown Executive Executive

Thank you. So Simon, I'll go on to your next question, which -- and I'll take the first part of it, which is around the scalability of YTB. And so this is using what we call our T-Charge platform. Vas refers to it as rapid CAR-T.

So Kymriah used the first-generation process, which actually took 10 days to grow up the T cells. And during that time, at this stage, we were obviously targeting on B-cell lymphomas and oncology. And we did a lot of correlative work of looking at the drug product and how that correlated with efficacy. And what we found is that when you first take out the T cells, they contain a lot of what we call stem-like T cells that are actually -- they proliferate. The longer you grow it up ex vivo, the more those mature, the less you get those stem-like cells.

And it was actually the more stem like they are, the more they can replicate in vivo and actually give you a very prolonged response.

So this led us to change to the next generation, which we call T-Charge where we actually have greatly reduced the timeline from a 10-day grow up of the cells to actually only 2 to 3 days, but the cells retained their stemness. So it really speeds things up. But importantly, those cells can now divide in -- back in the patient. And so you can give them a much lower dose. So it's a much lower dose.

So that allows scalability. And of course, the time to actually go through that process is also greatly enhanced.

And just to also make the comment that this is one aspect of targeting a sort of immune reset. We're also learning a lot by this to look at other types of modalities, for example, other immune cell engagers, for example, that would have the same type of approach to deplete B-cells.

But then in terms of the reimbursement and how we're thinking about that, I'll hand that over to Tracey.

Tracey Dawson Executive

Yes. And to be honest, it's too far -- too soon, too early to even comment on what we might choose from a price strategy or even any reimbursement strategy. What I will say is though,

that clearly, whether it'd be through Zolgensma with iptacopan or rare disease capabilities, we've built an incredible expertise and ensuring that we can make these therapies accessible to patients irrespective of the payers that we have to work with.

So that clearly stands us in good stead. So we are at a point ready and able to should we be successful to bring therapies like YTB to market or other gene therapies, we feel really confident that we've got the right set of knowledge, skills and capabilities to make that happen so patients get easy access.

Unknown Analyst Analyst

Two questions. Firstly, on one that I think it's come up, no one's mentioned it at all. I guess I'm sort of curious why no one has mentioned, but DLX313 in Parkinson's, I think we're expecting data, I'm assuming imminently. Just curious as to what in your mind would warrant a successful Phase II to justify taking this forward. And in particular, what sort of considering which endpoints would you be closely looking at given the mechanism as well of this?

And then secondly, just you mentioned with regards to Kate looking at myotrophic capsids. Any aspirations or thoughts on entering DMD? Obviously, there's programs there already, but I think there's a lot of debate on whether or not they really address the underlying concern and do much at all. In your mind, is it worth pursuing because other companies have decided to fall by the wayside and decide it's done now already?

Unknown Executive Executive

Okay. So first question is on DLX313. So this is an oral small molecule that disrupts alpha-synuclein aggregation, an important driver of Parkinson's disease. So trials are ongoing.

And Norman, so do you want to just say what we'd want to see in those trials to warrant taking forward?

Norman Putzki Executive

Yes. So you're rightly assuming we are on track. So we will see the data as we promised before the before the end of the year. It's kind of an unprecedented area that we work in disease and others to disease modification in Parkinson's disease.

So we have done a lot of work with the regulators over the past 2, 3 years to understand what acceptable endpoints would look like for disease modification because, as you know, everything else is just symptomatic treatments. Scales are established, but how do we use these scales to demonstrate that actually disease modification is happening.

So the agencies have been very open with us to discuss what potential endpoints could look like. So in terms of proceeding from the Phase II into Phase III will depend on the question, are we able to find a signal in the Phase II that would somehow match to an endpoint that the regulators have indicated acceptance to us. So I think it's fair to assume and also based on previous experiences that, it will take quite some work to tease out that signal that you need to see to be confident to take actually this program forward in a -- into Phase III. But this being said, our Phase II is almost 500 patient study, 2 dosages versus placebo. It's 18 months plus an open-label extension.

So if there is a signal in there that we can use to take it forward with confidence, this study will show it. So it will not require another Phase II in order to get to that signal.

Unknown Executive Executive

Okay. Thank you, Norman. So the next question, I'll send to you, Bob, is really about what indications we're thinking about with regard to the Kate myotropic capsids and how we're feeling about the DMD data from other?

Robert Weltevreden Executive

Sure. So yes, maybe I'll frame it in terms of the area first in general. I mean neuromuscular medicine, which is an area I used to work in as a physician scientist. And we see there in terms of the biology of these diseases, we know the genes that cause the -- our understanding of what modalities may be able to address them and then clinical developability really coming together. And while DMD is the one that you opened with, we're also -- and very excited about ones on there that you may not have ever heard of, right, so Charcot-Marie-Tooth disease type 1a, one of the most common inherited diseases of the nervous system.

Many, many patients with absolutely no treatments. Same for FSHD.

So it's this entire cluster of diseases built off of sort of the success that you've had in Zolgensma and in that space in general that we really decided we can be successful. And so for Kate, their capsids and specifically for DMD, I think the thing you would start with there is as you did, there's unmet need. We've seen this.

The patients need more. They're still looking for more effective therapies. And it's not a space that we expected would be perhaps like Zolgensma, where the first one in was so effective it wasn't clear what needed to be done and it's taking longer because those drugs are so successful. In DMD, I think we're going to be seeing a series of innovation around capsids, around payload approaches to try to bring in all of the patients and then to improve efficacy over time.

The first generations that you're talking about utilize dystrophin constructs that even at their best are going to make a person like a Becker patient. So fundamentally, that goal was always going to be, let's eventually make something better for those patients. They still need it. So that's how we see it. And we are very interested in the space because there's unmet need.

Graham Parry Analyst

Graham Parry. Just 2 follow-ups actually, just on the -- first one was on remibrutinib, just to confirm. So when you're saying you think that if you -- the drug performs as you would expect it to, you would be able to hit the relapse rate reduction. So do you have absolute relapse rate data in-house that's showing you're well below the 0.1 level that you'd expect the control arm to be with Aubagio. So that's the first follow-up.

And the second one is on DLX313. So in terms of what would warrant a successful Phase IIa readout for you. So I think based on what we've seen with prasinezumab, you probably missed the primary endpoint in that study, but maybe hit a motor symptom secondary endpoint. And

if you do that, were you suggesting you could go straight to Phase III because Roche went to a Phase IIb because they -- I think they need to expand the patient population size, et cetera. So just 2 follow-ups.

Norman Putzki Executive

So maybe...

Unknown Executive Executive

You go ahead, Norm, I mean they're very much in your area.

Norman Putzki Executive

Yes. We've done this a couple of times. So in terms of the methodology, I mean, yes, we are looking in the ongoing trial. We know event rates in terms of the relapses. We're also looking at disability.

Both of those event rates will determine when we read out the study. So we have a good understanding.

We also have data in-house to get a good understanding of how this blinded trial looks like because we look at the trial, the remodel trial is essentially identical to the ofatumumab trial that used the same comparator. So there's a lot of useful information that we can extract even from the blinded data set in an appropriate way that is methodologically helpful.

So I think all the safeguards are in place to see the efficacy that we assume will be needed for a successful BTKI to enter the market. We were not interested in just having a positive trial by a somewhat modest effect. So we really powered the trial to show Kesimpta like efficacy because we believe in the B-cell class. We do want to add in the B-cell class, and I think only a drug that plays at the same efficacy level will make sense. And so that's where we actually -- that's where we really want to get to.

If the arguments around why these medicines will impact the biology of progression, if that's true, it will also be true for remibrutinib. I actually think because of that pharmacologic profile that we have, we're actually in a great position to show that in addition to what we want to show on the relapses. So in that sense, I feel we are methodologically well positioned to read the trial positive if biology works out in the end of the day. For DLX, yes, so the -- as I said before, we will go if the data allows straight into Phase III, right? I think if the data allows us an important one, to tease out that right signal that we need to see in order to have a reasonable chance to demonstrate disease modification and get the drug approved with a profile that's acceptable to the community in terms of the effect size as well.

So we were not planning to do another Phase II trial.

Operator Operator

Do you go to this gentlemen who hasn't had a chance. Yes.

Eric Le Berrigaud Analyst

Eric Berrigaud, Stifel. 2 MS questions. First on remibrutinib, in the market seen probably as the best of the first 4 BTKs, but unfortunately, a little bit late and only in RMS.

So now you have a competitor that made the proof of concept that is working in progressive form of MS. But unfortunately, you don't have this kind of trial. Is it too late to start a trial in SPMS being active and inactive and now that the risk is lower, maybe the answer to this can be different.

And then with YTB, could you clarify the kind of population you would go after, especially in the RMS part? Would that be very traditional type of RMS patient population going against the existing therapy and then maybe upcoming in between now and then or kind of recycling people, having tried several type of therapies and then still relapsing and not stabilizing or just to understand where you would go and the kind of design we may expect in terms of Phase III.

Unknown Executive Executive

Okay. Do you want to start with remi and SPMS?

Unknown Executive Executive

Yes. I think I mean it's a great question. I will also start on the unmet need again, right? We -- of course, in MS, addressing progression is a huge unmet need. There's a substantial fraction of the population that is not controlled when it comes to disease progression across the entire spectrum, even those patients who have full disease control on anti-CD20.

Over time, you see sometimes disability progression in RMS and you see it certainly in SPMS more pronounced and PPMS is the most aggressively progressing population there.

When you look at the portfolio, you would appreciate that we're in a position where we can make choices, how we want to go after the biology of progression. YTB is already in the progressive MS trials. So that was the next step for us. What you also see on the slide is that, we have various opportunities in the space of immuno-neurology, where we can make choices. We haven't talked yet about our TREM2 modulator, for example, which could have wide applicability across a range of new degenerative diseases.

So that will certainly be on the table because targeting the innate immune system is an important component about addressing progression. So all of that will play a role and can be taken into consideration in terms of decision-making, how to best address progressive disease.

Unknown Executive Executive

And then the second question was around YTB in MS and what populations do you think would be...

Danny Bar-Zohar Executive

I think, Tracey, you already alluded to that, too. I think we are looking at refractory or immune conditions. Same is true for multiple sclerosis. I think ultimately, the benefit risk profile that we will see in the sentinel patients that are currently dosing, we will play a role where exactly we

can position it in the future. For these trials that we're currently looking at, we are thinking about patients who progressed despite -- who either relapsed or progressed despite preexisting disease modification.

There are no standard criteria that everybody accepts what refractory MS really looks like. So there is some flexibility to define that when we think about the later-stage trials. I think at this point, we want to show that in patients who have failed other options that are available on the market, we can use YTB safely and then we take it from there depending on what we're going to see.

Unknown Executive Executive

Yes. Do you want to add anything there...

Unknown Executive Executive

Just to build on the biology piece and really what's behind all of this, right? I mean -- and your question, I mean, what we understand is that the biology of relapses in the disease is different from what's driving the progressive disability at this stage, which is the major unmet need in the disease. And while we have some really exciting assets, which are going to be more proximal to BCL biology and with CAR-T, et cetera.

We also underneath the iceberg with all of the research that we have, but also all of the data sets that we have from these patients, we're really trying to understand what drives that? What are the cell types that drive that? What are the targets that drive progression. I think it's exciting to get early signals from the clinical space to bring them back because I think we can do better. I mean it has so much similarities with neurogeneration, one of our other pillars.

And it's partly why we look at the synergies between innate immune activation and function and targets in both Alzheimer's disease, ALS as well as in progression MS. So I think we're just at the front end of that really. And...

Eric Le Berrigaud Analyst

So I just wanted to go back to Kesimpta and just ask on the high dose Ocrevus that's going to, I think, read out next year. Just your thoughts there, I suppose, on the competitiveness, how that will affect Kesimpta, but also why you don't think you would do a high dose version given some of the PK data that was presented many years ago and thoughts on tolerability as well of such a high dose that would cause some side effects, mean side effects.

Unknown Executive Executive

Norman or Tracey, whether you...

Norman Putzki Executive

I can talk biology after whatever.

Tracey Dawson Executive

Yes. I mean I'll take the first stab and then I'll pass it to Norm. So it's interesting. I'm not too

concerned about the high dose Ocrevus, to be honest, because I mean we're talking about a patient population with treatment rates now, where you've already gone 97% to 99% suppression of relapses.

So there's really not a lot more room for what a high dose can do. And so my bigger concern with high dose frankly will be the side effect and tolerability profile. We already need to premedicate with their anti-CD20, you don't with us. And so -- so I do think -- I just don't see the value of a high dose to be frank. But like any good business person, I'll be watching for the data and curious to see what it shows.

But I just don't see the headroom. I mean, biologically, do you? I mean...

Norman Putzki Executive

I think from a biological perspective, we have not seen that there's any relationship of body mass index and with ofatumumab, right? So like for us, there's no biological rationale to think about a higher dose because we have seen similar efficacy across the entire spectrum and that looked somewhat different with the earlier PK data that was published for the comparator drug. So like for us, biologically, we have no reason to pursue such an approach.

Simon Baker Analyst

Simon Baker from Redburn Atlantic. Just a quick follow-up on Peter's question on DMD. You talked a bit about the work you've been doing on capsids and improving tropism. Have you managed to do anything on payload capacity? Are we sort of capped out around the sort of 5 kilobase pair level?

I'm just thinking from a DMD point of view, is it unrealistic we'll ever be able to deliver full dystrophin in a capsid and therefore, we need alternative nonviral delivery methods.

Unknown Executive Executive

Go ahead.

Unknown Executive Executive

Sure. I mean, the limits of what you can put into an AAV capsid are pretty well defined as you said. And so using standard gene replacement therapy doesn't work there, hence the use of microdystrophin. There are other approaches, clearly, which we're seeing one is using gene editing, one is using multiple [indiscernible], one using RNA splicing. And all of those are actually, I think, going to come into play.

Now whether you need to use a different delivery system or not is a good question. At this point, we're focusing on AAVs. We know what they can do, and we've seen with the evolution that we've put them through that they can deliver safety and targeting.

So we are working on alternative payload approaches and I think that's back to this iterative innovation, which we're going to see in the space. And so more to come, but I don't think we're going to move towards trying to solve at least in the near future full-length delivery with a different vector. I mean you're just adding 2 additional variables that could much further out in time. And I think we'll be more effective with that with some of these more innovative payload

approaches for AAV.

Unknown Executive Executive

Yes. I mean the other component is the extent to which you can deliver to the maximum number of cells. I mean -- and so if you're delivering a gene that may not be equivalent efficacy to what would be the natural one, you certainly want to make sure that you deliver it to as many myofibrils or neurons or whatever the target sellers as possible. And so that's one of the things that we see very promising with these capsids is the efficiency of the delivery. So it really gives the maximum chance for these modified genes products to be effective.

Peter Welford Analyst

Peter Welford, again, Jefferies. Coming back to sticking with Kesimpta. So I guess, have you -- you've on the market now for a while as your competitor in the CD20 class. Have you heard yet from clinicians or are you aware of any sort of perhaps growing reluctance or feeling as to how long some of these patients you want to leave on a CD20 given the -- obviously, the potential drawbacks, I guess, of long-term use of this mechanism? And any sort of thoughts on the way to ameliorate that?

And then just on the -- I guess, the way -- equally, this could evolve, there are a lot of these patients, obviously, you say have very low, if any, relapses at the moment. But some of those patients also have probably progressed to a nonrelapsing form of the disease.

So I guess curious, you're saying that you're beyond the potential BTK competitive threat, but any views on what perhaps proportion of those patients may perhaps actually have nonrelapsing disease and therefore, if an option is available for that, could actually still potentially consider that option.

Unknown Executive Executive

So I'll start and I'm going to -- yes, I'm happy to start. So first of all, take the first question around long-term treatment. I'm not aware of any issues yet with long-term treatment. In fact, the ECTRIMS, this year, we just published 6-year data, which Norm, I'm sure you could talk a little bit more about.

And so -- and I'm certainly not hearing any concerns from physicians in conversations around the long-term -- concerns around long-term B-cell depletion. That being said, obviously, with more and more treatment, we'll continue to monitor it, and we'll continue to look at that.

I mean, Norm, do you want to talk about the 6-year data that we had so -- because I think that's a great data, too.

Norman Putzki Executive

I think you're right that we don't hear a lot of concerns from physicians in terms of when do I discontinue? I'm going to talk about ofatumumab, specifically, not about the entire class. And the safety profile of ofatumumab and Kesimpta has been remarkably stable over time, right?

We had the 6-year deal at ECTRIMS where we have not seen any difference in the safety profile. What we have demonstrated was that generally the earlier use is associated with

better outcome also for long-term disability progression. We have not seen increased risks of infections over time. What differentiates ofatumumab is also that in terms of the immunoglobulins that are important for fighting infections, we haven't seen a decrease of IgMs or IgG to a level that it would raise a clinical concern. So I think at this point, the relative long-term use of this medicine has actually been pretty well established.

So I think at this point, I think there's not a lot of desire by prescribing physicians or patients to discontinue the treatment if it continues to be highly effective and there's no new safety concerns.

Unknown Executive Executive

Okay. So that brings us to the end of the session. Thank you all very much for joining us and for the far-ranging questions. I'd also like to thank the neuroscience leadership team. And hopefully, you have a sense of the excitement that we have both for our current pipeline as well as future emerging technologies and applications that we have coming through.

So thank you very much. And I think there's now a break for lunch. [Break]

Shreeram Aradhye Executive

Okay. Well, good afternoon. Hello, everyone on the web. I'm Shreeram Aradhye, I'm the President of Development and the Chief Medical Officer for Novartis. And welcome to this session, which covers our oncology therapeutic area.

And with me are Reshema Kemps-Polanco, our Chief Commercial Officer in the U.S., long oncology experience; Shiva Malek, who is the Head of Oncology Research; and Jeff Legos, who heads up Oncology Development. And over the next 45 minutes or so, we'll be happy to take your questions.

But let me reiterate our overall strategy in oncology, which, as you know, is anchored on our 3 major brands, Kisqali, Pluvicto and Scemblix, now with exciting recent data. Our plans to move therapeutics into earlier lines of therapy. As we've now done with Kisqali, our plans with Pluvicto and Scemblix first line just got approved.

Our big focus on Radioligand Therapeutics as an area and a platform that we believe gives us the opportunity to bring interventions with a great therapeutic index to patients with cancer and our deep commitment to this field, having developed over the last 5 to 6 years across all of the competencies at Novartis, and you'll hear more about that. And then overall, still, our efforts in hematology as well with ianalumab, which is not on the list that we're evaluating in immune thrombocytopenic purpura.

Shreeram Aradhye Executive

We can get into Q&A. My I ask of you since we're on the web is to please introduce yourself as you ask the question so that we have your name for the transcript, although we know most of you.

With that, I'm happy to open it up for questions. Matthew?

Graham Parry Analyst

It's Graham Parry from Bank of America. Just wanted to kick off on the -- Matthew's got his hand up. I just wanted to kick off on the initial launch directory on Kisqali, the adjuvant setting, so there's some interesting stats earlier. Just when you look at the patient populations that you're addressing there, are you starting to see that this is more coming from the intermediate risk group and the negative? And are you getting any traction at all in the high-risk patient population that [Vasant] has already indicated for?

So initial thoughts on penetration into the different populations would be useful. Thanks.

Shreeram Aradhye Executive

Reshema, do you want to take that?

Reshema Kemps-Polanco Executive

Sure. Really excited with what we are seeing with the Kisqali launch in the early breast cancer setting, very encouraging. Vas gave the stats earlier today. What we are seeing is, as you know, we have the broad label, right? And when you think about the label, it is double the size of the metastatic space as well as double the size of the previously approved competitor.

And so what we are seeing is, again, very early in the first 3 or 4 weeks, a patient population that is consistent with the label. So broad from no negative Stage II patients to those who have nodal involvement that are more high risk. So we're seeing it across the board, and we continue to be encouraged with that.

I will say that it is off to a strong trajectory. One of the things that I'm looking forward to understanding is who are the prescribers. Do we see that in a more concentrated setting, which is good, that's what you typically see in a launch. Are we seeing that more broad? If that is a more broad base of riders prescribing for a more broad group of patients, then that's even more encouraging around the launch trajectory.

But we continue to believe that this is a best-in-class medicine, CDK4/6 of choice, whether you're looking at early breast cancer or the metastatic space with the level of evidence that it has, and you saw today here that we've taken up the guidance now up to $8 billion. So really encouraged.

Shreeram Aradhye Executive

If you want to just comment on the 4-year data , go ahead.

Unknown Executive Executive

Yes. No, absolutely. I think some important data points were presented at ESMO, where the Kisqali response continues to deepen when you look at the 4-year landmark data. And Graham, if we look at particular into the groups that you mentioned, whether it's a Stage II group or an N0 group, I think there, we see very consistent benefit, roughly a 30% relative risk in reduction of invasive disease-free survival. .

And if you look at the landmark data at 4 years for each of these subgroups, we have about a

5% absolute difference between the Kisqali treated patients and then the control arm. I think the other big question is, are these patients at risk or at high risk for recurrence. And unfortunately, the short answer is yes. We see about 1/3 of patients with Stage II disease or no negative disease. We see their disease recurring over the course of their journey.

And if you look within the NATALEE trial itself, on the control arm, even within the first 3 years, we see more than 10% of patients who have recurred on the control arm.

So I think these are all reasons that because the data continues to deepen and this is a patient population who is at risk, albeit maybe slightly lower than a Stage III node positive risk, it's definitely important that they are treated.

Shreeram Aradhye Executive

Eric?

Eric Le Berrigaud Analyst

Eric Le Berrigaud, Stifel. Two other questions on Kisqali. The first on the peak sales so that we understand what the upside is coming -- where it is coming from. Previously, you were saying 3 plus 3, I think 3 metastatic, 3 adjuvant. Getting to 8, is the additional 2 coming or is it coming from adjuvant or spread over the 2?

And then in the understanding, you're going into CDK2 and skipping the CDK4, is it because Kisqali is already very much skewed to CDK4 versus 6 and so you don't see the benefit of having a pure CDK4 because you're too late into that game or because you're seeing some more differentiation between CDK2 versus what is on the market versus 4? And in which case with the CDK2 are you aiming at replacing the 4/6 or having a different positioning versus those ones?

Shreeram Aradhye Executive

So maybe we'll start with the end of your question. And Reshema, while you take -- think about his answer on the peak sales.

Reshema Kemps-Polanco Executive

Yes.

Shreeram Aradhye Executive

Shiva, do you want to talk about the CDK4/6 and 2?

Shiva Malek Executive

So happy to talk about our CDK portfolio. So yes, we believe Kisqali is the most CDK4 selective inhibitor of the approved molecules out there. It is a great medicine, and we're really excited to build upon that, which is why we are developing a CDK2 inhibitor and the plan is to combine with ribociclib as a first pass. Now you brought up CDK4 inhibition. I agree with you.

That's a really important area, and we remain committed to developing a next-gen molecule. Largely because we're, again, thinking long term around the combinations we'd like to do,

both within pathways, such as another CDK-CDK2 inhibitor, or orthogonal combinations such as with RLT. And so we really want to have the CDK4 selective inhibitor that has the broadest therapeutic index. And we know by hitting CDK4 as hard as possible, we can induce really significant cell cycle arrest.

And by sparing CDK6, we can widen that therapeutic window, and that may offer some opportunities for different combinations that haven't been realized before. And of course, we're in a unique position that we have RLTs that we can always think about combining. So that's kind of the excitement for the future.

Reshema Kemps-Polanco Executive

Yes. And if I can just close out on the peak sales. And I think what we previously said is $7 billion. And what gives us confidence in going up to $8 billion is what we're seeing in the metastatic space. We've really seen the velocity of seeing Ibrance come down and Kisqali really to take that leadership position, while the other CDK4/6 has been pretty much flat in the metastatic space, we still think there's area under the curve there to even grow even more share in that metastatic space.

And then thinking now about the broad label and looking at even early what we believe and what we see in leading indicators internally, what we believe will be potentially a stronger ramp than maybe we had anticipated in seeing like the 27% that Vas talked about and even with the early data approaching the 50s now, we have to see how that sticks. And that's also why it's important to see who's prescribing.

But I feel very encouraged that it's going to be off to a very strong start. And one of the reasons I believe that is because when you look at where the metastatic riders are, many of them are based in the community. They have the same patients. And so if they're bought in, in the metastatic space that this is the CDK4/6 of choice, given the data now that Jeff has just outlined in the early breast cancer space, it's not beyond imagination that those physicians we have [conferred] there will move Kisqali into their early breast cancer patients as well.

Shreeram Aradhye Executive

Okay. Matthew?

Richard Vosser Analyst

I mean, it was just -- just thinking about the metastatic setting and if the oral SERDs work and you've got a trial with one, most of them are with Ibrance to start with. Do you think that people just ignore that from talking to -- that it's with Ibrance? Because clearly, Kisqali is better. How do you see that playing out if they work?

Shreeram Aradhye Executive

We discussed this morning. Jeff, do you want to?

Jeff Legos Executive

Thanks, Richard. And maybe just starting with what we already know about the oral SERDs and where they appear to work or work best. And I think that's at the moment based on the

data is in the ESR1 mutant population and/or in the populations of patients who've done the best on prior endocrine therapy.

I think the next question is, can they be combined with the CDK4/6 inhibitors and in what setting? I think you've highlighted that we have an ongoing collaboration since 2020 with Alnylam, and the Phase I data that they presented at ESMO was quite encouraging. You could combine at full doses. There's no DLTs, there's no drug-drug interactions. The safety looks respectable, and we have some already encouraging signs of efficacy in terms of the number of PRs.

With respect to the ongoing palbo trials, I think the registration-directed trials are in a setting after first-line CDK4/6 treatment. So this would be where you would replace the fulvestrant component in what would be more of a second-line metastatic prior CDK4/6 exposed patient population. I think the next and the bigger questions are, can they go into frontline and displace or replace like the AI therapy or into the adjuvant setting where they could displace that or the tamoxifen piece. And those experiments are not part of the current Pfizer development plan, at least in the public domain.

Shreeram Aradhye Executive

Matthew?

Matthew Weston Analyst

It's Matthew Weston from UBS. If it's okay, I'm going to pivot to Radioligand therapy. And it's really about trying to understand the portfolio and this debate about Actinium.

So I recently had the opportunity to speak to somebody else in the field. And their argument was that Actinium therapy when linked to small molecules is going to have enormous nephrotox because the small molecules tend to be excreted through the kidney and the kidney is extremely susceptible to radioactivity. Whereas if you were to have a biologic radioligand therapy, then it would likely be excreted through the liver, and then you have a much more radio protective organ. And that's why your portfolio isn't the best because you tend to use small molecules from a targeting perspective. So I guess what I would love to do is, first of all, understand your perspective on that.

And then the second element is a much more commercial question about the handover from a medical oncologist to a radio onc and back again and how challenging that's proving in the field. And what it is that you can do either with development molecules with shorter handover or whether or not just helping that transition, you can improve the commercial penetration of Pluvicto?

Shreeram Aradhye Executive

So Reshema, while you think about that, Jeff, we've gotten this question several times now. So I think Jeff, why don't we start with the sort of comparisons of the principles behind alpha, beta, and then Shiva, add in your perspective from a research perspective, how we think about it.

Jeff Legos Executive

Yes. And Matthew, I'll come specifically to the nephrotox question in a moment because of the route of excretion. But maybe just to take a step back and kind of one of the most common questions we get is, Actinium versus Lutetium, why and which one?

Obviously, I think there's different theories as to which one should be used. And I think some of the basic principles follow suit around the amount of linear energy transfer, which is higher with an alpha matter like Actinium. The distance that the radioisotope can travel, which is greater with Lutetium, and you can potentially benefit from the crossfire activity. Or the types of DNA damage it could cause. A beta emitter causes a single-strand DNA damage, and an alpha emitter causes the double strand DNA damage.

I think the second principle that I think is very important -- and Shiva could speak to this even better than I can -- is just around the distribution of the receptor or the antigen of interest relative to the tumor versus healthy organs like the kidney. And I think we look exclusively at that throughout our preclinical and clinical development plans.

And then lastly, as you stated, it comes down to the route of administration. And I think our experience with Lutathera helped at least understand for Lutetium that some of this can be reabsorbed through the kidney through the proximal tubule and through things like amino acid washes, you could ultimately reduce that level of absorption to the kidney.

I think as we think about kind of the Actinium programs going forward, I think all of those principles that I just said apply to all of our Actinium programs. And we obviously are looking for the highest therapeutic index between tumor versus organ in terms of the ratio.

And for our PSMA molecules, we actually have 2 Actinium programs already that are in the clinic in Phase I and Phase Ib. One of them is on the [PSMA-617] ligand, which is the same for Pluvicto. Another one is on a second ligand, which we refer to [PSMA-R2].

We look very, very closely at any kidney-related AEs, changes in GFR, changes in creatinine throughout the entire development program. And we haven't seen those signs to date at full doses or beyond in the Phase I studies, and we have treated a fairly large number of patients. So I suspect, Matthew, some of this could be molecule dependent as to what others may be seeing. So I wouldn't generalize it as antibody versus a small molecule or peptide at this point in time. But Shiva, maybe...

Shiva Malek Executive

Yes. So this is a great question. And we -- in research, we think long and hard around both what format we're using, be it small molecule, a peptide or biologics, as you mentioned, as well as the radioisotope used, and we try to match that with the target as well as the tumor type.

So for example, a tumor antigen that has very low expression, such as, for example, DLL3, you might think about using a higher energy radioisotope in that case because that would probably what would be required for greater efficacy. In other cases where you have a target, say, that's expressed more on the stroma like a target like FAP where that crossfire effect is

going to be really important, you might consider Lutetium as the radioisotope of choice. Again, we're going to need to study these in clinic because this is all based on preclinical data and based on the physics behind these different radioisotopes.

Now with respect to safety, first, I would say one of the key experiments that we do in the preclinical space is what we call a biodistribution study where we look at the radiation that's absorbed across both tumor and normal tissue in the animal that we're studying, usually a mouse study. And what's important there is we look at multiple time points because drivers of efficacy as well as safety issues that arise, it's not just around the amount of radiation that's absorbed in that tissue, but the time that it stays there. So that remnant is really quite critical. And we're often looking at the tumor to kidney ratio and optimizing on that.

And then I would also add further because this platform, right, is to see what you treat paradigm, where you not only image, but you can use dosimetry at low doses, very early in clinical trials to understand the distribution of the energy that's emitted both the normal and tumor tissue, you can actually make a choice of radioisotope based on that as well. So there's some clear advantages, and we try to take a very thoughtful approach in making these choices.

Unknown Executive Executive

And Matthew, I just want to add 2 other points in terms of kind of just the safeguarding and the safety. I think first, right, the sort of radiation exposure limits to the kidney are set based on EBRT. And I think for all first in human, we make sure that we're never exceeding or approaching kind of that upper end of the absorbed grade in terms of radiation to the kidney. And secondly, the benefit we have is having a world-class nephrologist as our Chief Medical Officer. So we get a detailed case of valuation, right, of anything that we would like.

Shreeram Aradhye Executive

But I think I have to come up one level, Matthew. I think what you're hearing is that when you're speaking to people and they're telling you potential concerns, it is very clear that defining the appropriate therapeutic index for [athenium-based] therapeutic is work in progress. What you're seeing us do is to make sure that given our focus and given that we have all the learned experience over the last many years, we're staying ahead of the curve of being the ones that are actually defining it in an extremely thoughtful manner.

And to be honest, Jeff said it this morning earlier that there's hypothesis and then there is data, the reality is that this is a work in progress. So while everybody is getting excited about what's going to happen with alpha emitters, the reality is it's going to depend on what data gets generated. And we, with our commitment, expect to be the ones that actually deliver that data. And so stay tuned, and we'll see where things land. But maybe, Reshema, you can now talk about...

Reshema Kemps-Polanco Executive

Sure, sure. Round out what's happening on the ground with Pluvicto and the scaling of the infrastructure for RLT. And so I'm coming directly to your question, but maybe I'll just -- for the sake of a shared understanding, kind of outline what is really happening in prostate cancer.

So if you think about our vision population where we are currently indicated, that really is a launch in the back end of the disease, said another way, salvage therapy. What we saw in the beginning when Pluvicto was approved was almost this bolus of patients, right, that were waiting. And what we found out about those patients is that the physicians who were treating them had basically gone through all of the lines of therapy and have really exhausted them. So they have been moved out of the community and sent to an academic medical center. If you talk to those guys, those KOLs, they will complain that they were sent too late.

And so when Pluvicto was approved, that gave them something, right, before that patient actually gets put on palliative therapy or sent to hospice. And so we saw a lot of those patients, and that also impacted the duration of therapy. If you think about it, those patients, because they are sicker, didn't get the full duration of therapy. What we're really pleased with now in our transition as we prepare for the earlier indications, we are transitioning to the community setting because that's where the additional indications and the catalyst for growth are going to come from.

And so what you see in this steady state quarter-over-quarter is the steadiness because a lot of those patients were treated. And so what we're seeing now is that we're seeing more of the fitter patients in that post-taxane setting being treated, which is good, and we're seeing the use of chemotherapy coming down, what physicians were doing prior with cycling 2 chemotherapies back-to-back, 2 ARPIs back to back and then giving Pluvicto.

What we've been successful in doing is educating physicians that we believe -- along with the patients who will benefit the most are these patients that are much earlier in that post-taxane setting. And so therefore, we're seeing that chemotherapy go down and Pluvicto being used more earlier in that setting.

At the same time, so you're seeing that kind of go up. But at the same time, you're seeing those really severe patients, it's not being used as much. And so now you have this offsetting of kind of the steady state. So that's what's happening. It is a mix in the patient type, which is encouraging and a good thing as we run up to the PSMA 4 approval because that's what you want.

Then you want an approval, you want those patients before they had a taxane. And so the majority of those patients are going to be found in the community setting because they have not yet been referred to an academic medical center in general.

And so what's really important for us now is what you talked about, Matthew, is really how do you scale and how do you segment those accounts. And so in order for a physician to invest in this and set this up in their own practice, there are a few things they have to believe. One, is Pluvicto a transformational therapy, do they see clinical benefit in that? We believe that is a strong yes. The second one is am I going to do this and do I have enough patients in my practice to do this myself?

Or am I going to refer these patients out? For those really high-volume accounts, we do see strong interest for them to set this up and do it themselves. One, because one, they do believe in Pluvicto, but secondly, they see other companies coming into this space. So that gives them confidence that it's not just Novartis, and it's not just 1 or 2 products, but that this

is now going to be a new way to treat cancer and a new treatment modality and they want to have it under their roof.

And so if you think about the journey of a prostate cancer patient, they start off in urology, they end up in medical -- they go to medical oncology and then they end up in an academic medical center. And so it's really important for us to penetrate medical at large practices in medical oncology that has a lot of volume as well as urology, and that's what we've been scaling over time. And they see now the proliferation of clinical trials, not just in prostate cancer, but across multiple solid tumors.

What this is reminescent of -- and the reason I have so much confidence in this is we saw this happen with chemotherapy. When physicians in the community saw that there would be more than one chemotherapy, there was a proliferation of trials. They set up their own infusion suites. When targeted therapy became, Gleevec was one of the first. When they saw that there was a proliferation of targeted therapies, they opened dispensing pharmacies under their roof.

And so now they have the infusion suites, they have the dispensing pharmacies. And now they're figuring out how do I integrate RLT as part of my treatment paradigm, but also the business model.

And so that's what we're really busy focusing on now. And to set up those referral pathways for those segments of offices that say maybe I don't have that broad volume, but I still think this is important. And yes, I want to refer to the radiation oncologist, whereas they may be more reticent to refer to an academic medical center because there is fear I'll lose the patient, right? You finish my sentence.

And so these are the dynamics that you're working through -- we're working through from a nonclinical standpoint, but the scaling is going really, really well. And we feel that we're going to be really prepared for the PSMA 4 approval. As you know, it more than doubles the population for PSMA vision. And so we have the capacity in the academic centers. We have that today.

Some patients will be there, but we also feel confident that we're going to have the capacity in the community as well. And that will be a growth catalyst for us.

Simon Baker Analyst

Simon Baker from Redburn Atlantic. Just coming back to Actinium and then a question on Lutetium. You talked about the importance of maximizing the therapeutic index. How can that be achieved? Or how relevant is trying to achieve it by changing the isotope for Actinium to lead-212?

Because then you're moving from 9 days to what, about 10, 11 hours, half-life. Is that something you've thought about? Or is that not really the best way given the practicalities of short half-life isotopes of achieving that?

And then secondly, on Pluvicto. Pluvicto has established itself very strongly. And as a result, there were an awful lot of Lutetium PSMA products in development. It's hard to see how many

of them are going to differentiate themselves clinically. So how do they take a slice of the action?

And is there a risk that they try and do that on price? So what are your assumptions for the evolution of price within Pluvicto's market as these new me-too drugs come on up?

Shreeram Aradhye Executive

Maybe, Jeff, do you want to take the first question? And then...

Jeff Legos Executive

And maybe to start with, I think, for approved products with Lutetium, right? The question is how do you compete and how do you potentially expand the therapeutic index. And I think one opportunity is to explore other novel radioisotopes. I think very similar to the Actinium versus Lutetium question is, do these novel isotopes afford something different through the profile of their radio pharmaceutical properties? So through lead, do the [indiscernible] electrons or daughter electrons, or daughter molecules ultimately afford potentially greater efficacy without compromising on safety.

And I think the answer is still we don't know as of today. I think to your second point, Simon, if you're going to switch from a molecule that has a half-life of several days to one with several hours, we shouldn't underestimate the untoward logistical hurdles that would come to that, right? So if you think about the time it takes from order to produce, label, ship, receive and administer around the globe at scale, being able to do that within 3 to 5 days is something that Novartis has already achieved through our very expansive approved global manufacturing footprint. To do that same thing within 12 hours or less creates a whole another formidable challenge and potentially a different model.

Reshema Kemps-Polanco Executive

Yes. And maybe I can just cover off on the more commercial question. So while we don't disclose our pricing strategies, what I can say -- and Jeff, please chime in here. When you think about the Actinium and where we can see that playing, if you think about it as life cycle management as well in the prostate cancer space. Is this a place where you can rechallenge the patient with an RLT after they've had Pluvicto.

Pluvicto is going to be used earlier, even if you look at PSMA edition and the [Oligometastatic] space, then what would be left in terms of treating a patient with RLT later on. And so that's 1 question that I believe the studies are designed to look at.

But then the other one is really around when you think about IRA as well, there, we believe Pluvicto will not be impacted to more at the back end of the decade. But then having -- if, in fact, we can see that Actinium works well even in earlier disease stages, then that can also be in life cycle management strategy as well. But do you want to just comment on the segmentation?

Unknown Executive Executive

Yes. I think firstly, I think Pluvicto, we believe, has a very attractive data set and I do believe not

only is it best-in-class, but first-in-class. And I think the development program was initiated with a lot of new studies in parallel that affords us the ability to move into the pre-taxane setting, the hormone-sensitive setting with PSMA addition to actually a newly defined patient population in PSMA DC, so delay castration, which is an Oligometastatic patient population defined by PSMA-positive PET Imaging rather than conventional imaging. And then even going into like a high-risk localized prostate cancer. .

So I think we're looking at this across the journey. So new entrants will obviously have to factor that into the equation. I think for the Actinium programs that we are developing for prostate cancer, we're doing both. So after they've been treated with Lutetium like Pluvicto or in similar lines or potentially different patient subsets is how we're thinking about Actinium.

Shreeram Aradhye Executive

Your question about the number of other people and smaller companies thinking about Lutetium-based, Lu-PSMA products and how are they going to differentiate, I understand your concern. And the question on whether they will then just compete on price by changing things is hard. Yes. We will have the data that defends our -- with price.

Reshema Kemps-Polanco Executive

And the first mover advantage, and there's a nonclinical learning that goes along with it. And I think the best example I've been able to give just to give something analogous is if you think about the logistics that have to be involved with a company like Amazon to get those boxes to a patient, to a customer in like 2 days or what have you. That's not easily replicated. We have not seen another Amazon, right? And so that's kind of how we're thinking about it.

Each step has been well thought of. We've had a lot of learning as we've done this, but it's across the entire value chain. Every function has learned. Now how do you get this at scale to patients in this precision timing. And so now another company coming after us, they're going to have to learn that as well.

And so I think it's going to take some time. And then also, you've got to have a really competitive clinical profile, which we have yet to see, to be honest.

Holger Blum Analyst

Holger Blum, Patinex Management. Clearly, Kisqali and Pluvicto are key assets and RLTs. But going beyond that, what are your big ideas for the next -- what happens thereafter in terms of target indications or getting a bit broader apart, breast and prostate? Or the early stage, what are your key priorities there?

Shreeram Aradhye Executive

Shiva, do you want to start?

Shiva Malek Executive

Maybe I'll kick off. So yes, so clearly, very interested in building out our portfolio in both breast and prostate. In breast, definitely focused on the CDK franchise that we're bringing forward, again, built on the know-how and the expertise that we've gained from the Kisqali, both the

clinical studies, but also the medicinal chemistry know-how internally. In prostate, obviously, Pluvicto being our anchor asset there. One of the key advantages we have is we've learned from the clinical data from Pluvicto patients.

And we can now take those learnings back into research to understand what -- how can we design a next-gen molecule that could even give greater benefit to patients, say, for patients that have lower PSMA, more heterogeneous expression. And you can see with the recent deals that we've done in the past few weeks, really thinking about second gen molecules for both Pluvicto and Lutathera is definitely part of our strategy.

And then outside of RLT, we're obviously remain very excited about T cell-based therapies. Again, as an opportunity to get into small cell lung cancer. We have a cell therapy that we in-licensed from Legend where we're able to target DLL-3 through their CAR-T. It's a very novel CAR-T. Again, this is a clinically validated target in small cell lung cancer.

We think this is an opportunity to really bring great benefit to patients. And their CAR-T really is a nice way to synergize with our T-Charge platform where we think we can really leapfrog that cell therapy and bring better benefit to patients.

I'll turn it over to Jeff in terms of...

Jeff Legos Executive

So first, I wouldn't want to miss an opportunity to talk about Scemblix if I have the chance. It is a homegrown fully discovered and developed molecule for patients with CML, first approved in '22 in third-line CML. And a great example of real sort of in-line execution excellence.

And if I just think about 2024 alone, so first, the frontline trial in newly diagnosed CML recruited 1 year ahead of plan. We top lined the data at JPMorgan. We presented at ASCO this year and got approval in the New England Journal of Medicine. We submitted to the FDA, got priority review, breakthrough therapy designation, [R2R] acceleration and Orbis all simultaneously.

Got a very broad label by the FDA. And the recent NCCN guidelines reflect this as a preferred Category 1 treatment in newly diagnosed, an option for patients in second line, irrespective of the first-line TKI. And most importantly, really highlighted the importance around safety and tolerability by listing out all of the known safety concerns to the existing first and second gen TKI and offering an opportunity to switch to Scemblix for those patients in need. And then last but not least, the 96-week data will be presented at ASH this year.

And maybe 1 other hematology product -- because Shreeram mentioned in the beginning that we're quite excited about -- is ianalumab. I think this speaks to our overall commitments as a company in terms of focusing on B-cell depletion. We have a range of studies going across different autoimmune diseases, including hematology. Within hematology, the emphasis is on ITP, a space that we've known well over the past 20 years. And despite the advances, all of the existing therapies for patients with ITP are not disease-modifying.

Yes, they raise platelets or they reduce the immune system for corticosteroids, but there's no true disease-modifying agent.

And a product like ianalumab is a very unique MOA. Not only does it deplete the B-cells, but it actually reduces all residual functional bath downstream signaling in the pathogenic tissue. So we have 3 Phase III studies ongoing in hematology and probably at least another 5 in immunology. And the first data in third-line ITP will be shared at ASH this year. So something to look forward to in terms of a new MOA for us.

Unknown Executive Executive

Yes. And we should talk about PNH as well. Another very strong launch. So Fabhalta, as you know, iptacopan was approved about this time last year, right? In December.

And I remember because it was right before we went to ASH. And so that launch has done very well. As you can see by the market share that we've shown by Vas, 48%, taking leadership in market share versus a very entrenched competitor. But when you think about Fabhalta, that's -- we said that's a pipeline and the pill, another internally developed asset that we're -- PNH was the first indication. We also have the indication in igA nephropathy and then looking forward to bringing on additional indications in the near future in the renal space as well.

So that's one we're really excited about, and we're continuing to see a very strong launch trajectory there.

Unknown Executive Executive

And Shiva, do you want to close out with a little commentary on how we approach RLTs and ADC, and we have lots of capabilities in the company. And I think we keep getting that question.

Shiva Malek Executive

Yes, happy to. So we think long and hard around what modality is most appropriate for the right target and the right disease. And when we think about RLT versus ADCs and when you would use one or the other, I think there's some important considerations. First, RLT right is really about precision delivery of a radioisotope to tissue but it doesn't require saturating conditions, you can go at subsaturating levels. This is unlike ADCs, where you typically need to saturate the target, which is why oftentimes as a resistance mechanism, you might get down regulation of that tumor antigen.

So some unique opportunities there. Second key feature of RLT is that you can target the RLT to the tumor. It doesn't require internalization for efficacy, and you actually do have a crossfire effect especially depending on the radioisotope you're using. As we know for ADCs, you require internalization and you get release of that payload. And again, another resistance mechanism for ADCs as transporters that can transport that payload out.

And then the third and most critical and I think unique feature of RLT is the see what you treat paradigm, where in a noninvasive just image-based approach, you can actually see where your drug is going throughout the human body, image it, and see it in the tumor and all the metastatic lesions, but then even more importantly, calculate using dosimetry, the amount of radiation that's absorbed or energy admitted in these tissues. And so the reason that's really

important is that with the clinical data we have, particularly with the clinical data from Pluvicto and Lutathera, we understand the relationship of tumor absorbed dose and efficacy and we can use those insights to model that and be able to get early insights and early decisions on some of our early-stage clinical programs that are going forward. Now I think there's still a space for ADCs. And the way we're thinking about ADCs is really thinking about how we can leverage delivering a payload with an antibody by optimizing, expanding that therapeutic index, which hasn't necessarily been achieved with cytotoxic, the typical chemotherapy payloads. And so we're taking a different approach and really thinking about how we develop biology matched payloads where we get really great tumor kill but then really work on expanding that TI.

So that will be kind of hopefully something we can talk about down the road, but we see the 2 approaches quite different. Then maybe Jeff can speak to a little bit about the therapeutic index.

Jeff Legos Executive

Yes. I think coming back to what you see on the slide there and the core part of our strategy is to sort of move our medicines into the earliest line, earlier stages of disease. Because that's where just due to the evolution of tumor biology, we think it gives us the best shot to really provide patients with functional cures, treatment-free remission or actual cures. And based on kind of the existing characteristics of sort of the linker payloads, there are some inherent safety challenges that may relegate the existing therapies or the existing platform capabilities to later lines of therapy, right? So I think for all of those reasons, we have put more emphasis on the radioligand therapy, but fully open to ADCs where it makes sense if we're looking at certain subpopulations or later lines of therapies.

Eric Le Berrigaud Analyst

Eric Le Berrigaud, Stifel, again. 2 maybe questions on Scemblix. Just to understand what kind of assumptions you have behind your $3 billion-plus peak sales because we remember that Gleevec at the time, we were reaching $5 billion or $6 billion. So different times, of course. And we remember that you were saying that ex-U.S., you were probably a little bit more concerned about it being approved for first line and could well think that it's first on sustainability of the response.

So having maybe longer term data could help move the discussion with European authorities and other regions, maybe a little bit different. And we remember IRIS 6, 7, 8 years. I think people were staying in chronic phase, 90% of them are even above this. So how could we think about diverging over time, giving more confidence into payers to cover it for first line? And then any progress you can make on patient selection because -- and pretty much the same debate if 90% of patients on Gleevec do not progress, I mean giving Scemblix to every single patient may mean like overstatement of the benefit of the drug.

So probably only a subset would benefit. But is there any chance that over time you can better select who can most benefit from Scemblix versus any other treatment?

Unknown Executive Executive

Jeff, do you want to start?

Jeff Legos Executive

Yes. I'll try to cover off regulatory piece -- patient selection or the differentiation, and I'll leave it to Reshema to talk about the assumptions beyond $3 billion. So maybe I'll start with kind of the regulatory reimbursement payer questions you had for Europe. So in Europe, it wasn't a concern around the approvability in first line, but we know the regulatory agencies wanted longer follow-up beyond 48 weeks. And now that we'll have the 96-week data presented at ASH, we would have the full data package available.

The second part comes down to payer expectations and their requirement there. And they were specifically interested in patient-reported outcomes, time to treatment discontinuations related to AEs relative to the second-gen TKIs specifically. So a Phase III, Phase IIIb sister study was set up that we referred to as ask for start. That was the complementary trial to ask for first, which led to the approval in the U.S. That trial is fully recruited.

We are currently sort of capturing the data and expect to have the data in 2025. And I think on your second question, patient selection, I think the first thing that we should probably think about is the proportion of patients that either have a suboptimal MMR response or failed to reach their major molecular response goals and/or those that actually had to discontinue due to sort of tolerability or safety. In the past, the way physicians would usually think about which line of therapy to use in the front line, sometimes it's driven by age and other comorbidities which then ultimately decides is their treatment goal to maximize the chance of efficacy at the expense of maybe greater safety and tolerability or to compromise on efficacy because you want a safer or a more tolerable drug. With Scemblix, it's not an either/or, it's an and. The efficacy is clear as per the way the study was designed, a head-to-head against investigator-selected TKIs and then the substrata that actually looked at Scemblix versus imatinib directly, where you have almost a 30% delta in the major molecular response rate and improved safety and tolerability relative to imatinib alone.

So I think the data strongly supports use of Scemblix across all patients in a frontline newly diagnosed setting.

Reshema Kemps-Polanco Executive

Yes. Okay. So this one is close near and dear to me. Everybody knows that I used to actually lead the Gleevec and Tasigna team years over a decade ago for Novartis. And I would say, you're right.

You said it, it was a different time when you think about Gleevec, right. Before Gleevec came to market, patients died in 3 to 5 years. And so Gleevec was really a game changer, not that CML is a game, but totally transformed the space. And so now when you think about it, and I agree with what you said that this is the and product that you can get both because they've either done Gleevec for one reason or the second-gen TKIs for another reason. But ideally, they would want to have both of those, the efficacy and the tolerability.

Having said that, particularly in the U.S., we are very optimistic about the launch. And that is based on what we saw in third line, market share leadership and even started to see --

although we were clearly promoting it outside of label we actually start to see physicians start to just themselves move it earlier into the second line. And so now that we have the approval, which covers all lines of therapy, we are encouraged, but we also want to be responsible in understanding that we are launching in a market that is going to be -- likely be highly genericized. That is very different from the $4 billion-plus Gleevec context. Having said that, we have a very strong market access capability, and we are seeing now that we are steadily ensuring coverage for Scemblix, but the catch there is even with that coverage, to look at how well is it managed in terms of step edits.

Is there no step edit? Is there once step at it? Is there 2 step edits? And so looking at how well that's going to go as part of the ramp is what causes us to say yes, this is going to be a very meaningful and significant medicine. But we think around the $3 billion range is right.

Once we see how that ramp goes with market access, I think there could be an opportunity to revisit and that's what we said at ASCO.

Unknown Executive Executive

All right. I think with that, we're at end of time. Thank you very much for your attention. But I hope to have a good sense of our pure-play company with deep focus and as you can see or R-D-C continuum here at play on everybody working together to make transformative medicine and get them to patients. Thank you for your attention.

Unknown Executive Executive

Thank you. [Break]

Vasant Narasimhan Executive

Hello, and welcome to the last session for today's Novartis Meet the Management. This is the corporate session today. With me, I have Steffen Lang, our Head of Operations. Karen Hale, our Chief Legal Officer; Harry Kirsch, our Chief Financial Officer; and Ronny Gal, our Chief Strategy and Growth Officer. I think you all heard the presentation earlier today, really outlining our outlook as well as our pipeline.

So really, we can open the line for questions, and I think we already have a question from Richard Vosser.

Richard Vosser Analyst

Richard Vosser from JPMorgan. Maybe a couple of questions on what you were talking about this morning around, obviously, you've upgraded the guidance, but maybe you could talk about the shape of growth as you see it out. There are some LOEs during that period, how you think about that shape of growth? And maybe the margin profile, you've reiterated sort of in '27, 40-plus, but how we should think about that maybe be into the later midterm and development there?

Vasant Narasimhan Executive

Yes, absolutely. So I'll hand that margin profile to Harry. But I think when you look at the sales growth, one important point to highlight is given the profile of the business and the

momentum we're seeing right now, we're confident we'll have a solid growth year next year. We, of course, give the guidance in January, but both top, bottom line, and Harry will address continued margin progression. And then I think after we get through next year, we'll have a number of years with pretty limited LOE exposure until we get to Cosentyx at the end of the decade.

So I think we have a kind of a shape where next year, we do face some LOE headwinds, full-year effects maybe in 2026, which we think our launch trajectory will be able to enable us to manage. And then I think a pretty good run of a few years before we get to the Cosentyx expiry towards the end of the decade. Harry, on the margin?

Harry Kirsch Executive

Yes. In terms of margin, you have seen also this year a significant margin increase, right, over -- in constant currency, like over 300 basis points. So let's say, with the currency, it's always a little headwind, it seems. Last year, 36% this year, we end up somewhere around 38%, right? The 2 points to go over 3 years.

And then the improvement, I would expect each year some improvement but probably a bit more muted in '25, '26 and a bit more in '27 because if the generics play out as we guide for financial planning purposes, we would have mid-'25, 3 U.S. generic entries, then a full-year effect in '26, still good growth, but then '27 would have less of these LOE headwinds. So overall, I would say, good progress each year and a bit more up or down depending on the sales growth due to LOE.

Matthew Weston Analyst

It's Matthew Weston at UBS. 2 questions, if I can. First, Harry, on financials. This morning, you made a comment about -- or Vas made a comment about continuity of share buyback being an important consideration in terms of deployment of capital. And I think sort of traditionally, people have thought of Novartis' share buyback has been a unit and when it's done, wait and see if you reload.

Am I right in saying that the message that you'd like to give is that we should think of that as a much more consistent deployment of capital over time and something we should embed in the model in terms of an incremental earnings lever going forward? And then the second question is one really about U.S. politics and how it impacts managing a pharma company in the current period. There's a lot of debate about personalities that will be in place and leadership in the U.S., which is a critical market. Basically, it's just a period of uncertainty.

And I'd love to understand how in a business, whether it's thinking about the future of FDA, PDUFA, how you go about managing that uncertainty over the coming period?

Harry Kirsch Executive

On the share buybacks. Yes, it's always distinctive decision, right, that we discuss, of course, as an executive team with the Board. And then we go to our AGM, right? But overall, you have seen us do share buybacks almost on a continuous basis, at a bit higher when we sold at a very good price to share -- the road stake, right? And we're just executing the second $15

billion.

But when you look over the last 10 years, like each year, $5 billion to $7 billion on average. Now is it a formula to put forward each exact year. But I think overall, share buybacks will always be part of our capital allocation strategy. And given our strong cash flow, right, in the first 9 months, already $13 billion so clearly on our way to $16 billion this year, then the dividend is growing, yes, but we also do share buybacks of around $8 billion. And then bolt-on M&A, it depends on how much we find and how big they are, right?

And so I would expect that share buyback is always part of the future capital allocation. But we will inform you, depending on what we find almost on M&A and BD&L, what sizes we are talking about.

Vasant Narasimhan Executive

And one point to build on, Harry, when we look at -- when you look at the kind of M&A we're focused on, it's not a trade-off. I mean we're able, as you've seen, to balance our M&A, BD&L approach with the dividend growth and appropriate share buyback. So I often get the question, is this a trade-off. We will always focus on deploying the capital on good M&A and BD opportunities. But we believe with our free cash flow strength, we have excess capital, certainly to deploy the work share buybacks.

I think on the political side of things, maybe a couple of points. First, from a big picture standpoint, we have to take a long-run view on these things. I mean this is a new administration, we'll have to evaluate it, but it's also 4 years and then we'll have a new constellation of things. In an industry where we have 10 years to develop a product and then 15-plus years on the market, I think we have to appropriately react but not overreact to any of the things we're seeing in the environment. When you look also with respect to what we're hearing, there's what's being said, then what will ultimately be attempted to enact over the course of the coming years.

And what can you actually accomplish from a legal standpoint, from a policy standpoint and what time frame. This is, of course, a much smaller subset of what's possible. I think overall, when we look at, at least what we can surmise so far, on the positive side, there seems to be a large focus on noncommunicable diseases. That's a net positive for our company with a focus like us, a focus on prevention, also, I think a net positive. When you look at some of the commentary on regulation of the industry trying to enable faster access to medicines for patients who have high unmet needs or are suffering from really debilitating rare diseases, I think those are all net positives.

And then on the flip side, we have to, of course, ensure that we don't undermine public trust and science, public trust in vaccines. We also want to make, I think, increasing clear as an industry, the FDA is the world's best and most independent regulatory body. And we need to make sure we maintain the talent in the FDA to be able to keep reviews on an ongoing basis. And also that the PDUFA system is absolutely critical for the well-functioning regulation of our industry. We can't have the PDUFA system called into question.

We need those user fees -- the user fee-based system to enable FDA to have the resources to keep reviews on time, and that's high in our mind. I think one other thing I'll note, we do

think there's an opportunity here to as an industry to push for the needed reforms on IRA, the 9% to 13% fix that we think is something that needs to happen, perhaps PBM reform and further PBM reforms that might be accomplished as well. So there are also, I think, policy opportunities that we can have, given the current constellation in the Senate and the house to try to push forward as well. Graham? I don't know who has the mic, you guys are -- okay.

Simon, go ahead, Simon.

Simon Baker Analyst

Simon Baker from Redburn Atlantic. 2, if I may. This morning, as you outlined the changes that have taken place within R&D around do less with more. And I just wanted to know how from a deal point of view, how that's affected the choice or the balance and the appetite for internal versus external? And while you gave us some -- your sort of sweet spot in terms of deal size, I wonder if there's anything more, perhaps you could say, Harry, in terms of hurdle rates, payback period, how we can think about deal selection?

And then a second, completely unrelated question since we have Karen on the panel. There were some interesting moves around product litigation in the U.S. and Europe. In the U.S., you've got Litigation Transparency Act which potentially could make these actions harder to do because it would disclose the funders of litigation more readily. And then on the flip side, you've got the EU Product Liability Directive that potentially makes something that we don't really think about in Europe a bit easier to do.

So your perspectives on the outlook on litigation for Novartis and the industry would be really helpful.

Vasant Narasimhan Executive

Thanks. So, Ronny, first on our deal approach and maintaining focus the deals versus internal?

Aharon Gal Executive

Yes. So we are focused, as you know, on 2 -- on 4 therapeutic areas that are quite well defined. And we've got other corporate initiatives, for example, enhancing our capabilities in AI. So what you've seen in the slide this morning was essentially our entire transaction portfolio was based around those therapeutic areas and those priorities. And in general, you would expect the vast majority of our future transaction to also focus on the same therapeutic areas and the same priorities.

So that is generally what we do. We are big believers that in therapeutic areas, we have the internal knowledge about the diseases, about how to execute trials. We are much better developers both internal assets and external assets. And therefore, we will tend to evaluate those and also assign probably a more accurate probability of success and commercial value to those assets.

So our transaction reports will continue to be focused. You're seeing quite a number of deals that are relatively early Phase I, sometimes Phase I and preclinical should expect those to be continue to be the majority because that's the majority of opportunities. Obviously, if we find

an attractive opportunities within our core therapeutic areas that is later, we will obviously prioritize that for the obvious reason. We -- I've discovered personally that our scientists are very excited about evaluating external ideas that could accelerate their internal programs. They generally are very much focused on treating patients that have those conditions that dedicated their lives to and therefore, are great partners when it comes to evaluating external ideas.

Vasant Narasimhan Executive

And I think on the internal external mix before I give it to Harry in the hurdle, right, I mean we -- without a real specific goal, we've ended up kind of in the 65%, 35%, 65% internal 35%. And we seem to end up trending towards that based on the historical data. that will fluctuate, but we have a big commitment to internal research. And I think it's one of the things that makes us unique is we're very consistent in our belief that the internal research pipeline is what generates medicines like KISQALI, like SCEMBLIX like FABHALTA that we've all gotten approved this year. Harry on hurdle rates?

Harry Kirsch Executive

Yes. First, I also want to say, I think what's important is that we're in a situation that when we bring in external opportunities. They are welcome and our colleagues who have to assess them, don't have to say what they will depriotize internally. So we keep running the internal high-value programs, and these are welcomed additions right? So there's not a bias in assessing external opportunities because people would be afraid that internal stuff would have to be deprioritized.

And you see even with that, at increased dealmaking, actually, our R&D in percent of sales is even below 18% at the moment, right? We like to have a little bit higher.

But of course, we don't waste money just because we grow 10%. So we have a lot of room there, and -- but it has to be scientifically strong and on strategy. And of course, from a financial standpoint, attractive. So as you know, our cost of capital is around 7% and right at the moment and it came a bit down last year 8%, now 7% given the lowering interest rates. And of course, we look at asset discount rates according to the pipeline stage of it.

And with that, when we do deals, we are, of course, from an eNPV standpoint, eIRR standpoint, certainly, we want to be in a position to create also the properized standpoint, value.

Now the matter of the thing is we will never see IRRs and eNPVs, right, either will be successful and then highly successful. So we look at that as well. right? What is it? How big could it be if successful?

Or of course, there is, again, a stage appropriate risk. It doesn't work out. But from that, we are always financially disciplined. But also, of course, has to be on strategy.

Vasant Narasimhan Executive

And then Karen on the litigation shifts?

Karen Hale Executive

Yes. So with respect to the funding transparency in the U.S., this is certainly a movement that we support and that is supported across all industries. From a policy perspective, we think it's a very important one for the parties to understand exactly who's involved in the litigation and what their interests are and certainly very relevant to the judiciary as well. So it's something that we're closely watching and actually really support. So we're actually hoping for some significant developments along those lines.

With respect to the EU directive regarding product liability, I would say this is something that is a part of the European General Counsel Association. All of us have been watching quite closely. There are many litigation trends that are exported from the U.S. into other countries in product liability, depending on how it's done, is one of those that could be beneficial if the incentives are truly aligned around patients and individuals who've been harmed.

However, the concern is, is that there is a direction of trying to import those incentives that really in, I guess, instant plaintiffs firms and many of them have set up office in Europe to actually help push forward the directive. So we remain involved and supportive in ways that are appropriate and that are truly aligned with ensuring that patients who are injured are appropriately compensated and that the system really works for the public versus for the legal community.

Vasant Narasimhan Executive

Now Graham, Graham.

Graham Parry Analyst

Just a question about your post-2029 mid-single-digit growth aspiration. Just I think last time we talked about the sort of post guide, it was post '27 and you said you're guiding 5-year income and so you could clarify. Is that a post 29 mid-single digits for 5 years? And the reason for asking is you included KISQALI and Kesimpta in the slide on some of the drivers there, and they lose exclusivity over that time frame. So just wanted to make sure that whether they're included or not in as growth drivers there.

Similarly, should we think about the margin over that time frame is once you've reached the peak 40% in the guide. Is that really a flat margin we should be thinking about over that time frame. I think that was the implication from comments this morning.

And then secondly, just on the main litigations that you've got going on at the moment. We had the KISQALI patent litigation trial in February and Entresto hearings in November, the 13th. Just your best guess on timings of outcomes for those and how they might impact your -- how you guide for 2025 in January 31. Thank you.

Vasant Narasimhan Executive

Yes. Thanks, Graham. So the guidance is clear, the 6% and 5%, '28 and '29. And then beyond '29, it's our aspiration to maintain a mid-single-digit guidance. I wouldn't give a certain time period on that.

It's just more that, that's the shape of the business we want to maintain. We certainly model our business out into the 2030s, and we also model it beyond Kesimpta and KISQALI. We model in, based on our assessment, the pipeline that you've seen on these slides as well as other clinical stage assets that we have.

We also -- I think as Harry noted, an important point, which I think is not always fully assessed is given Novartis strength as often the #1 company in emerging markets, we have a longer tail on a lot of our established medicines than I think TheStreet generally appreciates. If you actually look at it, we assess, and Ronny did a nice post on this, that actually, for us, over the entire lifespan of a product, a product with a more EU orientation is worth as much. The ex U.S. side of the valuation equals the U.S. side of the valuation just because ex U.S., we have such a long tail given our strong position in many emerging markets.

So we model all of that in.

We also model our historical success rates in VR, our historical deal flow, and that's what gives us confidence in the mid-single-digit guide into the 2030s. But there's not like a CAGR, your point that I can offer you at this point in time. I think as we get more clarity, we can go there. I think on the margin, we want to get to the 40% plus. I mean, naturally, you can see given the incredible productivity that Steffen and the whole organization has driven.

We have a lot of momentum. I think more what we want to indicate is we don't believe we'll get significantly more credit for pushing that margin higher or tying ourselves to a given margin guidance rather to say, we want to fully invest in our launches. So we continue to increase our investment on our U.S. launches, KISQALI, PLUVICTO, SCEMBLIX, et cetera. And we want the flexibility to go after any R&D opportunity we see to help us drive growth.

Because I think once we get to that 40% plus space, it's going to be more about the top line than incrementally pushing up the margin. I don't know, Harry, anything you want to add?

Harry Kirsch Executive

Absolutely. I mean, short answer would be, yes, keep that for you in your model 40%, right, going forward. And the thing is also gross margin at the moment, 20%, a little bit more right? Core margin, 40%, we're kind of 40% to play with, right, from an R&D standpoint, and SG&A standpoint. And we just have to see what is then the product mix, right, at that point in time.

And so absolutely, we keep at it at 40% at the moment, and then we see how the product mix develops. And again, as I mentioned several times, we don't want to walk away from midterm guidances or if you don't want to walk away from excellent investments because we call it ourselves with too ambitious margin.

I think this has guided us well to go from really almost worst-in-class productivity or core margin in the mid- to high 20s, right, to benchmark levels or slightly above benchmark levels. And beyond that, let's see where the mix takes us.

Vasant Narasimhan Executive

And then, Karen, I know you've been gearing up to talk to Graham all day on legal topics. So now is your chance.

Karen Hale Executive

Thank you, Graham, for the question. On KISQALI, as you noted, the trial occurred in February of this year. And currently, we are awaiting a decision. We expect it should be at the end of the year or by year-end, but have not received any indications of anything before then. I would note, I'm sure you're aware, it's a composition of matter patent.

We feel very strongly about the innovation that is contained in KISQALI, which is underscored by the commercial differentiation that we see playing out in the market. So we remain very confident in receiving a favorable decision by year-end.

With respect to Entresto as well as noted, there was an oral argument last week related to 2 of the patent cases. One, on the combination patent, a review of an unfavorable lower court decision. And then the second was on the amorphous complex patent, which essentially only involves the appeal of the denial of the preliminary injunction. Those were consolidated. We are expecting a decision by the end of the year.

It's important to note that there are 2 stays which remain in place, pending that decision at this time. And we continue to feel confident in guiding towards mid-2025 for a potential LOE.

Eric Le Berrigaud Analyst

Eric Berrigaud, Stifel. One question again about margin midterm. The issue probably is that providing mid-single-digit top line growth over the long term with no leverage on margins, give the impression that you may grow earnings also in the mid-single digit that may look not so attractive. The companies as peers that are into the high 40s margin or more specialty care than you are, but after attending all the sessions today, it very much looks like you're getting more specialty care.

And especially in immunology, even in cardiovascular, where Entresto is probably the more gen med type of product you're moving into other products that are less Gen-med over time. So is it a right or wrong impression? And if you're getting more specialty care, why not moving into the mid high 40s like your peers in specialty. And then the second question is on CapEx. Several companies are not only the ones in we are talking about getting into a phase where they need some new requirements in terms of CapEx?

Is it also your case? And should we expect sometimes of adjustment in terms of CapEx requirements in the coming years or kind of no big change for that going.

Vasant Narasimhan Executive

So I'll give Harry the CapEx. So on the first part of the question, yes, I think we are moving to more a specialty business across all therapeutic areas, even in cardiovascular disease, as I'm sure you heard from the team, we see the best opportunity to reach patients as we focus more on high-risk patients and focus on physician groups. So whether that's like physician groups that are more specialty, whether that's Leqvio, whether that's pelacarsen, the future siRNAs. So certainly, we have a general shift to more specialty medicines for sure.

And I think when you think about the margin, what we're trying to say is we don't want to commit to anything right now. I mean in 2027, we feel confident we will deliver the 40% plus.

In 2027, we'll give a perspective on where we want to go from there. But we don't see much value sitting here today, committing to a bigger number when we have so many launches ongoing, and we want to invest in a very large mid-stage pipeline. I would rather prioritize that.

And then eventually, we can come back to where -- because, of course, as we generate that sales on high-margin specialty sales, of course, the margin over a longer period of time, you would expect to trend up. But I don't think it's prudent at this moment in time to commit to that on CapEx.

Harry Kirsch Executive

Yes. A few thoughts on the margins still. I mean we have a gross margin of 80% plus, right, on cost of goods, roughly 20%. And we have products which have a bit lower margin than average. Leqvio, yes, you can say specialty, but Leqvio we expect to become very big, right, over time.

PLUVICTO, it's a specialty, but cost of goods and royalties are a bit higher. Do you want us as shareholders to walk away if we're a bit below average on margin? Absolutely not, right?

And that's because these are very good businesses, very good cash flows, very good returns. So that's why we have to see how the whole situation is once we get to the 40%. Is there opportunity, yes, there is. But I think we have to get a bit more visibility. So we don't corner ourselves to do the right investments for continued and maybe even better growth opportunities than we at the moment in vision.

So that's there.

And then on CapEx, I mean Steffen should speak to it as well. But I have seen since Steffen and team have streamlined our manufacturing footprint from over 60 manufacturing sites to now mid-30s, including RLT, which is actually not that CapEx intensive, we have lived very well in the range of 2% to 3% of sales CapEx, right? And I don't expect that to change. I don't know whether that answers your question or whether they have more details with Steffen.

Vasant Narasimhan Executive

Maybe, Steffen, you want to say a word on our global footprint?

Steffen Lang Executive

Yes. I think we moved over the past few years from more than 70 manufacturing sites to a footprint, which is now really fit for purpose for our portfolio of around 35 sites. And we'll continue to adjust as the portfolio evolves. What currently is, of course, in scope is large investments, building new capacity, more capacity for RLT where we have 6 sites. We have plans for additional sites, not only making the product but also in-sourcing the isotope.

But all in all, we have, over the past few years, always recapitalized and kept our manufacturing assets up to date. So there is not a backlog.

And as Harry said, it's not that CapEx intense ROT when you compare to building a new biotech side. And as such, this is in the range of what we typically allocate every year in the range, what you say.

Holger Blum Analyst

Holger Blum, Patinex Management. Whilst you sounded very confident on the technologies, current portfolio momentum pipeline, and although the team did a good job highlighting the strength. I would appreciate if you can share your thoughts maybe on the darker side of things on the weaknesses of Novartis and what provides you a headache as of today? And maybe if you have a kind of self-assessment of the company from 0 to 10, 10 being the best, how far are you away from being a perfect pharma company?

Vasant Narasimhan Executive

Well, I've learned they always think of ourselves as the 5. We always have opportunity to improve, but it's never as kind of bad as it seems. So maybe we're like a 6 or 6.5 now. Yes. I think what's been very positive is if you're coming out of this transformation, we've clearly streamlined the organization.

We have much better focus, much better commercial execution. And I think overall, a really strong mid-stage pipeline. And if you look at the trajectory out through 2030, we feel extremely confident we can deliver these numbers, and we hope to do even better.

I think for us, the grand task now looking ahead is how can we really drive even better R&D productivity? And if you look at the history Unfortunately, I mean, our -- despite a significant amount of spend, and I would still say relative success based on the launches, our research productivity has not been as good as we had hoped. I mean, we still had a very large number of proof of concepts and a large number of TAs, which never ultimately went into development. In an organization like ours, if you can imagine, if we didn't have that, how good would we be right now? If you didn't have 60%, 70% of proof-of-concepts not advancing in the history.

And so I think we have to prove that. We have the aspiration now to have much better alignment. All of the pieces are in place, we have to deliver now that research portfolio coming into development consistent. So that's one thing high on our minds, I'd say. Second is development speed.

I mean, we are fast when we need to be. I mean if you look at iptacopan, SCEMBLIX, I mean, these were very fast developments, we need to be more consistently fast. We don't fare on the high end of the industry on development time lines, and we need to get there now because we're focused, we have the opportunity to go much, much, much faster. So I think on that whole R&D productivity spectrum, we have an opportunity to do much better.

I think before this year, I would have said launches, I mean we are pretty mixed on our launch delivery. But this year has been really, I would have to say, outstanding. I mean, iptacopan delivered SCEMBLIX so far has delivered KISQALI early breast cancer delivering. PLUVICTO, you could say is mix, but we got to $1 billion pretty fast. It's just that the expectations probably got too far ahead of us.

But I think that's been very, very good. And so I think that if we can consistently now demonstrate over the coming years, we can consistently launch these products well.

That, of course, will lead to further re-ratings also. So I think those would all kind of be a rough estimate. We've done very well on ESG. I mean it's more a hygiene factor, right? But I think the turnaround in ESG has been a net positive.

But if I had to pick one thing, we got to drive more R&D productivity, and that's going to be the key as a pure-play company. Matthew.

Matthew Weston Analyst

Sorry. It's Matthew Weston from UBS. I'm going to try my luck with the 2025 guidance question, but ask for no numbers. Looking at where you are now, I think the one thing -- I mean, you said it on the 3Q call, you said growth and the market reacted quite negatively for that because -- and today, you've said solid growth, I think, which hopefully will give people some comfort. But if I look at next year, obviously, the world is very focused on the LOEs and they're very sizable, and you've given us a relatively fixed time line, at least to work on, which I realize might not be the actual time line, but it is what it is.

But looking now, there's not a lot of time for you to scale for you to, in your mind, scale the launch potential of a lot of assets that fill the gap, whether it's KISQALI, whether it's more growth in PLUVICTO, whether it's SCEMBLIX. So is next year a year where we should expect you to be cautious at the beginning of the year because the launch is you still not got a lot of visibility and build as we see them progress? Or you actually in-house feel you've got sufficient visibility to really tell us what you see at the beginning of the year.

Vasant Narasimhan Executive

I think we have very good visibility. It's never -- it's always imperfect, right? I think in general, in January, we view ourselves as prudent. I don't know about conservative but prudent, right?

Harry Kirsch Executive

Slightly conservative.

Vasant Narasimhan Executive

Slightly conservative. So we'll probably be around where we usually are. But look, we feel very confident when we look at the outlook for these brands that next year will be a very solid year. I mean I think Harry has highlighted over the course of today. We have volume growth when you look at the volume growth in the mid-teens.

And yes, we lose a couple of points because of generics and a couple of points because of price. And so this year, we've guided to the low teens, and that's we'll be. Next year, we'll have a little bit more on the generics. But that underlying growth outside of that is continuing very strong. And so you guys can all model.

I've seen a few of your models. I know where Richard is. I think I know where Graham is, I'm not sure if I've seen your number yet, Matthew. So I have a pretty good sense. And yes, I mean, I think we feel very confident about a good year.

Harry Kirsch Executive

Consensus is at the moment that -- consensus at the moment of 4%, as you know, right, there's a bit of FX on that, but so 4% to 5%, if you will. So from that. But the volume Vas mentioned, right? At the moment, we are running at 14% volume growth. We have minus 2 generics, minus 1% pricing that gives us a level right roughly on a year-to-date.

Similarly, last year. I expect that volume growth with the strong launches we expect with KISQALI, SCEMBLIX to go up. Now the generics, I mean, half year of Entresto 3 points, right, $1.5 billion. So from that standpoint, you can quickly model down, of course, Tasigna, Promacta also a little bit, but not too much. So from that standpoint, we expect a good year in '25.

And we just will update you end of January when we have a bit more visibility on average.

Vasant Narasimhan Executive

And quarter 4 numbers.

Harry Kirsch Executive

Yes.

Matthew Weston Analyst

I'm going to consider the question a win because I got Vas to go from solid to very solid. And then Harry to take it further.

Harry Kirsch Executive

Without any numbers. But I do have to say I'm sometimes surprised that we often had a question Will you grow at all in '25? I think that's no question, really.

Simon Baker Analyst

Simon Baker from Redburn Atlantic. Just picking up on something you said a Vas about historically, launch has maybe been a bit weak, but certainly not in the last year. We've heard an awful lot about what's changed in R&D. Can you tell us what's changed in commercial? I mean, have there been fundamental changes in commercial or is there an element of you just had great products in '24 and not that they sold themselves, but they were easier commercial opportunities than perhaps in the past.

Vasant Narasimhan Executive

Yes. I think it's probably we haven't spoken enough about how our commercial execution is improving. Some of that structure, some of that is management, some of it is mindset. So from a structure standpoint, to remind you, it's just really a little over 2 years ago. If you were to show up in our U.S.

market, let's say, our most important market, you had 5, 6 different units going around the country. You had pharmaceuticals, you had oncology. You had cell therapy, you had gene therapy and you had radioligand therapy. And of course, you also had the Sandoz generics unit and biosimilars unit. So 7 different units now going around.

Now in every single country we operate in, you have one commercial organization for Sandoz generics, and we consolidate all of the functions, so market access, marketing, field force performance, all under one accountable leader, who's trying to drive our performance. And so you see an acceleration just from the fact that we simplified the structure, clarified accountabilities and then can resource allocate much more quickly. These pots of money are no longer sitting in individual units but a one empowered team can decide, okay, we have an opportunity in therapeutic area x, and we're going to differentially invest, I think so that was a structure-based benefit that we've seen.

And we've seen that really consistently around the world. I mean market access alone in the U.S., bringing together all of market access under one leader who you met today, Rob Rubinsky has unlocked so much potential for us on our key brands versus where we were before. So we think that's the right operating model. Second is that 4 TAs and 9, 10 key brands. We used to have kind of an approach where all brands were important.

We've been very disciplined to say 4 TAs the key brands and deinvest in the other items, other tail brands.

And that differential investment is also leading to better performance, more investment in launches, Interestingly, less investment in tail brands, but actually, the tailwinds do very well. It has not actually affected the tail brand performance. So the carryover goes over. So that's just a pure efficiency gain. Third, as a leadership team, we focus on U.S., Germany, China and Japan first, at 75% of the growth of the company or up to 80% depending on the year.

And the dollars go there. And then, of course, we invest in the other markets as appropriate, that allows us to appropriately scale those markets.

And then less visible, I think, are just a huge focus on execution now. I mean we -- as a pure play company, you have the individual countries now one over one from me or in the case of the U.S. coming directly to me. We also are, I think, the only global pharma company that no longer has a global marketing organization but simply has the U.S. and international reporting to the CEO.

So we actually go through field force execution numbers. We go through medical affairs, execution figures, and we just are really on top of are we executing in the market.

Whereas in the prior Novartis kind of more conglomerate structure, that was 3, 4 levels down, hard to kind of get visibility. And that really matters. That really drives a lot of performance. If you get field forces on the ball, executing on a consistent way. So all of those things, I think, have led to a much better execution that you should see continue, I hope, at least in the coming years.

Richard?

Richard Vosser Analyst

Maybe building on that on the de-investing in the nonpriority brands. Do you think they -- you've effectively dine out on previous investments? And then after a time you get churn so that they can fall off not year 1, year 2, but year 3 you get more of a decline. Just thoughts

there. Maybe also one on China.

We're seeing some issues with other companies in China again. Does that sort of slow down any of your growth? Is there any blowback from that?

Vasant Narasimhan Executive

Maybe Harry, do you want to talk about like the AI finance work we've done to see how deinvesting in established brands?

Harry Kirsch Executive

So of course, there's a little bit of investment on the established brands in the emerging markets, but it's relatively little right? And of course, the thing is an organization always overestimate promotional and sensitivities on established medicines and underestimate the carryover effect. And so we have introduced everywhere digital AI-driven resource allocation models that just show how you can really optimize the established medicines. And that has benefited us a lot. They are not falling off the cliff.

They just continue to be [milked], if you will, but wonderful development of these established medicines.

So from that standpoint, I feel very confident that they don't fall off the cliff. And we have now seen this for a while. And of course, the other thing is we usually are other than in respiratory and after, where we don't have so much left. We usually anyway, in these TAs and see similar doctors, if you will, than prior. There's a bit of a halo effect.

I've seen that before in hypertension and how we see it also in other area. So the carryovers are surprisingly high, and that has now been institutionalized with the way we do resource allocation and also leverage new technologies.

Vasant Narasimhan Executive

And just to call out as well, I mean, everyone talks about AI and R&D. We use AI and finance to centrally plan out the business and give countries guidance on how much money they should be spending on different brands, a dedicated unit in Barcelona, does a lot of that work. And I think that does make a difference. On China, we have looked very closely at our own situation there. We don't feel like we have any at least visible liabilities.

We've really looked into field force activity. We've looked at the flow of goods in the country.

So we feel like we're in a good place, but we have to stay very vigilant. We have a large compliance organization. As with all companies, we do have low levels of rep investigations that various provinces undertake, and we have to, of course, manage that. I think the 2 notable trends we do see in China is there is more economic pressure in the country. And I think that is putting more pressure on the reimbursement system Hopefully, that short lived, it doesn't change our commitment to keep investing and growing our business in China, but something we're certainly watching.

And then I think there is a general view to clean corruption in the health care system, which I think in the end, will be a net positive for large companies like ours. But we do have to go

through this process now as that unfolds and the rightful view to kind of remove any of the inappropriate financial incentives in the system. Graham?

Graham Parry Analyst

Yes. So a couple of follow-ups actually. So you talked about your growth in 2029 or you gave the guidance this morning. It's actually about 2% above TheStreet. So we're also focusing on flat margins, but you're actually guiding to sales that are above TheStreet at the moment.

So just what would you pick out as being when you look across sell-side models or buy side expectations? Where do you think your expectations are higher. So what are people missing there?

And then secondly, just following on Entresto. If you win both the preliminary injunction hearing and the 659 and you have a ruling before the year-end, that will be before you guide for next year. So could at that point, if you want on both of those, would that give you enough confidence to guide to 2026 launch of Entresto rather mid-'25?

Vasant Narasimhan Executive

Yes. So on 2029, the big differences are KISQALI, maybe not necessarily for your model, Graham. But I think in general, I think on KISQALI, I think the early breast cancer uptake that we've seen gives us a lot of confidence in the trend on that brand. So I think KISQALI, Leqvio where we believe the momentum we're seeing is going to continue to carry forward. And Leqvio.

I think peaks out in the consensus at $2.53 billion, and we just guided this morning to over $4 billion. So we think there's an opportunity on Leqvio. And then I think TheStreet has come down on PLUVICTO whereas we think as we continue to have the opportunities in the metastatic and the hormone sensitive that PLUVICTO will outperform.

And then the last one is the pipeline, of course. We think remibrutinib has a significant opportunity just in CSU alone. And then if you take probabilized ianalumab, ZOLGENSMA, IT, pelacarsen and put aside everything else, you take that probabilized basket, any one of those hits and unprobablizes in Europe, of course, in a pretty strong position. So those are the big drivers. I think the other SCEMBLIX, Fabhalta that are reasonably modeled.

And then I think on the litigation, Karen?

Karen Hale Executive

So on the combination patent, that is probably the only decision that is technically binary. But of course, you can imagine whichever way it goes, both parties will appeal and there won't be any decisions prior to January on that piece. With respect to the complex patent the decision or ruling will be on whether or not a preliminary injunction should have been granted either way, the case will be remanded back to the district court for a trial that will occur in December. And therefore, we will not have a decision outcome determinative by the time we do the guidance.

So again, with these things fluctuating, our current thoughts are still mid-2025. I'm not sure

we're going to have the outcome determinative data from all of the litigations that are pending. Note there's also an FDA lawsuit that could impact the approvability of MSN's ANDA and others. So I can't promise you that we will have what we need to determine if there are any changes needed for the guidance.

Vasant Narasimhan Executive

I think we have time for one last question. Any final questions for a long full day. Okay. Very good. Well, I want to also thank -- I want to thank all of you here in the audience for spending a long full day here and engaging with all of our teams.

I really sincerely hope it was helpful and useful, and we really appreciate the interest and commitment to continuing to understand our story. I also want to thank everyone on the webcast for joining as well.

We hope the information is informative, and we look forward to continue to keep you all updated. And with that, we'll, of course, close this year's Novartis meet the management. We'll continue with our quarterly updates and periodic pipeline updates. And next year, we would plan on an R&D day to go really deep on to the pipeline in a more traditional format. So thank you again, and we wish you all a great rest of the year.