Takeda R&D Day 2024:
Focus on Late-stage Pipeline & Market Opportunity

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1) Call Participants

Christophe Weber
President & CEO

Andrew S. Plump
President of Research & Development

Ramona Sequeira
President of Global Portfolio Division

Teresa Bitetti
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Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

2) Presentation

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

Good morning, everyone. Thank you very much for joining Takeda R&D Day 2024 out of your very busy schedule. My name is Christopher O'Reilly. I'm the Head of IR and I'm your moderator today. Very nice to meet you. First, about the interpretation service: If you are here in the venue, please use the receiver in front of you. Channel 1 is for Japanese. Channel 2 is for English. If you are joining online, please click on the language button at the bottom of the Zoom window and select Japanese or English or original audio.

Before starting, I'd like to remind everyone that we will be discussing forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those discussed today. The factors that could cause our actual results to differ materially are discussed in our most recent Form 20-F and in our other SEC filings.

Today's presentation also covers elritercept, which is included for reference only. Takeda entered into an exclusive license agreement with Keros for global rights in all territories outside of Mainland China, Hong Kong and Macau to elritercept. The closing of the transaction is subject to receipt of regulatory approvals expected in the first calendar quarter of 2025. Takeda does not currently have rights to elritercept.

Please also refer to the important notice on Page 2 of the presentation.

Now let me introduce today's agenda and today's presenters. First, “A Global, Innovation-driven Biopharmaceutical Company” to be presented by Christophe Weber, President and CEO. Next, “R&D Strategy and Pipeline Highlights” to be presented by Andy Plump, President of Research & Development. And next, “Neuroscience: Deep-dive on Orexin Franchise” to be presented by Sarah Sheikh, Head of Neuroscience Therapeutic Area Unit & Head of Global Development and Ramona Sequeira, President of Global Portfolio Division.

And after a break, we will have “Gastrointestinal and Inflammation (GI&I): Deep-dive on Zasocitinib, Rusfertide, Mezagitamab and Fazirsiran”. The presenters are Ramona Sequeira and Chinwe Ukomadu, Head of GI&I Therapeutic Area Unit.

And after lunch, we will have “Oncology: Deep-dive on Elritercept – newly announced BD deal”. The presenters are P.K. Morrow, Head of Oncology Therapeutic Area and Teresa Bitetti, President of Global Oncology Business Unit.

After all the presentations are made, we will have a Q&A session, which will be joined by the 7 presenters and Milano Furuta, Chief Financial Officer. If you're here in the venue, we have prepared a reception for you to join. So please stay until the end. Let's get started with the presentations.

Christophe Weber
President & CEO

Good morning, everyone. Good evening, if you are in the U.S. I think we have about 200 people connected online. It's really a great pleasure to be with you today for this R&D Day. Last time we did an R&D Day was about 5 years ago. It was exactly 5 years ago. Time has passed. I hope you will feel today that the maturity level of our pipeline, and of our R&D organization to deliver on this pipeline has improved so much since 2019, which is great because in 2019 not everything played out as we had it in mind. You will feel today, I'm sure, that again the majority of the pipeline, the data we have on these molecules, the stage they are in, but also the way we develop this pipeline has progressed so much in the last 5 years. I'm very excited about sharing that with you.

We will focus really on our vision, which is to discover and deliver life-transforming treatments. You will see that all the molecules that we are highlighting today have the potential to transform the life of patients. They are differentiated. They will change the standard of care. We are convinced that they can compete often in a quite competitive therapy areas and environment. This is really core to our vision and what we do.

At Takeda, we now have the ability to develop these molecules globally. Many of our clinical trials are done in multiple countries. We have this ability to globally develop these molecules. And we also have the scale and the ability to launch these new products globally by ourselves. That is very important if you want to be a global biopharmaceutical company and a competitive one, you need to have this true capability, you need to have the capital to invest in R&D. We invest about USD 5 billion per year in R&D. You need to be able to globally develop these products.

Many of our trials are done in many countries at the same time with many centers. We have this capability to globally launch these products. What we will see today is our late-stage pipeline. Many of these products will be launched before the end of this decade, before 2030. They will have a significant revenue potential, which will help us to grow in the long term. You will see that we believe that this pipeline will allow us to grow in the decade post 2030, when we will start facing biosimilars against one of our main products, ENTYVIO. This pipeline will allow us to grow in the very long term.

In between now and 2031, once VYVANSE impact is behind us – we are facing significant generic exposure on one of our key products, VYVANSE, it's almost behind us – then we will grow because of our Growth & Launch Products, which represent 50% of our revenue, and this group of products is growing double-digit. Between now and 2031, our growth agenda will be driven by Growth & Launch Products. We'll start launching some of these pipeline assets pretty soon – you will see that. And then, post-2031, when we will start facing biosimilars of Entyvio, this pipeline will help us to continue to grow.

Revenue growth is key, in the short, mid, long term. We have a very strong cost management as well, which will translate into margin improvement. Again, once VYVANSE is washed out, that's how we will generate shareholder value in the mid, short and long term. So here are the 6 molecules that we'll focus on today. You will have a broader perspective on our pipeline, but those are the 6 that are late stage in Phase III or about to enter Phase III, and that's the potential that we see in these molecules between USD 10 billion and USD 20 billion peak revenue for these 6 molecules.

And we will explain how we ended up with these numbers. That's of course, very material, and that's why we believe that it will help us to grow in the long term. And actually, of these 6, 3 will have Phase III readout in the next 12 months in 2025, and filing will happen right after. We are talking about a really late-stage pipeline with potential launch for at least 3 of these assets in the next 3 years. So that's also very, very exciting. It's truly a new era for us because we have never launched so many potential assets with that type of revenue potential. And we are obviously very excited about it, especially now that we have again that presence, that scale to be able to launch it globally. So very exciting time.

And without further due, I'll ask Andy to join me to kickoff this pipeline day. Thank you very much.

Andrew S. Plump
President of Research & Development

Thank you very much, Christophe, and hello everybody. I have 2 takeaways for you to carry with you from today's R&D Day. One: As Christophe just mentioned, we have a very exciting high-value, late-stage pipeline, and we are very confident that we can deliver on this pipeline. The second is: We have an R&D organization that's primed to sustain Takeda for the long term based on our cutting-edge research engine, our early and mid-stage pipeline, and our partnership and business development model.

Let me start, though, by grounding you to our strategy. This is a strategy that for almost a decade now has been unwavering, but of course, evolving. Evolving based on changes in the dynamic external landscape, evolving based on our successes and on our failures. We've pivoted this strategy over time. But it's an unwavering strategy. And that strategy is that we discover, develop and deliver life-transforming medicines for rare and more prevalent diseases across our 3 core therapeutic areas.

Those are oncology, neuroscience and gastrointestinal and inflammation. We have 2 smaller R&D organizations in plasma-derived therapeutics and vaccines that support their respective businesses. Our research laboratories are outstanding. They can and do innovate from within, but they're also inverted to nurture our large network of partnerships. And then, wrapped around everything we do, is data science and operational excellence.

We are committed to this strategy. And as you'll see over the course of this morning, this strategy is working. 90% of our R&D budget is in our 3 core therapeutic areas. That's what we will focus on today, and in particular on the 6 programs that Christophe just articulated. But before moving on, it's important for you to have some foundation of the journey that we've been on over the last 8 to 10 years.

The complexion of Takeda and Takeda R&D has changed immensely over the last decade. In 2015, we were a smaller organization. We were regionally focused, predominantly here in Japan. We had essentially 1 therapeutic modality, that was small molecules, and we worked across many therapeutic areas. Today, as I just mentioned, we're a much larger organization. We are a global R&D organization with 3 therapeutic areas and now 4 core therapeutic modalities.

Those are small molecules, biologics, antibody drug conjugates and allogeneic cell therapies. And most importantly in that transition is that we now have a mature, rich, high-value late-stage pipeline. I've been here for this entire journey, and I have to tell you, it's not been easy. We've had successes and we've had setbacks. But we are absolutely 100% a learning organization. And we've taken those setbacks, and we've persevered, we've pivoted, and we've learned. And we've translated those learnings into capabilities that have fueled the pipeline that you will hear about today and that will carry us forward as we deliver on this pipeline into the next few years.

Today we are in a privileged position. It's quite a unique position in the history of Takeda. Let me tell you a little bit why. This is a slide that you will see 10 times throughout the day. It is our North Star slide for today. We have a very exciting late-stage pipeline. And today, through all the speakers, you'll hear about the differentiated science. You'll hear about the transformational potential of each of these assets for patients. You'll hear about our development timelines. And in many places, those development timelines are greatly accelerated. And then you'll hear about the market potential of each of these assets.

As Christophe just mentioned, 2025, just a month from now, next year is a critical year for us as we have 3 of these 6 programs with pivotal Phase III readouts. Oveporexton, which is TAK-861 for narcolepsy type 1; zasocitinib, which is TAK-279 in psoriasis; and rusfertide in polycythemia vera.

Beyond next year, we'll have pivotal readouts in 5 additional indications across 4 molecules: zasocitinib in psoriatic arthritis; mezagitamab in IgA nephropathy and immune thrombocytopenia; fazirsiran in alpha-1 antitrypsin-associated liver disease; and elritercept, our newest addition to the pipeline in myelodysplastic syndrome. And we are very confident that we can deliver on this.

Let me help you understand why we feel so confident that we can deliver on this. The first reason is that we've had demonstrated success. If you look at this slide, look at the top row, we've had 5 new molecular entities approved by the FDA over the last 3 years. This puts us in the top 50% of our biopharmaceutical peers. We've had important life cycle management programs that we've brought through the finish line like the ENTYVIO Pen, like HYQVIA for the CIDP maintenance indication. And importantly, when you look across our major markets, U.S., China, Japan, Europe, we've had a substantial number of approvals. And in fact, our success rate is close to 100%, significantly above the industry average.

Now I don't think that the outside world is familiar with this level of success. Why? Many of these indications are smaller indications. Many of these approvals are regional approvals. In many cases, the revenue potential is not as high as what we perhaps need to sustain our future. But with that said, what this tells us is that we can execute, and we can deliver. We look at this as a leading measure of what's to come over the next few years.

The second reason that we're confident is the rigorous prioritization that we've undertaken over the last 1 to 2 years, and I'll walk you through this in a little bit of detail. Firstly, we've been working hard to advance our pipeline to get to this point. 1.5 years ago, we started to really look at our pipeline, and we instituted a new set of prioritization criteria. And you can see them here, unmet medical need, scientific validity, an accelerated development path and commercial opportunity. That led to this transition, as you can see in the pie chart, that's quite dramatic. Just in 2021, we had 3 Phase III programs and 4 Phase III studies. Fast forward just 3 years today, 6 Phase III programs and 14 Phase III studies.

Secondly, if you look to the right-hand side of the slide, our investment thesis. In 2021, the majority of our R&D investment was in our early-stage pipeline. We were signal seeking. We were looking for those next great assets that we can bring to patients.

As you fast forward now to our current time in 2024, you can see that now the majority of our investment is behind these 6 late-stage assets. And as we project out in our forecast over the next 2 to 3 years, that percentage will increase as these Phase III programs continue to evolve. And the third reason that we're confident is that over the last 3 years, we fundamentally changed our development model. A lot of work has gone into this over the last 3 years. It's a model that we've named Future Fit. And we've named it Future Fit, because it's supposed to impart a mindset around a very dynamic development model. It's a model that will not be static. It will evolve as the rapidly evolving external landscape changes.

There are 2 core features to Future Fit. The first is that we've rebuilt capabilities within Takeda. These are strategic nodes. These are parts of development that we do better internally than sourcing. And since we had such a highly outsourced model for so many years, we've learned from that. We've learned what capabilities we absolutely need to have, and we've built those capabilities without overbuilding.

And the second core element of Future Fit is data, digital and technology. Everything that we do in Future Fit is enabled in some way today by data, digital and technology. And as we advance towards the future and as the world becomes more and more sophisticated, we're able to continue to integrate those new tools into our operating model.

I'll give you one example, and maybe it's not exciting to you, but I tell you it's very exciting to me. And that's a tool that we have called COMPASS. It's a very sophisticated tool, and it's like a control tower. It allows us in real-time, at the push of a button, to track and to monitor every one of our clinical trials: the level of information that could be of

interest to me and the level of information that could be of interest to someone who's running one of our trials, someone with boots on the ground. The kind of data that we can get from COMPASS are not just data that tell us where we are, but they're leading measures of whether a trial is actually going well or not going well, that allows us to intervene more quickly.

In the past, we waited oftentimes months, sometimes years before we'd see issues with trials. With COMPASS, we're now way ahead of the game. Now it's really hard for me to describe Future Fit because it's so large and so substantial. Perhaps the best way to explain Future Fit to you is to give you 2 examples. The first 2 programs that we put into this new operating model, of course, 2 of our most important programs, are zasocitinib and oveporexton.

In both cases, we've seen dramatic effects on both quality and speed. For zasocitinib, you can see that our 2 Phase III trials completed enrollment 7 months ahead of schedule. And the schedule wasn't a number that we put down. It was the actual number that it took deucravacitinib to run its similar studies.

And then for oveporexton, we're actually looking at a 3-year acceleration from first-in-human to filing relative to what other sleep medicines have accomplished. This is where we are today. It's a late-stage pipeline that sets up Takeda for success, 6 programs, all high value, all with robust Phase II data sets and high probabilities of success and all, as you'll hear over the course of the day, with substantive revenue potential.

Let me spend a few minutes now switching gears. The majority of today, almost all of today, will be about these 6 programs. So let me just spend a few minutes telling you about how we will drive the second key message: sustainability. There are 3 core drivers to our sustainability strategy. The first is our strong internal research laboratory. The second is our early and mid-stage clinical pipeline. And the third is our partnering and business development capability.

Let's start with the first. I won't go into much detail, but our research organization is an outstanding organization that has the ability both to discover medicines on its own, but also, because it's so integrated with our network of partners, to enable partnership and external innovation. We have 2 main research centers today, one close to where we are at Shonan. This is at our iPark. At our iPark, we focus predominantly on neuroscience, and it was the labs that brought us orexin. We are the industry leaders in this really exciting biology that came from Shonan.

The second laboratory is in Boston. And we're in the process over the next couple of years of consolidating all of our labs to a new facility in Cambridge at 585 Kendall, and we call this the Lab of the Future. We call it the Lab of the Future because we're designing it with an eye towards automation and AI. It's not like automation and AI will solve every problem, but we know more and more as these tools become more and more sophisticated, they will become integral to how we work.

We're building a capability from the ground up and a way of working that will fully embrace these new tools. And in fact, we've already been successful in using AI to enable our drug discovery: TAK-360, of which you'll hear a little bit about, our next-generation orexin agonist, was developed in part leveraging several AI-enabled tools.

The second reason we believe we have sustainability is our early to mid-stage pipeline. As you'll see here, we have about 20 programs in this pipeline. You won't hear about these today. All of them are creative science, addressing unmet need and significant commercial opportunities. Let me just highlight 2 that you may not be so familiar with because these are option-based deals. One is a partnership with a company in Switzerland called AC Immune. This is ACI-24.060. It's an active immunization therapy for Alzheimer's disease, has the potential to transform treatment of this disease with a safe and efficacious vaccine. And the second is olverembatinib, which is a partnership that we have with a Chinese company called Ascentage Pharma. Olverembatinib is a next-generation BCR-ABL inhibitor for the treatment of CML. And you think CML, we know that there are agents that treat CML. But the reality is that the majority of patients still end up dying from this disease. There is still very significant unmet medical need.

And then the third pillar of our sustainability is our BD and partnering model. You saw earlier that we're organized by therapeutic area. Our strategy is very much therapeutic area aligned. And that's how we align as you'll see in the presentations today from research to development to commercial. We have immense alignment across those 3 tiers. This gives us the ability to come up with really compelling strategies that recognize the science, the

development challenges and the commercial opportunities.

It allows us to put these strategies rapidly in place so that we can identify opportunities externally so that we can quickly diligence those opportunities and rapidly work through deal structures. We are, in most situations, when we're excited about an asset, the partner of choice. Now I've talked to you about 2 of the option-based deals that we have with olverembatinib and ACI-24.060, as you can see in the lower right. These option-based deals are really creative.

They have 2 benefits for us. One, is they're less expensive because you're starting earlier in the process. And the second, which is very important to the comments that Christophe made earlier, is we're very focused on bringing our margins up. And we're very thoughtful about the level of R&D investment and the increases in R&D investment that we're making. These option deals give us the ability to expand our pipeline without expanding our R&D budget. And there are many other examples of successful business development. I'll say that in every case, all of these are positive NPVs. And if successful, all of these can be highly profitable for Takeda.

All right. You're in for a really fun and exciting day. So let me just ground you again in the 2 key messages. The first is: We have a very exciting, very robust late-stage pipeline. And I hope after today, you understand why we feel that way. We also feel very confident in our ability to execute on that pipeline with all the learnings and capabilities that we've built into our organization. Secondly, what you won't hear so much about today is sustainability. We recognize that Takeda has a goal. We are a 243-year-old company. We want to live for another 243 years. Sustainability is critical, and I've talked to you about the elements of sustainability.

With that said, it's my pleasure to now hand it off to Sarah Sheikh and Ramona Sequeira to talk about neuroscience and our orexin franchise.

Sarah Sheikh
Head of Neuroscience Therapeutic Area Unit and Head of Global Development

Thank you, Andy. Good morning and good evening, everybody. Now we have a chance to talk about neuroscience, and in particular, orexin. At Takeda, we're doubling down on neuroscience as a key therapeutic area really for 3 main reasons. The first is the significant unmet need in an area that robs us of the essence of what it means to be human. Our ability to use language, our ability to lay down memories, even our ability to sleep can actually be affected. And neurological diseases in aggregate plays an enormous burden and cost on aging societies.

The second reason is our growing scientific understanding of the underlying pathophysiology of disease, our ability to drug previously undruggable targets in the central nervous system and our ability to derisk programs much earlier in development. And our narcolepsy type 1 program, NT1 program, is a great example of that. And then the third reason is our ability to have success in bringing meaningful medicines to patients as evidenced by approvals in diseases like ALS and Alzheimer's disease just recently. In diseases previously thought too difficult to treat.

So then with that, our vision here at Takeda is to be a leader and partner in neuroscience by discovering and delivering life-changing medicines for patients and society. Our focus is in 3 areas: Our leading orexin franchise, which is the topic of today's discussion. We're also focused on advancing treatments in neurodegenerative diseases. And we're building in rare neurology, particularly in neuromuscular disease.

What you've all been waiting for is to hear about our leading orexin franchise. What I want to share with you today is just how well our pioneering orexin franchise is progressing. And I want to focus on 2 areas. Our lead molecule, TAK-861, newly called oveporexton, which is being developed first and fast in narcolepsy type 1, NT1. And then we'll talk about additional assets and indications led by TAK-360, which is about to enter Phase II.

As you heard, we are confident that we will soon have the first and best-in-class treatment for narcolepsy Type 1 with an oral orexin 2 receptor agonist that addresses the underlying pathophysiology of disease. And we are confident in our ability to accelerate the Phase III trials with readouts in 2025 and an expeditious filing soon thereafter.

Why this confidence? Three reasons. Number one, our Phase II data, which I'll share with you today, shows for the first time the potential for a treatment to address the broad spectrum of disease symptoms with potential for a functional cure. Number two, again, our ability to execute. We've gained deep experience and learnings in the orexin field from our previous molecules. And our focus on execution, of course in partnership with sites, patients and investigators, have allowed us to substantially accelerate our programs. And then the third reason is that these outstanding data and the potential for patients are being recognized by regulators. And in recognition of that, we've been granted breakthrough therapy designation.

Today, we'll also focus on TAK-360, which has a differentiated profile in development for orexin normal indications. Phase II studies will commence later this fiscal year, so 2024, in idiopathic hypersomnia and narcolepsy type 2, and Phase II results are than expected in fiscal year 2025. And we're also pursuing other tailored molecules to address additional indications pertinent to orexin biology, including sleep-wake cycle, respiration and metabolism.

Let's talk about narcolepsy type 1, NT1. What is it like for patients to live with NT1? Our ability to both stay awake during the day, when we need to be awake, and experience restorative sleep at night is critically for us to live healthy and productive lives. But when sleep intrudes into wakefulness and wakefulness intrudes into sleep, our ability to function is significantly impaired. This is a relentless disease. Patients experience symptoms both during the day and at night. And I'll take you through the symptoms from left to right, as you see here on the slide.

Excessive daytime sleepiness is one of the most commonly recognized symptoms and it manifests in the most inopportune of situations like in a meeting like this or in class or while driving, often with serious consequences, not just to patients' grades, but to their lives. A second very well identified symptom is cataplexy, which describes the sudden loss of muscle tone upon experiencing an emotional stimulus, such as hearing a joke or hearing something profoundly moving. And how it manifests can be various, such as a very subtle drop of the face, a facial droop, or it can be quite dramatic like falling to the ground. And it can be absolutely terrifying because the patient is fully awake, unable to move, but able to hear and see everything.

You can imagine that this isn't just socially stigmatizing if you literally fall over laughing and then lie down paralyzed on the ground unable to move. But very quickly, patients then avoid social interactions. They limit themselves to feel emotions for fear of bringing on the cataplectic event and in extreme events, it can cause serious injury. The third symptom is cognitive symptoms. And the domains predominantly affected are things like executive function, learning and memory and sustained attention, which can have profound effects on our ability to function at work or school, even at home and then social interactions.

There's no respite at night either from this disease. At night, sleep is disrupted by increased number of awakenings and terrifying nightmares. And then at the peripheries of sleep, so while falling asleep or waking up, patients experience sleep paralysis and hallucinations. These are phenomenon of a part of sleep, REM sleep, occurring where it shouldn't be occurring and significantly impacting quality of sleep. With this constellation of symptoms, you can easily see why patients are often misdiagnosed and misjudged, not just by their health care providers, but by their families.

Being ridiculed, poor job performance, poor school performance are just a few of the devastating socioeconomical consequences of this disease. Today, patients have to take multiple medicines dosed multiple times a day, some multiple times at night, to control these different symptoms. And despite that, patients can't live up to their full potential. They have to limit themselves in everything they do. These patients do deserve better treatments to live better lives.

What causes NT1? And how might we address the broad spectrum of symptoms to help patients in this quest to live normal and fulfilling lives? Up on the top Panel 1 shows you healthy orexin neurons, which are located at the base of the brain in an area called the lateral hypothalamus. What they do is they produce orexin. And the function of orexin is to couple the demands of the external world with the internal state as a master regulator of the sleep-wake cycle, respiration and metabolism.

Panel 2 here shows you the cause of narcolepsy type 1. Based on the discovery of Professors Yanagisawa and Mignot who were recently awarded the Breakthrough Prize in Life Sciences, we know that the cause of NT1 is the loss of orexin neurons. And we also know that while the neurons are lost, the orexin receptors remain intact,

offering us a unique opportunity for a pharmacological intervention to address the underlying pathophysiology. And then Panel 3 just shows you that: That stimulating the receptor with a selective orexin-2 receptor agonist allows you the ability to modulate downstream neurotransmitters. And, as I'll show you in just a minute, allows us the ability to improve symptoms across the range with restoration of patient function and improved quality of life.

With this goal of functional normalization in mind, we've designed our clinical trials to evaluate the full spectrum of NT1 using established and also some more novel endpoints. And what you'll see, as I take you through this program, are regulatory endpoints, that for example assess excessive daytime sleepiness such as the objective maintenance of wakefulness test, the MWT, or the patient reported Epworth Sleepiness Scale, the ESS. You will see measures to assess cataplexy, for example, the weekly cataplexy rate. But you will also see novel endpoints that have never before been measured in an NT1 trial such as the psychomotor vigilance test, the PVT, which is a measure of cognitive function or a sleep diary to assess the quality of sleep as well as other quality of life measures.

Let's talk about the longest and most comprehensive data set of any oral orexin agonist to date, which has laid a solid foundation for our Phase III program. In this Phase II study, 112 patients were randomized equally into 1 of 5 arms, placebo of 4 active doses, 3 BID doses and 1 QD dose. 95% of patients after 8 weeks entered a long-term extension study. And I have to emphasize here something that's important, and that is that longer-term data are critically enabling to treat a chronic disease. We have a data cut here from the long-term extension for an additional 6 months of dosing that I'll show you. But at this point in time, some patients have been on the study drug for up to 18 months.

The endpoints that we just discussed also feature in this trial. But before we go into the results, I'll just hold you on tenterhooks for a little bit longer, what I want to show you here is the compellingness of the dosing regimen we've chosen, the BID dose. On the left-hand side, what you see is orexin tone in a nonhuman primate. And what you see is it gradually increases during the day, probably to fight against the mounting sleep pressure that we all experience as the day wears on. And then it abruptly falls at night, but it doesn't go to 0. There's a small amount of orexin present even in the night. And then when you go to the right-hand panel, you see an idealized profile here that we're able to reach with oveporexton BID dosing, which is able to mimic the natural orexin tone and makes this molecule uniquely suited to the treatment of narcolepsy type 1.

I'm going to take you through a number of different endpoints. And as I take you through the data, the 2 themes that will be emerging are: Normalization of symptoms, so look out for the gray box which indicates normal on these slides, and maintenance over the longer term.

Remember, the parent study was 8 weeks. We've now got an additional 6 months at week 34. On this slide, we see the maintenance of wakefulness test, the primary endpoint which is an objective measure of excessive daytime sleepiness. It's an important validated regulatory endpoint, but it's rarely used in the clinical setting. You'll see the reason why in a second. It is a truly boring test. Patients have to lie in a dark and quiet room and are asked to stay awake for as long as possible. The test lasts 40 minutes and is repeated 4 times.

Now look at the gray box here at the top. Healthy people in the soporific setting are able to stay awake for 20 minutes or longer with significant interindividual variability. It depends how well you slept the night before, for example. Compared to NT1 patients, who are only able to stay awake for between 3 to 5 minutes. You don't need to be a statistician here to see that the MWT values, particularly for the higher twice-daily doses fall well into the normal range of healthy individuals. And what that means is that NT1 patients can now stay similarly awake to healthy people. It can't really get much better than that. But what's more, these effects are maintained for an additional 6 months of dosing.

Now let's turn to a different measure of excessive daytime sleepiness, the more subjective endpoint called the Epworth Sleepiness Scale, which recalls the patient experience and again, shows normalization of function and is consistent with the MWT. What the ESS is, is a short self-assessment to identify how likely one would be to fall asleep during the daytime in 8 different hypothetical situations like watching TV, being a passenger in a car, being a driver in a car, et cetera. And each question can receive between 0 to 3 points. The more points you have, the more sleepy you are.

Scores from 0 to 10 reflect normal levels of daytime sleepiness and scores over 10 are considered to reflect

excessive daytime sleepiness. The results, again, speak for themselves in that the vast majority of patients achieved normal levels on the ESS, putting them, again, firmly in congruence with the maintenance of wakefulness test. And again, results are sustained over 6 months of treatment.

So that was excessive daytime sleepiness. Now we'll move to a different symptom, to cataplexy. What we see here, again, is profound reductions in the weekly cataplexy rate. Patients record their cataplexy episodes using a daily diary, which then is used to calculate the weekly cataplexy rate. What you can see here again is that the twice daily arms had the strongest reductions in cataplexy showing statistically significant and, again, clinically meaningful improvements versus placebo with cataplexy rates close to 0 maintained again for an additional 6 months.

Okay, if that wasn't exciting enough, we're going to get to something really exciting and novel that speaks to the normalization of cognitive function. And I'm only going to share one of the domains with you as I wasn't given more time. To illustrate this, I'm going to share 1 measure of cognitive function using the psychomotor vigilance test, which measures sustained attention. What the PVT is, it's actually a widely used reaction performance task where a subject is asked to press a button when a signal appears on a screen.

The signal occurs randomly every few seconds, and the main measure of the test is to count the number of mistakes or lapses in attention. This test is routinely used in situations where sustained attention is critical to performance. For example, it's regularly used by astronauts in space, where lapses and attention can actually lead to a disaster. In the broader context, this test can be linked to the inability to function at work or even the ability to maintain a conversation.

Again, focus on the gray box. The results don't just show statistically significant improvement in this measure, but normalization of sustained attention in all dose arms, and that's 7 hours after the first dose. That's important, 7 hours after the first dose. That's roughly in the middle of the afternoon. The middle of the afternoon happens to be the time when most patients on standard of care today struggle. They struggle to keep awake, they struggle to function, they struggle to do their job. I can also tell you that we've looked at additional endpoints measuring executive function and memory, which show similarly impressive results.

Now we'll turn to symptoms experienced at night. We heard that sleep is nonrestorative at night despite the overwhelming tiredness experienced during the day. It sounds really like torture. In the Phase II trial, we included exploratory, both qualitative and quantitative assessments of nighttime sleep, including sleep diaries that record what the patient actually experiences and how they feel. And these data we haven't shared before, but what patients reported were significantly fewer disturbing dreams and hallucinations. And again, the theme here of normalization of function comes through even on sleep.

We talked about a number of different established and more novel endpoints. And I want to end the efficacy assessment here on the Narcolepsy Severity Scale for clinical trials, which we also included in Phase II, which is a self-administered 15-item scale that evaluates the frequency and severity of the key narcolepsy symptoms, and higher scores mean the patient is doing worse. And what you see here, again, is that oveporexton resulted in clinically meaningful changes rendering all patients to the lowest scores on the NSS-CT. And these results correlated very nicely with other measures of patient-reported outcomes. This will all be part of our Phase III program.

Of course, I can't not talk about safety. This is an important thing for these molecules. And so, let's talk about safety and tolerability. We now have many patients treated for more than a year and up to 18 months in this study. Oveporexton was generally safe and well tolerated. There were no treatment-related serious adverse events and no discontinuations due to adverse events were seen.

The most common treatment-emergent adverse events were insomnia, urinary urgency and frequency and salivary hypersecretion, which were all mild to moderate and occurred within 1 to 2 weeks of treatment and were transient and self-limiting without intervention. Importantly, there were no cases of hepatotoxicity or visual disturbances that were reported in this study or in the ongoing long-term extension study. Based on these Phase II data and in consultation with global health authorities, we've initiated 2 pivotal Phase III studies, which are rapidly enrolling patients.

Patients who complete the 12-week duration of the study can then enroll into a long-term extension. We've

optimized the study design to allow for inclusion of key endpoints that have the ability to capture the holistic effect of oveporexton across the spectrum of disease. We're exploring 2 dose levels to enable flexibility of dosing for patients and physicians. And I can tell you, again, that our focus on excellence in study execution, along with our own experiences in the orexin field, have allowed us and continue to allow us to turbocharge those Phase III programs.

We aim to complete the studies this coming year, 2025, have readouts and then have an expeditious filing soon thereafter. These data that I just shared should leave you similarly excited and confident as they do us. You have seen the longest and most comprehensive data set in over 100 patients, where efficacy is seen across the whole spectrum of symptoms affecting patients with NT1, both by established and more novel endpoints. And what's more, these effects are maintained over the longer term.

Specifically, the majority of patients reached normalization of the excessive daytime sleepiness symptoms across multiple measures, the cataplexy rate is approaching 0 in most dosed groups and this efficacy profile across endpoints is sustained over the longer term. You've also seen, for the first time, improvements related to cognitive function and to nocturnal sleep. The first time this has ever been shown with an orexin 2receptor agonist.

And we just went over the safety: Oveporexton was generally safe and well tolerated. And again, importantly, no hepatotoxicity or visual disturbances were seen. In summary, this profile of oveporexton is optimized to balance efficacy and safety with the potential for a functional cure.

There's more. Let's switch gears and talk about other assets and potential indications. We know from our previous experience of orexin 2 receptor agonist that they lend themselves to the treatment of orexin-deficient conditions like NT1. But they also have potential in the treatment of certain conditions where patients have normal or near normal levels of orexin.

We also know from emerging biology that orexin pathways are involved in far more than just the sleep-wake cycle and play important roles in respiration and metabolism. And with these insights, we are developing a suite of tailored molecules that could address this breadth of indications to really maximize the potential that this biology is guiding us to and our leadership in the field.

The furnace along on this journey is TAK-360, which is currently in Phase I and due to start Phase II in idiopathic hypersomnia, IH, and narcolepsy type 2, NT2, within this fiscal year, in 2024. Here is a bit of an overview of these diseases. Like NT1, NT2 and IH are hypersomnolence disorders with significant unmet need. But unlike NT1, where we know the cause, very little is known about the pathophysiology of NT2 and IH that have normal or at least near normal orexin levels, they’re different disorders with overlapping clinical features and especially the excessive daytime sleepiness and that, you can easily see, can lead to diagnostic challenges. That, in turn, can then lead to a more heterogeneous patient population.

Our clinical experience in this field positions us very nicely to successfully meet this challenge and to develop medicines to help these patient populations. What we also know from our own data with past molecules is that higher exposures are likely required to address the needs of people who have sleep-wake disorders with normal orexin levels. What we've done is we've designed tailored orexin agonists like TAK-360 with completely new chemistry and distinct pharmacodynamic and pharmacokinetic profiles.

TAK-360 filed its IND in April of this year and is gearing towards Phase II study starts in IH and NT2 this fiscal year. We're very encouraged by the initial safety, PK and PD markers that are emerging, and in conjunction with our internal capabilities and deep relationship with sites and investigators, those are going to support us in progressing TAK-360 very quickly. I believe that TAK-360 has the potential for a first and best in class for NT2 and IH and potentially additional indications.

In closing, we are excited about how far we have come with our multi-asset orexin franchise. We have accelerated Oveporexton developments with a readout expected in 2025 and the filing soon thereafter. And we're making great progress with our next-generation molecule, TAK-360, that's currently dosing in healthy volunteers with the goal to start Phase II studies, as I just mentioned, later this fiscal year and then to read out these Phase II studies in fiscal year 2025.

And of course, we're continuing to work in our labs on the discovery and development of additional tailored orexin profiles that have the potential to address the vast unmet need in areas where orexin plays a role.

And now I'd like to pass the mic to my colleague, Ramona Sequeira, to talk about the commercial aspects of NT1.

Ramona Sequeira
President of Global Portfolio Division

Good morning, everyone. It's really nice to be here to follow up from Sarah and talk to you about how we are excited to be commercializing TAK-861 in the future and bringing it to patients. And let me just say first that in our global commercial organization, we work in a very close and integrated way with our R&D organization. We base all of our commercial strategies and our positioning off the data that we see based on the asset and the particular molecule. And then we work very closely with them to develop evidence generation, including our Phase III registration packages, so that the molecules will have the best access to the patients who can most benefit and so that we can truly win in our marketplace.

And I think you'll see that as we go through TAK-861. As Sarah mentioned, really the symptoms that we see, the excessive daytime sleepiness, the cataplexy, are just the tip of the iceberg for patients with narcolepsy. It has a huge level of functional impairment on their daily lives. And many of these patients are afraid to engage in the highs and the lows and the joys of daily life because of the risk of a cataplexy attack and they're functionally impaired in being able to just go back to the daily activities of their lives because of all of the plethora of symptoms around narcolepsy type 1.

Thinking about the patient journey here, it's a long journey. Patients can take on average 10 to 15 years to get diagnosed with narcolepsy and narcolepsy type 1 in particular. So why is that? Often, this will present in late teens, early adulthood. Patients might be misdiagnosed. Think about the symptoms they're presented with: Sleepiness and disrupted nighttime sleep. They might be misdiagnosed with a psychiatric disorder, maybe depression, maybe anxiety, maybe an intention disorder. They cycle through different specialists and different medication regimens that are not at all addressing the root cause of treating narcolepsy.

Then, over time, they're fortunate enough to get referred to a sleep center. Often for a sleep center, whether in the U.S. or many other countries, there's multiple months wait involved to actually get in to see a sleep specialist. And then surprisingly, even when they get in to see a sleep specialist, particularly for narcolepsy type 1, patients can be misdiagnosed. There's a high overlap of narcolepsy type 1 with, for instance, obstructive sleep apnea, so they may get diagnosed with sleep apnea. Or we know that about 1/4 of patients diagnosed with narcolepsy type 2 actually progress to having cataplexy and have orexin deficiency. They might get misdiagnosed even within narcolepsy.

Then once they reach the diagnosis of narcolepsy type 1, they have this plethora of treatments to address all the various symptoms. And Sarah talked in great detail about all the types of symptoms these patients are experiencing. You can think about the number of medications that need to be used to manage these symptoms on a day-to-day basis. So many of these patients end up with polypharmacy, multiple medications and often, they will even discontinue therapy.

So really, this leads to a huge opportunity for us to think about how we can do a better job of helping these patients get diagnosed for narcolepsy type 1 and then connecting them with a treatment that can actually address holistically the burden of narcolepsy type 1 on their lives. And really, today, there is nothing that exists that is able to treat the root cause of narcolepsy type 1 and address the functional burden across all of these symptoms for the patients.

We know that the diagnostic journey is long, and there are delays in diagnosis. There's a significant amount of misdiagnosis that occurs along that way. We know that about 80% of patients, even when they're on multiple therapies, are experiencing residual symptoms. We know that about 25% of patients actually end up discontinuing their therapy because of the number of different medications that they need to take. There are low treatment

expectations today, I would say, and a huge, continued burden of illness even on the existing standard of care, and we have the opportunity to change that.

Thinking about the prevalence of narcolepsy type 1, there's a lot of information that sometimes is conflicting on the prevalence of narcolepsy type 1. Our estimate, as you look at all the published data as well as research and information that we have gathered, is that here are about 95,000 to 120,000 people in the U.S. with narcolepsy type 1. And that prevalence is similar globally. We have an opportunity now to really think about how these patients can have a very different experience in their treatment journey.

TAK-861, as Sarah mentioned, from all of the data we have in patients with narcolepsy through our trials, through our long-term extensions really has an impact across the holistic treatment spectrum of symptoms that patients experience. We get patients into normative ranges for things like excessive daytime sleepiness, cataplexy. We act on cognition, so patients improve in multiple cognitive domains, including attention, as Sarah mentioned. We see very high treatment satisfaction for patients. And really, we believe that's related to the functional improvements these patients are seeing. They do tell us they feel different, and they feel better on TAK-861.

Across the board, there are so many improvements in their quality of life, in their functionality, in their symptoms of daytime sleepiness, in their symptoms of cataplexy and in their symptoms of cognition. And we've got amazing data on safe and well-tolerated medicine over a significant period of time so far and more to even come.

We have the first potentially transformative treatment to treat the root cause of orexin deficiency in narcolepsy type 1, bring patients into normative ranges and restore their functionality in their lives.

Now there's a lot of work that we need to do in order to really make sure the patients who need this medicine can get it as quickly as possible once we're able to bring it to the market. On either end here, I've got a summary of some of the work we're doing around evidence generation and patient-reported outcomes. There's still a lack of information on the true burden of illness of narcolepsy, and we need to be able to make that argument to payers and to health care systems around the world. And we can really use patient-reported outcomes to show what good looks like when being treated for narcolepsy type 1.

In the middle is some of the work we're doing that we're very excited about on the diagnosis of narcolepsy type 1. As I mentioned, many of these patients take a long time cycling through other treatments and other specialists before they even get to a sleep center, there's many misdiagnoses along the way before they finally get diagnosed. We have an opportunity to shorten the time to diagnosis, so we can accelerate those patients' ability to get treated properly and to improve the specificity of diagnosis of narcolepsy type 1, because today there is no medicine specifically geared to narcolepsy type 1 and treating the whole patient. And so that differential diagnosis doesn't always occur.

As I mentioned, up to 25% of patients might get diagnosed with narcolepsy type 2, but are found to be orexin-deficient and will progress to cataplexy. And in some of these patients, actually cataplexy can be very hard to diagnose. We've got a number of initiatives in place, and we're actually partnering with other companies to be able to do this, where we can build on our skills and on people who have skills in the data, analytics and technology spaces as well.

For instance, we're looking at algorithms. When patients go to a sleep center, they have a multitude of tests done on them. And still, there is sometimes misdiagnosis. We're looking at algorithms that can be used to interpret results and actually improve the specificity of diagnosis of narcolepsy type 1, so we can really identify those patients.

But even before that, we're looking at ways to improve patient self-diagnosis, so they can recognize their symptoms and communicate with their doctors. And we're looking at ways to allow sleep centers to have some at-home diagnostic testing done, so that patients don't necessarily need to wait months and months in order to come into a sleep center. Across the board, as I mentioned, we're looking at ways to accelerate diagnosis and improve the specificity of diagnosis for narcolepsy type 1. And this will help us to really tap into that prevalence of narcolepsy type 1 patients globally.

A little bit about the commercial opportunity here, and I'm sure you can imagine from what Sarah's talked about, when I'm talking about the fact that the commercial opportunity is significant for this asset. We've got about 95,000 to 120,000 patients in the U.S. and the prevalence is similar globally.

We believe through our initiatives that we can improve diagnosis by 10% to 20% both by accelerating diagnosis and improving the differential diagnosis of narcolepsy type 1. We expect an increase in patients staying on treatment, and this is what we're seeing in our trials, because of the way they feel and because they do no longer need polypharmacy, they have 1 treatment addressing the root cause of narcolepsy, and we expect a significant preference share given the way that we bring patients into normative ranges across these symptoms. That gives us a potential revenue of $2 billion to $3 billion globally.

As Sarah mentioned, this is the beginning of our journey into sleep-wake disorders. We're also looking at TAK-360, very excited about its potential to support patients with narcolepsy type 2 and idiopathic hypersomnia. Those are patients that are not necessarily orexin deficient, but orexin addition will help them. We're looking at that quickly. And we're also looking at other opportunities across sleep-wake disorders, respiratory conditions and even metabolic disorders where we believe orexin can play a role.

However, really at the beginning, and as Sarah mentioned, our main focus is TAK-861. We've got a very special asset here, and our goal is to get this to the finish line, show these results in Phase III that we've seen in Phase II and be able to bring this to patients as quickly as possible.

To summarize, we've got the first potentially best-in-class transformative treatment specifically geared to the underlying cause of narcolepsy type 1. We've got unprecedented data already from Phase II and long-term extension showing that we can normalize symptoms for patients across multiple domains. We've got a franchise that we're looking at building on over time. And we're really uniquely positioned with the work we're doing around diagnosis to transform the treatment landscape and the treatment paradigm for narcolepsy type 1 and other indications in the future. Today, for narcolepsy type 1, we see that translating to a global peak revenue potential of $2 billion to $3 billion.

With that, I'm going to turn it over to Chris to take us through the rest of the day.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

Now I'd like to move on to the next presentation. It is the gastrointestinal and inflammation presentation. And the first speaker is Chinwe Ukomadu, Head of GI&I Therapeutic Area Unit.

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

Good morning, good evening, everyone. My name is Chinwe Ukomadu. I come to you from the gastrointestinal and inflammation therapeutic area. It's a pleasure to be here. Traditionally, our therapeutic area has developed drugs for patients with a variety of gastrointestinal elements, and we are moving away from this tissue and organ-specific paradigm of drug development to one where we embrace adjacent indications. Adjacencies that are linked by 1 common threat: The underlying scientific underpinnings of the diseases themselves.

As a result, we have an exciting and diverse pipeline in our therapeutic area. Currently, we have 11 unique assets that are in development across 13 indications with potentially more to come. We remain entrenched in GI, where we are developing programs in IBD as we always have. But at the same time, we are developing new therapies for celiac and for liver diseases. With regards to the adjacencies that I mentioned, we have programs in dermatology, in rheumatology and in hematology. We have multiple Phase III programs ongoing with a few more to come.

Should you ask what the strategic thread is for what we are trying to do? It's really simple. We are moving towards being able to develop therapies for patients with a variety of chronic inflammatory conditions. Andy has already

shared with you the excitement that is building in our company over the next year. He told you we will have 3 pivotal readouts in the next 12 months. 2 of those, zasocitinib for psoriasis and rusfertide for polycythemia vera reside in the GI&I therapeutic pipeline. We are going to talk about those 2 programs today.

In addition, we will also talk about 2 other assets, which are mezagitamab and fazirsiran. We are going to dive deep into 4 total programs. zasocitinib in its entirety, rusfertide, mezagitamab and fazirsiran. I will handle the research and development aspects of this presentation and Ramona Sequeira will talk about the commercial aspects of the programs.

First off is zasocitinib, our next-generation TYK2 inhibitor. TYK2 is an intracellular enzyme that conveys signals from cytokines to the cell interior where it leads its proinflammatory pathway signaling. These same pathways and these same cytokines have been evolved and implicated in a number of autoimmune disorders: psoriasis, psoriatic arthritis and IBD among them. Therefore, the hypothesis is that if you can antagonize this molecule, you should be able to dampen the signaling through it and reduce the burden of disease.

What is the scientific evidence for that, you might ask? Well, nature, in a sense, has helped us do the very first experiment. What I'm showing you here is genetic data that shows that there are people who have very reduced levels of TYK2 kinase activity. In fact, as much as 80% of the signaling is lost. These people are protected from a variety of autoimmune diseases.

And as you can see on the graphs on the right-hand side of this slide, those carrying 2 copies of this alteration are protected more than those who are carrying 1 copy, as you can see, the circles moving to the left of the slides. Protection from autoimmune diseases if you inhibit or you decrease signaling through this kinase.

But even more important is the fact that the alteration itself is very well tolerated. These are healthy people. They have no increased risk of mortality, malignancy or serious infections. What it says is that if you can make a good drug, and you can reproduce this natural experiment, you can probably decrease disease burden. TYK2 is a member of the Janus kinase family of enzymes. People have wanted to drug this target, but the problem is that when they try to do it, they encroach on the related family members that are known as JAKs.

The uniqueness of zasocitinib is that it avoids this problem. To do this, zasocitinib binds a regulatory domain, not the active side of the enzyme, it locks the enzyme in an active confirmation, as shown by the padlock on this graph, rendering it inhibited, and therefore, reducing signaling through the pathway. This uniqueness allows it to solve part of the problem that has plagued a number of attempts to make drugs against TYK2. And I share the evidence on the right side of the graph to prove this.

The selectivity of zasocitinib for TYK2 is so vastly superior to that of JAK. In essence, there's hardly any JAK activity with over 1.7-million-fold difference in selectivity for TYK2 over JAK1/3. If you compare that to similar activity of deucravacitinib, it is a 20,000-fold more selective than deucravacitinib for the TYK2 enzyme. Why keep talking about the selectivity? Because it offers us a unique opportunity, an opportunity to dose higher especially in conditions where we need more drug to have an effect without having to worry about JAK like adverse events.

And I'm going to tell you some more about this. Shown in this slide is probably the biggest message I want you to get today. And I'm going to take my time, a minute or so, to explain what is on this slide. There are 2 graphs. The left-hand side is zasocitinib. The right-hand side is deucravacitinib. Both graphs are the same layout. On the Y-axis, its concentration of drug. I'd like to point out to you that it's a logarithmic scale on the Y-axis and the X-axis is time in hours.

I will start with the left graph. There are 3 sort of horizontal lines on this graph. The lower one, the dash red line, is the IC50 of zasocitinib for TYK2. That is the concentration of the drug needed to inhibit 50% of the enzyme. The top line, dash gray line is the IC50 for JAK1/3. The concentration needed to inhibit 50% of JAK1 or JAK3. The middle red line is the blood concentration from subjects who received 30 milligrams daily of zasocitinib.

And there are 3 points I'd like to make about that specific curve. 1) The concentration of zasocitinib in the blood of these subjects, is way above the IC50 for TYK2; 2) that concentration is maintained for over 24 hours; and 3) there is a large safety margin between that concentration and JAK1/3. And I'd like you to compare that to the second graph

which is from deucravacitinib and 6 milligrams daily, which is the approved dose of this drug. You see similar things, but different magnitude.

The concentration in the blood does reach IC50, but it doesn't stay there for 24 hours. And that margin to JAK is much narrower. This in total offers us the opportunity to dose, and we believe safely, especially in situations where more drug might be needed, to arrive at the desired efficacy. With this drug, we are now beginning to study a number of indications. Our Phase II lead indications are psoriasis and psoriatic arthritis, and I'll take a minute to tell you about these 2 diseases.

Psoriasis affects more than 60 million people. These are painful, disfiguring, disabling, often scaly and reddish lesions that are on the skin of people. The lesions commonly affect the trunk, the scalp, but they can occur anywhere in your body. And the consequences of having this is not just the uncomfortableness, but also the social isolation and all the other issues that it presents to the people who have it. The disease is also associated with a number of comorbid conditions. People are more likely to be more obese or have type 2 diabetes, for example.

Psoriatic arthritis on the other hand is a chronic, progressive, inflammatory condition of the joints. Patients have painful swollen joints. And the goal of therapy here is really to prevent this before the joints themselves are destroyed. 30% of people with psoriasis will have psoriatic arthritis and up to 80% of people with psoriatic arthritis have psoriasis. So, an interaction between the skin and the joint lesions in this case.

The data we have for this molecule so far really excites us. I'm going to first share with you the data for psoriasis from our Phase IIb study. In this study, which is only 12 weeks long, 4 active doses of zasocitinib were compared to placebo. The primary endpoint is PASI 75. The PASI score is a reflection of how effective the drug is percentagewise from the time of treatment to the time of measurement. So PASI 75, for example, in simple terms means a 75% improvement; PASI 90, 90% improvement; and PASI 100 is what we call clear skin. If you look at this data, what you see is just over 12 weeks, that the high doses of this drug, the 15- and 30-milligram, are really similar with respect to PASI 75.

But I want to call your attention to the PASI 100. The black parts, which is clear skin. And what you see there is that 1/3 of the patients in the highest dose, 30-milligram, achieved clear skin. This is remarkable for a once-a-day oral molecule and only over a 12-week period of time. The drug was very well tolerated. There were no JAK-like adverse events and it is good because science really does work. I told you earlier that we have people walking around who have inhibition of reduced TYK2 signaling and they are healthy. And here again, we show that they do not manifest JAK-like activity even in the clinical set, so the drug is safe so far.

Secondly, we also have data for psoriatic arthritis. And this is also a Phase IIb study comparing 3 active doses of zasocitinib against placebo. On the left, is a graph that measures the endpoints that really focus on the improvement of the joints. The primary endpoint is ACR 20. And what you see is that the 2 highest doses here also were really superior to lower dose and the placebo with respect to ACR 20.

If you look to the upper right-hand corner of the slide, you will see what happened in the patients who had skin manifestation. They had joint involvement and they had psoriasis in the skin. And again, show an improvement with the highest dose offering more improvement on the skin than the other doses. There are other ways to look at the data. The lower right-hand corner is the minimal disease activity, which is a composite that looks at 7 different things associated with this disease: the joints, the skin, how patients feel and 5 of them go towards accounting for response. And you also see that 1/3 of the patients who got the highest dose of this drug improved in the study.

In the case of psoriasis: Well-tolerated drug, no JAK-like safety events noted. With this in our back, we have begun studies, first in psoriasis, where we are running 2 pivotal studies. Both studies compare zasocitinib to apremilast, a drug that's already being used for the treatment of psoriasis and placebo. We began these studies in November of last year and the last patient enrolled in this study in October of this year, 7 months ahead of schedule.

This rapid enrollment, we think, is a manifestation of the excitement that patients and investigators feel about the possibility of using this drug in treating psoriasis. At the moment, we are expecting pivotal data readout by the end of the calendar year 2025. Because we believe in this drug, we are going to go a step further. And we are going to run a head-to-head study of zasocitinib against deucravacitinib. That study is expected to start in the second half of

fiscal year 2025.

For psoriatic arthritis, we are a few months away from starting our Phase III studies. There are 2 studies being planned here. The first, 2 doses of zasocitinib against apremilast and placebo; and the second, 2 doses of zasocitinib against placebo. As I've mentioned, the study should start before the end of our fiscal year, and we expect filing for this indication in fiscal year '28 to '29.

But there is more. Among the things that excite us for this drug is the possibility that it could be a treatment in IBD. Patients with IBD continue to need medicines that push the boundaries of what is possible in treating this disease. They need more safe, more efficacious and more convenient therapies available to them. We think zasocitinib should be able to help in this regard. And why do we say that?

I've already mentioned to you the strong genetic link between IBD and TYK2. I have told you that zasocitinib can achieve and maintain near complete TYK2 inhibition without concerns about antagonizing JAK. And here, I show you data from our own preclinical studies that show, when you dose high enough, in these animal models with zasocitinib, you see improvement that it parallels what you see with a biologic in this disease. That's shown in the third bar in red compared to the fourth bar, which is the biologic.

We believe this is indeed an exciting opportunity. But the way to really do this is to prove it, and we're doing just that. We have an ongoing Phase IIb study in Crohn's disease with 3 active doses of zasocitinib compared to placebo and a study in ulcerative colitis with 2 active doses compared to placebo. Both studies are in progress, and patients will have the option in this study to move to a long-term extension to be followed for safety and remission.

In summary, I'd like to share with you what we've done with zasocitinib over this period of time in which we've had this asset in our hands. For psoriasis, we've shared with the world our Phase IIb readout. We started Phase III, and we've enrolled the last patient into the pivotal studies. We plan to start the head-to-head study against deucra in FY 25 with a target filing in FY 2026. For psoriatic arthritis, we have Phase II data that we shared with the world targeting Phase III start in FY 2024 with a filing planned for '28/'29.

For the IBD studies, we are in the midst of the Phase II studies with target readout for these Phase IIb studies in FY 2026. And because of the unique biology and the promise we think this molecule holds, we are looking at potentially other indications where we can use zasocitinib.

And now I turn you over to my colleague, Ramona, to talk you through the commercial aspect.

Ramona Sequeira
President of Global Portfolio Division

Thank you, Chinwe. I'm really excited to talk to you about the commercial potential and our commercial strategies for zasocitinib as we move forward. And let me start by reminding you that for these patients with psoriasis, it is so much more than just a rash. Patients with this autoimmune disease have visible plaques. They can feel very stigmatized. They could come into a setting such as this and find that people don't want to sit near them, and they can have trouble in social settings where their plaques are visible and sometimes difficulty even touching loved ones.

This disease impacts so many aspects of their life and has a very high mental burden on their lives as well. And 30% of patients with psoriasis go on to develop psoriatic arthritis, and this even has a higher disease burden. This one can be a little harder to diagnose. It can take a bit longer given the types of symptoms that present chronic pain and fatigue. Once diagnosed, more patients end up being treated on an advanced therapy, but doctors need to make a trade-off between the safety of the product and the efficacy of the product because they're worried about irreversible joint damage leading to potential disability down the line.

So again, a difficult one to diagnose and a difficult one to treat as well as a significant burden on patients' quality of life and significant mental and psychological burden. We're really excited to be able to bring a product that can transform patients' lives in psoriatic disease.

Thinking about the market opportunity here. This graph shows the number of patients in the U.S. market. We expect the market in psoriasis, which is significant today, $23 billion, to grow over time with the advent of new therapies. And in particular, we expect the advanced therapy market to grow from about 1/3 of patients today – so the majority of patients today are not on an advanced therapy – to about 45% of patients over the next 10 years. And this will be led by the advent of new therapies, including products like zasocitinib that can really change the treatment paradigm for psoriatic disease.

We expect similar growth in psoriatic arthritis, so it's about a $7 billion market. We expect it also to grow over time. Advanced therapies are about 50% of that market now, and we expect that to grow to about 60% of that market in the future. And I think that just shows us that the way the market is today, there is still an unmet need and an opportunity to provide better care for so many patients with these devastating diseases.

Now, thinking about that growth that I talked about in advanced therapies, I'm going to talk a little bit about the use of orals within those advanced therapies. Today, orals are used as a stop on the journey to a biologic. In the future, with the product like zasocitinib, orals will be able to be used as a first stop and the destination on that journey with the number of patients achieving clear skin and minimal disease activity.

We expect the oral segment, which is small today because of the lower efficacy expectations that are in this space, to more than double over the next 10 years, really led by products like zaso, which we know from our research with physicians and patients, has the potential to change the treatment paradigm for psoriasis and psoriatic arthritis.

And really, as we talk to clinicians around the world, they feel that this is where the market is going to head, it’s the use of orals earlier and really to get high efficacy with patients. And I think this is where zaso is very exciting, and I'm going to talk a little bit more about our profile and why we believe this product can actually redefine what's possible with oral therapy for psoriatic disease.

Now we know, when we talk to patients, exactly what they are looking for in treatment. We know what their wishlist is. They want something that's going to give them clear skin. I mean that is absolutely their goal because of these visible plaques that they have, whether they've got psoriasis or psoriatic arthritis with comorbid psoriasis. They want something that's going to be safe to take because many of these patients are young and otherwise healthy. They may have a few other comorbidities, but they lead very active and busy lives, and they're going to be taking this medication for a long period of time.

They want it to be well tolerated. Without unwanted side effects that impact their daily lives, and they want it to be easy to take and fitting into their active lives and potentially other medication regimens that they may have. We believe zasocitinib, based on the data that Chinwe showed you, has a very unique opportunity to actually meet the exact profile that patients and clinicians are looking for in an oral. And we will have, as we launch the product, data against both apremilast, which is being used as an active comparator in our Phase III trials, as well as data against deucra, which is involved in our head-to-head that we are getting ready to do now.

At launch, we will have data comparing zaso to apremilast and deucravacitinib to be able to show that this profile offers patients the efficacy, the safety and the ease of use that is really on their wishlist for treating psoriasis.

Thinking about the data that Chinwe showed you about the greater and longer inhibition of TYK2. Remember, he showed you well above IC50 levels for 24 hours and a big safety margin for JAK. No JAK effects at the doses that we're using. And he showed you that it was highly selective. He showed you a slide saying that it was 20,000 times more selective for TYK2 versus JAK than deucra. Because of that, we end up with a very unique profile for this molecule.

We get biologic-like efficacy because we're able to use that selectivity to dose to a level that can really provide clear skin to patients. Patients with psoriasis in our Phase II trials saw 1/3 of patients with completely clear skin; patients with psoriatic arthritis, 1/3 of patients had minimal disease activity. So truly high efficacy in an oral formulation because we're able to dose to a level that really maximizes the impact this product can have on patients.

And yet at the same time, because of the high, high differential selectivity for TYK2, we don't get JAK-related side

effects. We've got a product that has this amazing biologic-like efficacy with a very clean safety profile. And then it's a once-daily oral, very easy to take. It can be taken any time of the day without regard to food. Thinking about these patients who lead very active lives may be on other medication regimens, they're going to be able to fit this product very easily into their day. And importantly, how and when they take this product will not impact the efficacy that they're going to get from zasocitinib.

And really, this is the profile that gives us the belief in the potential of this asset to change the treatment paradigm in psoriatic disease. What does this mean from a commercial opportunity perspective? This is a U.S. market evolution, these numbers, but of course, this is going to be a global brand for Takeda. That's how we get to our overall forecast. We know that the number of diagnosed patients with psoriasis and psoriatic arthritis will grow over the next 10 years. We know that advanced therapy will grow from roughly for both markets about 39% on average to 50% for both markets.

We know that the number of patients treated with an oral therapy given the advent of a new oral like zaso, which provides clear skin and minimal disease activity to so many patients, the number of oral treated patients will more than double in this space. So that orals can be an initial treatment and a destination for these patients.

And we know that zaso has a profile that when we talk to patients, and we talk to clinicians really puts it out front as a first-choice advanced therapy. And certainly, we saw this as we saw how quickly our trials enrolled as we went out to do these psoriasis trials. There's a great deal of excitement about the potential for zasocitinib to change the treatment paradigm for psoriasis and psoriatic arthritis. This gives us a global peak revenue potential between $3 billion to $6 billion.

And in addition, as Chinwe mentioned, the unique profile of zaso gives us confidence in investigating it in diseases like IBD because of the ability to dose to a level where you can get efficacy, high coverage of TYK2 without the JAK side effects. We're doing work now on both Crohn's and ulcerative colitis, really an area of strength for Takeda. And then we're looking at other indications down the line as well. We really see this product as being something that we can develop in multiple indications over time, but really starting and most importantly, focusing today on psoriasis and psoriatic arthritis and working to bring this to patients in the marketplace as soon as possible.

Let me also mention that we recognize this is a busy marketplace and that launch execution is going to be critical to our success. We're working very closely with all of our markets to make sure that we're preparing for best-in-class launch execution. We're looking at how we ensure we're targeting the right physicians and working closely with all of our key opinion leaders as well as community clinicians.

We're looking at making sure the onboarding process is simplified and streamlined. And we're looking at making sure there's early access, early in therapy for the right patients, so people can really see the benefit and value of zasocitinib immediately as we bring it into the marketplace. The launch execution, combined with having head-to-head superiority data against both the apremilast from our Phase III trials where it's active competitors as well as deucra from our head-to-head will allow us to really make an impact in this market and change the way psoriasis is treated today.

To summarize, we have large and growing markets in both psoriasis and psoriatic arthritis. And we know today that the majority of patients are actually not on an advanced therapy. There is an opportunity to actually treat patients so much more effectively with the advent of a product like zaso that provides efficacy and safety and convenience.

We know that we are poised to be the first-line advanced therapy, really changing the treatment paradigm where orals are not a stop on to delay onset to a biologic, but actually are a destination for many patients, given the 1/3 of patients with clear skin - the 1/3 of patients with minimal disease activity that we saw in our Phase II trials. And all of this gives us confidence in a global peak revenue forecast of between $3 billion and $6 billion.

With that, let me turn it over to Chinwe to talk a little bit more about what's happening in GI2.

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

Thank you. We're going to move on to our second asset for the day, and that's rusfertide, which is a therapy we are developing for the treatment of polycythemia vera. In January of this year, we entered into a worldwide license and collaboration agreement with Protagonist Therapeutics for this asset, which is a synthetic hepcidin mimetic. This drug is being developed for patients with a rare blood cancer known as polycythemia vera.

Polycythemia vera is characterized by the presence of excessive red blood cell production. The consequences of having that includes sort of a sluggishness and thrombosis of the blood, but these patients over time can also go on to develop other complications such as myelofibrosis and acute leukemias.

At the heart of this disease is the elevated blood count, and it is due to overproduction. And one of the critical ingredients needed to produce excessive red blood cells is iron. We are going to talk about how rusfertide works to blunt this effect and reduce blood counts. Currently, there are around 155,000 patients with this disease in the U.S. with the goal of therapy for most of these patients, the reduction of hematocrit to less than 45%.

There are therapies available already. So why need another one? Well, there is room to do something better for these patients. Real-world evidence suggests that even though there is a goal to reduce the blood count - either by therapeutic phlebotomy, which is removing the blood from them, or with a number of drugs - that 78% of these patients continue to have uncontrolled hematocrit.

These patients have a risk of thrombotic events, so they can develop acute coronary syndromes, they can have strokes, they can have deep vein thrombosis. They can have pulmonary embolism as a result. Their quality of life is really poor. They are tired all the time and spend days in bed. A therapy that could help alleviate all of that, is very much in need.

Rusfertide, as I told you, mimics hepcidin. And hepcidin is a hormone that is the master regulator of iron metabolism in the body. And the way hepcidin works is simply to block a channel known as ferroportin that allows iron to exit the cell, go into the serum and be available to the bone marrow to make red blood cells. Rusfertide mimics that and blocks this channel, ferroportin, therefore, decreasing the amount of iron available to the bone marrow for the production of red blood cells.

This is the principal mechanism: to control the blood count by this drug. If this works, one would expect a consistent and sustained maintenance of hematocrit, the abrogation of the need to do phlebotomies by removing blood time after time for patients and a more stable course of the disease improvement and symptoms as such because you stabilize the mechanism of iron metabolism. Our colleagues at Protagonist have already done this experiment and published the data in the New England Journal.

I want to take a minute to walk you through what is shown on this graph. This was a study called the REVIVE study. And there are essentially 3 parts to the graph that you're looking at and I'll start with the first part of the graph, which I'll call Part 1. That is the part before the area that says placebo period. It's the period between week 1 and week 29 on the graph that you're looking at. During this time, patients got rusfertide. And what you can see is that the hematocrit is maintained at below that 45% level that I mentioned.

In the gray part where it says placebo period, which is Part 2 of the study, there was a randomized withdrawal of rusfertide. Half the patients who were previously on rusfertide had to remove and the other half continued to stay on. And what you see is that removal of the drug led to a rise in the hematocrit.

And when it was reinstituted, which is now under Part 3, which is continuing, you see a return of the hematocrit to the normal level. This study is ongoing. What it simply shows is that the drug can maintain hematocrit. When you remove it, the hematocrit goes back. When you give it back, the hematocrit returns to its normal level.

So sustained, rapid and durable, and that's what we think patients who have the disease would want. The drug itself was tolerable. The major adverse events were things that you would expect: some injection side reactions, fatigue,

COVID-19. Serious adverse events, most were not attributable to the drug in this study.

With this in the back of pocket, there is now a Phase III study called the VERIFY study that is ongoing. This study randomizes rusfertide on top of ongoing therapy against placebo on top of ongoing therapy. The first part of the study is 32 weeks, is double blind in that period and then the patients can roll over to an open-label extension cohort. The primary endpoint of this study is a response rate between week 20 and 32 versus placebo, the response of the absence of phlebotomy as defined in this slide.

And now I'll turn over to Ramona to talk to you about the commercial aspect.

Ramona Sequeira
President of Global Portfolio Division

Thank you, Chinwe. I'm really excited to talk to you about the planning that we're doing for launching rusfertide. We signed this partnership agreement about a year ago. And as Andy mentioned in his slides, our partner is doing the research and development for this at this stage, and we are doing all the commercial planning and launch planning. And it's been a really unique opportunity to combine our rare disease commercial capabilities with our deep, deep expertise in hematology and apply that to a program like rusfertide for polycythemia vera.

And actually, if you look at our hematology portfolio now, our rare hematology portfolio with ADZYNMA for cTTP being studied for iTTP, with meza that you'll hear about next for immune thrombocytopenia and now with rusfertide, it allows us to bring our rare hematology portfolio to growth over the coming years. So how are we going to do that? Well, looking at the patient journey in polycythemia vera, I'm going to talk to you a little bit about how these patients are diagnosed and then the roller coaster they go on through their treatment journey.

So many of these patients will be diagnosed either by presenting with a thrombotic event or they might have symptoms, and they might have a routine blood work done with their physician and then will be diagnosed with polycythemia vera. Remember, they have excessive red blood cell production. They have too many red blood cells in their body, and that puts them at risk, as Chinwe mentioned, for many different types of disease problems.

For instance, cardiovascular disease and pulmonary embolism, thrombotic events, acute coronary syndrome, there's a high, high cardiovascular and thrombotic risk for these patients. And this is a chronic disease. Often, they're diagnosed around 50 or 60 years old, but then they're going to live with this disease for 10, 15, 20, 30 years living with this increased risk of serious cardiovascular and thrombotic events. The initial treatment is, as Chinwe mentioned, very rudimentary, a phlebotomy, a therapeutic phlebotomy. They take blood out of the patient. And in essence, that actually exacerbates a lot of the symptoms they experience from polycythemia vera.

As they have these blood draws, they end up feeling very anemic, tired, fatigued. We know that about 20% of patients can spend all day in bed, multiple days in a row, they have trouble functioning, they have brain fog and cognitive challenges. And the phlebotomy is actually making it worse and exacerbating the actual symptoms of polycythemia vera. But today, it's the only way to quickly bring their red blood cell count down. However, it's not permanent. It's temporary. They have to go through a cycle of regular phlebotomies over time, which exacerbates their anemia and their symptoms.

Then for patients who are higher risk, they often get put on 1 or 2 cytoreductive therapies. These therapies can be very difficult to take and have their own side effects and impacts on patients. And in fact, sometimes patients will tell us that their doctors who are very comfortable with these cytoreductive therapies will tell them “Don't worry, you're doing a lot better than my other patients”. But yet these patients don't feel better, they feel worse. And then they feel guilty for feeling worse. There's a real need here to amplify the patient's voice and think about treatment that really helps to make them feel better. And that's where we have an opportunity with rusfertide.

With rusfertide, we have the opportunity to deliver rapid, as Chinwe mentioned, consistent and sustained hematocrit control for these patients with polycythemia vera. The first thing I want you to notice here is that half of the patients are actually not on any regimented treatment. So many of these patients are sitting out, being cared for by their primary care doctor and a community hematologist. They might be on aspirin, and they might

occasionally have a phlebotomy when their hematocrit gets really high, but they still have this disease, and they are still at risk for these cardiovascular and thrombotic events.

Then, when the patients progress to even higher risk and they get treated, they're on the cycle of phlebotomy in a repetitive way over time that's exacerbating symptoms and/or adding cytoreductive therapies, which again, causes its own side effects and symptoms.

So really, if you look at the whole treatment landscape, there's an opportunity for earlier on in the journey to be able to be on a product like rusfertide that through redistribution of iron stores actually helps patients achieve hematocrit control without inducing anemia early in their therapy, but even as they get on other therapies, whether it's phlebotomy or cytoreductive therapies, there's the opportunity to use rusfertide to help these patients feel better.

And really, that's something we hear as we talk to patients who have been in the trials for rusfertide: they feel better. It is just such a game changer for them in the way they are able to manage and live with their disease for the rest of their lives. There's a lot of excitement in the patient community about the potential for rusfertide for polycythemia vera. We're working really hard to drive awareness of the unmet need here to really find and identify risks for these patients who are sitting in the community and are not under treatment. We're working to look at including this product into broad access guidelines, but really amplifying the patient voice into those guidelines, so it can be used earlier in therapy.

We're engaging with key stakeholders to do education, which will be key to this market and also to really amplify the patient's voice, which will also be key in this market as we see in many of the rare diseases. So what this does is: It gives us the opportunity to have a product that could come in, be used with or without phlebotomy and cytoreductive therapies, and we actually have many patients coming into our trials who are only on phlebotomy, potentially remove the need for phlebotomy, which can really change the treatment that they can come to expect and give us a potential commercial opportunity of $1 billion to $2 billion.

To summarize the potential here, we have about 155,000 patients diagnosed with polycythemia vera, about 78,000 only are currently treated. So huge opportunity to find and support these untreated patients in the community as well as patients who are currently being treated and remove the need for phlebotomy in these patients. The goal is hematocrit control less than 45%. And we know today that even cycling through the many treatment options that are used, 78% of patients are not meeting that goal and are at elevated risk for cardiovascular disease and thrombotic events.

And because this is a chronic disease, this will last for the rest of their lives. We know that current treatments can actually exacerbate the symptoms patients feel and can actually make it worse for them. We have an opportunity with rusfertide to really change the way polycythemia vera is treated to diagnose, to treat earlier and to give these patients a much better quality of life.

Thank you very much. And I'm going to turn it back over to Chinwe.

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

Thank you. We're going to talk about mezagitamab, another really beautiful asset in our pipeline. Mezagitamab is a monoclonal antibody and is directed against CD38. We think it has the potential to be a best-in-class agent and the potential to be a pipeline in a product. We have amazing proof-of-concept data in 2 indications, ITP and IgA nephropathy and I'm going to share that with you today.

Mezagitamab is a monoclonal antibody that binds CD38. And in doing so, it selectively depletes long-lived and short-lived plasma cells. The reason this is important is because plasma cells are the factories that make the auto antibodies that cause a variety of autoimmune diseases. By using this drug in treatment of autoimmune diseases, we essentially saying that we're going after the cause of the disease itself.

When you do this, you get a readout that is really remarkable. You have a rapid and robust reduction in antibody levels as a marker that you deplete in the plasma cells. IgG is decreased by 41%, IgA by 70%. And in the case of IgA nephropathy, which we're going to talk about, a specific autoantibody seen in that disease goes down by 62%. On the graph below on the right, there are a few other points that are worth making. In that study, patients got a dosing free period. The last 14 weeks of this 36-week monitoring period were dose free. And during that time, the levels of these autoantibodies remained low and stable, suggesting that we have the opportunity to have something durable when we use this drug for treating patients.

I'm going to talk first about IgA nephropathy. IgA nephropathy is a kidney disease. It's due to autoimmune antibodies directed against the kidney, and it destroys the kidney over time. The way this actually leads to a disease is illustrated in the figure in the middle of this slide. We've described this process as a series of hits going from, Hit 1 to Hit 4. In Hit 1, in IgA nephropathy, a plasma cell of the IgA variety makes an abnormal antibody known as galactose-deficient IgA1. That antibody is recognized by a plasma cell of the IgG variety, that's Hit 2, makes an antibody against the previous antibody. And then in Hit 3, both antibodies combine to form an immune complex and that immune complex in Hit 4 is deposited into the kidney causing kidney damage.

The consequences for the patient include hematuria, proteinuria, progression to kidney failure, potential dialysis, kidney transplant or death. Therefore, mezagitamab goes after the causative etiology of this disease. We call this a disease-modifying agent. It eliminates these plasma cells, the factories that make the injurious antibodies, preventing their accumulation in the kidney and then preventing the disease subsequently.

There are therapies available right now trying to remediate in IgA nephropathy. But as shown here on the left-hand side, in the black curve, the standard of care therapies don't quite do the job that well because patients continue to lose renal function over time compared to their healthy non-injured colleagues as shown in the green.

We believe that mezagitamab can do this, push the curve back towards the natural attrition you see in healthy people. It can do this because we feel that what patients actually need is something that's able to stop the injury from happening in the first place. That prevents additional injury on top of what is already there that is safe and tolerated. And of course, there is a convenience factor, something they can take at home and maybe give themselves a break while they are taking the medicine without fear that their kidneys will worsen again.

That's what we think mezagitamab can do. And why are we feeling confident about this? I'm going to show you just 2 data specifics that we've generated from a study. The top left hand is a measure of ongoing kidney damage, it's proteinuria, the loss of protein through the kidney. It's usually measured by something known as the urine protein creatinine ratio. Subjects who received mezagitamab at 600 milligrams were able to reduce the amount of protein loss through the kidney to a level 55% below their starting point at week 36.

I want to point your attention again to this dosing free period, during which we weren't dosing patients anymore, but the prevention of protein loss from the kidney was maintained. More importantly, though, the reason we treat patient is not just to make the protein decrease, but to stabilize kidney function over time. And what you see is during these 34 weeks that the kidney function, as measured by the eGFR, stayed stable. And once again, it stayed stable during the dosing free portion of this study.

We are continuing to gather data from these patients. And hopefully, we have that data presented in an upcoming conference. This drug was safe. No discontinuations in the study. And we are now planning to start our Phase III studies in the fiscal year 2025. Why are we so invested in mezagitamab and IgA nephropathy? One could argue there are quite a few medicines out there, and there is a pipeline of new medicines coming down. What makes us feel so sure that we have something that is really unique here? A number of reasons.

We say disease modifying, which I've noted here. There are other agents that are disease-modifying that also target B cells. But we think targeting CD38, the specificity of just going after the cells that cause the injury, offers something unique. For one, we see a very rapid and sustained reduction in the immunoglobulins, as I've told you. We go after the disease-causing factory itself, the plasma cells. We maintain eGFR over a long period of time showing that we are not losing more kidney function, and we offer patients a treatment holiday. That's what we think this drug will offer to patients.

The second indication where we have data is immune thrombocytopenia, or ITP. Similar to IgA nephropathy, the cause here is also plasma cell that makes an antibody, but this time directed against platelets or its precursors. As a result, the platelets are destroyed, and platelet count is low. When platelet counts drop, especially when they drop below 50,000, patients are at risk of bleeding. These patients can have significant bleeding, sometimes fatal bleeding as a result of low platelet counts.

The idea here is that if you eliminate these disease-causing plasma cells, the antibodies that destroy the platelets with decreased platelet counts will rise and patients should be free of bleeding. That's what we hope to find. And our data suggests that we may well be going there, and I'll share that in a minute.

For this particular indication, what you really need is something that is very rapid. You don't want patients to bleed. If the platelet counts drop, the risk of bleeding goes up. So rapid onset of action that is durable and stable over time, that offers long-term remission to these patients, prevents bleeding, and of course, as I've said before, is safe and also has potential for a holiday, should you require one.

So here is the data that really drives what we are thinking about this. I'm showing just 3 data sets in this slide. On the upper left-hand side corner, it's a marker of response. Here, we've titled this 'platelet response'. This simply says: Did a patient who entered the study raise their platelet count to 50,000 or above in at least 2 visits when compared to what they came in at baseline? And the platelet count they came in with had to be more than 20,000. The gray bar is the placebo, and then there are increasing doses, 100 milligrams, 300 milligrams and 600 milligrams. And you can see, the active doses are far superior to the placebo.

On upper right-hand side, it's another measure of response, what we call complete response. We are asking here, did the patients have platelet counts that rose to over 100,000 on at least 2 separate visits? And you can see that while the active doses have some effect, 0 was seen in the placebo group. And then below that is the time course of how this happens over those doses that I just mentioned.

What you can see is that the response is rapid. You can see the platelets rise from the dotted line, that's around 20 by my read on this graph, go up and then stay sustained over a long period of time. And that platelet count remains elevated even during that dosing free period that I told you about. What's more important, in that 600-milligram dose, there were no bleeding events noted. There were 14 such events in the placebo arm, and the drug was safe and well tolerated.

With this, we are about to start our Phase III study in ITP. The study is mezagitamab 600-milligram given subcutaneously every week on top of background therapy versus placebo on top of background therapy. Patients will get 8 weekly doses, blinded fashion, have a dosing free period and be potentially re-treated should they need it in the second half. The primary endpoint here is durable platelet response, which is defined as a platelet count that's greater than 50,000 on at least 4 of 6 weekly platelet visits at the very end of the 24-week study.

And with that, I will pass it on to Ramona.

Ramona Sequeira
President of Global Portfolio Division

Thanks, Chinwe. A little bit about the market opportunity for mezagitamab, given the number of indications we'll be focused on 2 to start with. And then obviously, over time, we'll continue to evaluate other indications because this is such a unique molecule, and we believe it's going to have applicability in other types of diseases down the line. Starting with why we believe this is such a unique molecule: it targets plasma cells, as Chinwe mentioned. The direct source of autoantibody production. So really getting to the root cause of some of these diseases that we're studying it in. It's got the potential because of that to be disease-modifying because of the rapid and sustained remission that you see in these patients.

And then it's got a dosing holiday. Patients can take the drug for a certain period of time, stop taking the drug for a period of time and actually have a durable response and then go back on the drug. Over their lives, they can have multiple periods of treatment holidays, as well it's in a subcutaneous formulation. Thinking about the IgA

nephropathy patient as Chinwe talked about. These patients will show up first with blood in their urine, they're diagnosed often as teens or young adults. But because of the formation of these immune complexes that are being deposited in their kidney, they have a steady progression of kidney disease and loss of kidney function.

Over time, 1 in 2 patients will experience loss of kidney function with IgAN, and that is while on standard of care, and 1 in 5 patients – and remember how young these patients are – 1 in 5 patients within a decade will end up with the need for dialysis and a kidney transplant.

And because of the nature of this disease, unfortunately, even if a patient were to receive a kidney transplant, the autoantibodies are still causing these immune complexes to be formed and deposited. The new kidney will start to have the same challenges with loss of kidney function over time. Really, there's nothing here today in the market that allows for disease modification in this area, meaning stopping the progressive decline of kidney function. And that's why we're so excited about the potential of mezagitamab.

Thinking about the patients in the IgAN market, IgA nephropathy, we've got about 1.5 million diagnosed IgAN patients largely globally. I will say IgAN, IgA nephropathy, has a very high burden of illness in Asian populations. And so really, our presence and ability to commercialize this asset across multiple markets around the world is going to be really important to be able to make a meaningful impact on patients' lives.

We know today of those patients, about 90% are treated with standard of care. They might start with a steroid that can't be taken long term but can be taken for a short period of time. They might have a number of other medications that are used to treat proteinuria. However, none of the medications today, being used as standard of care, actually stop that steady disease progression and loss of kidney function. Half of the patients, despite being treated on standard of care today, are progressing with loss of kidney function. And really, there's nothing today to help those patients.

What we want to do is really establish the CD38 class as a unique and transformative approach because it's targeting the direct source of autoantibody production. The direct source of the autoantibodies that are forming those immune complexes that are being deposited in the kidneys. We believe this class, the anti-CD38 class, has a unique approach to treating IgA nephropathy, is a disease-modifying agent and as Chinwe showed can have a sustained and durable effect on patients and can stop the progression of disease.

And then we also want to differentiate meza as a very unique anti-CD38. As Chinwe mentioned, we get a very rapid and durable response in patients, and we have a subcutaneous formulation that allows for more convenience and ability to use it as well as these regular treatment holidays. And think about these patients being young patients and taking this product over many, many decades.

Let's switch gears a little bit now and talk about immune thrombocytopenia, ITP, that Chinwe also showed you data on. This is a disease that is diagnosed following a severe bleed coming into the emergency or seeing their physician. And first-line treatment is a short course of steroids.

Sometimes ITP, immune thrombocytopenia is only acute in nature. Some of these patients might be okay after a short course of steroids, particularly if they're younger, children tend to get this and it's only a onetime acute disease. But older patients as they are in adulthood, actually more often get persistent or chronic ITP, meaning it doesn't go away but persists.

These patients, because of the lack of platelets, have a lot of bleeding throughout their body. They have bleeding in their nose, in their mouth, bleeding under their skin leading to bruising and in rare cases, can lead to fatal hemorrhages or fatal brain bleeds and that risk of rare complications actually increases as patients get older.

Now there are treatments today in addition to corticosteroids that are used to manage these patients. And actually, many of these patients are managed on standard of care. TPO-RAs would be some of the agents that are used in these patients. However, we know that about 20% of patients either don't respond to standard of care or might be on standard of care, but their platelet destruction continues to the point where they're no longer well treated or well controlled on standard of care. They need something else.

And today, there really is nothing else for these patients. Our focus with mezagitamab in immune thrombocytopenia is really to focus on the patients that are not well controlled on standard of care or progress past standard of care, have ITP and really don't have other options for themselves.

So, thinking about ITP, it's again another very rare hematology asset. There are about 200,000 diagnosed ITP patients globally and about 50,000 of those are in the U.S. About 20% today have an inadequate or progressed past response to the current standard of care and have need for an effective treatment. And really, this is where we can come in and help these patients.

However, given the profile of meza, there's certainly an opportunity for this to be used even earlier in treatment as well, given the rapid platelet response, the direct source of auto antibody production and really getting to that direct source and the safety and efficacy and utilization of the product with the treatment holidays. So, we really feel that meza has a unique opportunity, both in IgAN and in ITP to meet high, high unmet patient needs.

Thinking about the potential, the commercial potential with these 2 indications for mezagitamab, for IgAN, really, we aim to be the first choice anti-CD38, a disease-modifying agent that stops progression of kidney disease, the promise of a treatment holiday and a subcutaneous dosing in a very, very rapid and sustained response.

If you look at ITP, we want to be the first choice for patients who are not responding well to the current standard of care. Today, there is nothing for those patients. There's a high unmet need, and we believe we have a role to play with meza in really helping those patients because we get sustained platelet restoration with treatment-free remission periods, and we have a very favorable safety and tolerability profile.

Both these assets together have great potential. Today, it's a little more heavily skewed to IgAN versus ITP. But as I mentioned, as we do more work, as we learn more about the profile and see the data coming out of our trials, there is a potential for this to be used even earlier in therapy in ITP as well. The global peak revenue potential for IgAN and ITP combined is $1 billion to $3 billion, and we're really excited about the mechanism for mezagitamab, as Chinwe mentioned, getting to the direct source of autoantibody production. There are a number of other areas where we'd like to study this and we're doing work now to look at potential additional indications where there's a high unmet need, and we can come in with something that is transformative and disease-modifying.

To summarize, we're really well positioned given the unique profile of meza to be a best-in-class anti-CD38 agent with disease-modifying potential, treatment holidays, subcutaneous dosing, rapid and durable response and able to really transform the treatment paradigm for IgA nephropathy and immune thrombocytopenia.

We've got our proof-of-concept studies that demonstrate stabilization of kidney function in IgAN, and rapid restoration of platelet count in ITP with a durable response off treatment and subcutaneous dosing. And we continue to look at the asset, expanding the potential beyond IgAN and ITP, see other indications where there's a high unmet need, and this unique asset could be of great service to patients and the health care community. Today, we see global peak revenue of $1 billion to $3 billion for these first 2 indications, IgA nephropathy and immune thrombocytopenia. Thank you.

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

All right. And now we'll go to our last asset, which is fazirsiran. We've done a small molecule peptide mimetic, a monoclonal antibody and now an siRNA therapy. All of them exciting in their own unique ways. We're going to talk about the disease known as alpha-1 antitrypsin deficiency liver disease. So alpha-1 antitrypsin is a protein that is made in the liver and secreted into the blood where its major job is to go pretty much to the lungs and protect it from destruction by another enzyme known as neutrophil elastase.

For this to work and protect the lung, the protein has to be made normally, it has to be shipped out of the liver and protect the lungs. When it's unable to do that, patients can have a lung disease. However, today, we are not talking about the lung disease, we are going to talk about the liver disease because patients who have alpha-1 antitrypsin deficiency can have a mutation that leads to accumulation of an improperly misfolded protein.

That protein gloms up the liver cells, causes cellular stress and injury and patients can get a liver disease as a result. The disease itself is largely asymptomatic, like most chronic liver diseases. But when clinical effects manifest, there are no treatments that are available, except for liver transplantation. So fazirsiran is a treatment that is geared towards reducing the accumulation of this abnormal protein in the liver and the hypothesis is that removing the injury, prevents sequela of the injurious protein in the liver. Less inflammation, less fibrosis, less liver damage, and that's the goal of this therapy.

This is shown pictorially here. Blown up on the left is the process of how injury is caused in the liver. Those little red patches you see on the liver cell are depictions of this accumulated toxic protein that is building up in liver. In consequence, it causes inflammation and cellular stress, and that usually leads to fibrosis, typical of any chronic liver condition, not just alpha-1 antitrypsin, but the fibrosis follows. After you kill liver cells, caused inflammation leads to fibrosis.

The fibrosis itself can lead to the very end stage process of fibrosis in the liver that's called cirrhosis, and cirrhosis is a precursor to clinical decompensation. All the things you associate with people who have a liver that's not working, the yellowness in the eyes, the fluid in the belly, all of those come in patients who have cirrhosis. Some patients who have alpha-1 antitrypsin deficiency and fibrosis also develop liver cancer. There are multiple ways, at the end your liver stops working, either because of clinical demise or because you get cancer. And the only treatment, as I've said, at this point, is a liver transplantation.

So fazirsiran works to thwart the accumulation of this toxic protein. And I'll take a minute to just illustrate how this works. In this figure, one is the molecule fazirsiran, a double-stranded siRNA, which is taken up into the liver cells. There it finds – #2 on the graph – a piece of our messenger RNA carrying this abnormal mutation of alpha-1 antitrypsin. It forms a double-stranded RNA molecule, which has been destroyed inside the liver cells, so the protein is not made, that's #3 on this graph. And over time, the accumulated proteins are then resolved, and the liver health is improved. That is the goal of this therapy that we have. Our partners at Arrowhead had done 2 studies, and I'm going to share both of those with you.

The first one is shown here. In this study, the goal is to simply ask how much of this toxic accumulated protein deliver can you reduce? There's a 6-month arm and a 12-month arm to this. In the 6-month arm, patients were dosed with either 100 milligrams of fazirsiran or 200 milligrams of fazirsiran. They all have biopsies at baseline and biopsies at week 24.

There's a third cohort that got 1,200 milligrams of fazirsiran, a biopsy at baseline and another biopsy at least 48 weeks after the first dose. And the biopsy was then analyzed for the content of this toxic protein liver, which is shown on the left-hand side in this graph. And what you see is that between baseline and the end of the study, where it was the 24-week or when they had the second biopsy, there was an 83% relative change in the accumulated amount of this toxic protein in the liver. In the serum, you can also see some of these abnormal proteins. And what you also notice is the marked reduction in the amount of this abnormal protein in the serum over that period of time.

A second study was also run. This time, a randomized study comparing 3 active doses of fazirsiran against placebo. The primary endpoint here is the amount of this abnormal protein in the serum. The dosing schedule is at the bottom, a biopsy at baseline and a biopsy at week 48 – or later, depending on the patient. And what you see in the next graph is a nice dose response over time in the serum on the left-hand side and in the liver on the right-hand side.

You notice a 94% decrease in the accumulated amount of this protein in the liver and you see a nice dose response of the serum content of this protein at the same time. This drug is well tolerated. We followed patients now for over 1.5 years. There have been no deaths, no discontinuation and no dose interruptions.

We are in the middle of a Phase III study known as the Redwood study. This is a study where patients are randomized 1:1 to fazirsiran at 200 milligrams subcutaneous against placebo. The dosing schedule is shown at the bottom. There's a biopsy baseline. There's another biopsy at week 106, which is the primary endpoint of the study. There is a third biopsy at week 202. The primary endpoint here is a 1-point reduction in fibrosis content at week 106

of this study, and there are a number of secondary endpoints.

And now I will turn it over to Ramona to talk to you about the commercial aspects of this drug.

Ramona Sequeira
President of Global Portfolio Division

All right. Thank you so much, Chinwe. This is my last one, and I'll say it's been such an exciting time for those of us at Takeda learning about all these amazing assets in our pipeline and really benefiting from the amazing work happening in our R&D organization, in our global commercial organization and in our business development organization. We feel really fortunate to be able to bring such transformative assets, that are uniquely positioned to make a significant impact on patients' lives and build Takeda's sustainable growth story over time.

We're going to talk a little bit about fazirsiran, and this is a story on the slide here about a woman named Linda who's actually given us the okay to share her story with you. She is very typical of a patient with alpha-1 antitrypsin-deficient liver disease. She lives her whole life, not knowing that she had a double genetic mutation. She was healthy and happy until suddenly, she presented with very, very severe end-stage liver disease.

She got on a transplant list. And with only hours left was given a transplant that was able to save her life. Now since she's been diagnosed, her family has now recognized that this is a genetic disease, and her family is able to go and have genetic testing and screening to say if they also have the double mutation.

However, even if they were to have that double mutation and be at risk of developing alpha-1 antitrypsin-deficient liver disease, there's nothing today to treat or cure this disease. This community, it's similar to many of the others that we have here, are waiting anxiously for Takeda to be able to bring a solution to the health care system.

Linda's journey is very typical of patients with this disease. In general, liver disease is a silent disease. It progresses over many years. They don't know they have it. These patients have a very specific type of liver disease due to this buildup of the mutated protein in their liver, but they don't know. And often, they don't get diagnosed until they are at end-stage liver disease. They present with liver cancer, on a transplant list and are near death.

Sometimes these patients will present earlier with a pulmonologist because they've got 2 mutations of the alpha-1 gene, so they don't have enough healthy circulating alpha-1 to be able to preserve lung function. Sometimes they'll present to a pulmonologist, but even then, today, if they are to be presented and then monitored for liver disease, there's nothing specifically to treat the alpha antitrypsin-deficient patient.

Thinking about the situation we find ourselves in this place, it's almost a cycle. There's nothing to treat alpha-1 antitrypsin-deficient liver disease today. Because of that, there's low awareness and a low urgency to find and screen these patients today. Because of that, we see constant underdiagnosis in very long timelines with people getting diagnosed very much at a late stage when they are in end-stage liver disease.

And there's a very poor disease understanding. There's very poor understanding that there is a genetic mutation that exists, that mutation can cause buildup of the mutated protein in your liver and can lead to long-term liver disease. There's really an opportunity for Takeda. Bringing the product is not going to be enough here. We really need to transform the diagnostic journey to be able to find these patients earlier to ensure that they can be treated.

And we think there's a great opportunity to take advantage of enhanced liver screening that's happening in health care systems around the world now with the advent for more products in the MASH space. This is unrelated, but it can be done as part of the general liver screening with a simple genetic screening. It's a blood test, a simple blood test. We're going to do a lot of work as we prepare to bring fazirsiran to market to really make sure we can insert this genetic screening into liver testing regimens, so we can find these patients earlier and offer them hope.

Thinking about the opportunity for this asset in its very unique space, rare space, where there's nothing else available to treat these patients, we've got about 250,000 patients prevalent globally with this genetic mutation. And again, these are patients that have both genes that produce alpha-1, are producing the mutated protein. Of

that, about 35% of patients will get this buildup of the mutated protein in their liver and develop liver disease.

Today, only about 10% to 15% of these patients sadly are diagnosed, and as I mentioned, they're diagnosed very, very late stage when they're presenting with liver cancer or the need for a liver transplant. And today, there's no available treatment.

So there's a huge opportunity for us, if we can take advantage of the advancement in liver screening that's happening in health care systems around the world, if we can insert genetic testing and genetic screening into that liver screening so we can identify these patients with alpha antitrypsin-deficient liver disease, if we can do education so that patients go in and get screening and family members also can be watched, we can accelerate diagnosis, be able to intervene earlier with these patients and be able to give them hope for a long and fulfilling life and really position fazirsiran as a standard of care for early treatment of alpha antitrypsin-deficient liver disease. This gives us a global peak revenue potential of between $1 billion and $3 billion.

To summarize, we will be the first available treatment indicated for alpha antitrypsin-deficient liver disease. We have strong Phase II clinical data, as Chinwe showed you. It demonstrates that fazirsiran reduces the levels of mutated protein in the serum, reduces the levels of the mutated protein in the liver, reverses fibrosis and restores liver health. That is significant for these patients.

Because of this significance, fazirsiran has been granted breakthrough therapy designation by the FDA and orphan designation by the EC. And we are well positioned to be able to really transform the journey for these patients so we can find them earlier, monitor and intervene at the right time to restore their liver health. This gives us a global peak revenue potential between $1 billion and $3 billion.

Thank you very much, and I'm going to turn it over to Chris now to take us through the rest of the day.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

Now I would like to move on to the next presentation. It is a presentation about oncology. The first presenter is P.K. Morrow, Head of Oncology Therapeutic Area.

Phuong Khanh Morrow
Head of Oncology Therapeutic Area

Good afternoon, good evening. It's great to present to you today. And on the heels of the recent late development programs that we've just discussed, I am delighted to present to you a deep dive on elritercept. Last week, we disclosed our plans to license this potentially best-in-class program in collaboration with Keros Therapeutics.

Elritercept will be in an exclusive licensing agreement between Takeda and Keros Therapeutics, enabling us to have global rights in all territories for development and commercialization outside of China, Macau and Hong Kong. Of course, the closing of this is subject to receipt of regulatory approvals, which are anticipated to occur in the first quarter of calendar year 2025.

But what I want to emphasize to you is that this in-licensing continues to solidify and broaden our footprint in hematologic malignancies, building upon our legacy and it confirms our deep commitment to serving patients with blood cancers. As you can see here, elritercept truly fits hand in glove into our oncology strategy. While our vision, which has always been inspired by patients and powered by innovation, remains constant: the desire to aspire to cure cancer.

We have refined our areas of focus to specifically 3 disease areas and 4 therapeutic modalities. And to accomplish this vision, what we've determined is we need to refresh the oncology pipeline through internal and particularly external innovation in order to create a robust and an impactful pipeline that's designed to address critical areas of unmet need for patients with cancer. Our pipeline is truly a paradigm of prioritization.

If I can walk you through from left to right. On the left-hand side, we'll be spending a lot of time discussing hematologic malignancies today. We start with our successes in acute lymphoblastic leukemia, which we still continue to feel passionate about in development. And we've achieved successes, for example, the recent approval in frontline based upon a novel endpoint, which was MRD-negative complete response for Iclusig. In addition to this, today will be spent discussing the potential treatment with a best-in-class asset for myelodysplastic syndrome, which exists on a continuous myeloid spectrum towards acute myelogenous leukemia, a truly urgent and life-threatening condition.

And last, but definitely not least within our hematologic malignancies focus, we will continue to focus upon the development in chronic myelogenous leukemia, including not just ponatinib, but as Andy alluded to, also the option agreement for olverembatinib, which gives us the potential to treat critical TI 315I mutations that occur in the treatment evolution of patients, who are being treated for chronic myelogenous leukemia.

Beyond that, the second step is in GI malignancies. And what I'd like to bring your attention to is the fact that, building upon our success, we are developing, commercializing and launching a potential chemotherapy-free option in the form of FRUZAQLA for patients with colorectal cancer. We will continue to investigate therapies to treat malignancies in gastric cancer, pancreas cancer as well as hepatocellular carcinoma, which continue to represent areas of critical unmet need.

And finally, we will continue to prioritize investigations in thoracic cancers, including non-small cell lung cancer, small cell lung cancer as well as head and neck cancer. On the right-hand side, you can see that we are continuing to prioritize and build upon our legacy of successful small molecule development. We're expanding that to include antibody drug conjugates, including the recent in-licensing and agreements related to ADCETRIS as well as mirvetuximab and complex biologics, including our bispecific platform and, of course, the fusion protein elritercept and gamma delta cell therapies.

To realize this vision, we've really leveraged the power of external innovation. And if I can briefly walk you through this slide, let me start from the left-hand corner, and note that with FRUZAQLA, this enabled us to have global development and commercialization rights ex China and this has really helped us to bring forward, as I noted, a truly chemo-free option for patients suffering from this grevious disease.

In addition to this, the regional in-licensing of Elahere, a novel ADC to serve patients with ovarian cancer in Japan, enabled us to truly address a critical unmet need. On the left bottom hand corner, you can see that with olverembatinib, this option agreement will allow us to address the mutations that develop during the course of treatment in patients who are treated for CML as well as potentially have the benefit for patients with acute lymphoblastic leukemia.

And last but not least, elritercept is what we will spend much of our time today speaking about. This is a potentially best-in-class fusion protein and marks our fourth late development business development deal in the past 2 years. This really marks and reinforces our commitment to helping patients who are suffering from hematologic malignancies as well as solid tumors.

To succinctly sum up elritercept, this is a potentially best-in-class fusion protein that potently inhibited activin A and B and has potential to help patients with anemia associated myelodysplastic syndrome, myelofibrosis and other anemia associated diseases.

Let's now deep dive on our reason to believe in this program. Can you see on the left-hand side why we believe in elritercept with such conviction? Well, first of all, elritercept has a very differentiated mechanism of action. It's potent inhibition of both activin A and activin B allows it to act at the osteohematopoietic niche, enabling it to increase all cell lineages, including red blood cells, white blood cells and platelets.

As a result, we believe this is potentially a pipeline in a molecule, enabling us to treat not just MDS and myelofibrosis, but potentially through life cycle management, additional anemia associated hematologic indications. And this fits perfectly with our oncology strategy, as I presented to you.

As you see on this slide, I want to talk to you a little bit about myelodysplastic syndrome because this is very dear to my heart. In myelodysplastic syndrome, there is an imbalance in transforming growth factor beta superfamily. And as a result of this, there's an inhibition of normal blood cell production. As a result, patients are not able to produce red blood cells, white blood cells and platelets normally.

What does that mean? Well, related to this anemia, patients can develop increasing fatigue, require chronic red blood cell transfusions and also may develop iron overload characterized by iron deposition in critical organs such as the liver, the pancreas and the heart. In addition to this, the decrease in white blood cell count and platelets can increase the risk of infection and hemorrhage.

And last but definitely not least, as I mentioned before, MDS is on a continuous spectrum with acute myeloid leukemia and about 10% to 15% of patients with MDS may progress to this life-threatening disease. As a result, and I hope I have convinced you, that this disease has a critical unmet need. Now you might say, well, there's therapies on the market right now that can address this. Absolutely, there are therapies on the market that can address some elements of myelodysplastic syndrome.

However, they have hurdles, including early cytopenias, more frequent administration, slower onset of administration and inability to treat across segments as well as treatment burden. Those are all elements, to be frank, that elritercept can address. And I will talk to you about this in the subsequent slides.

By acting at the osteohematopoietic niche, elritercept inhibits activin A and B. It impacts red blood cell development, both on the early and late stages of blood cell development, truly taking the breakoff of normal production. What does that do? Not only does it enable us to have a very rapid onset of action, strong efficacy and a tolerable safety profile but it also allows elritercept to treat across a very broad population of myelodysplastic syndrome patients.

As I alluded to, our competitors may have issues with certain histologies. Elritercept, as I will present to you, has strong efficacy in both Ring Sideroblast negative and positive disease as well as in patients with high and low transfusion burden, couple that with a generally well-tolerated safety profile. I hope you can sense the importance of this therapy for patients with anemia-associated hematologic diseases.

This slide is fresh off the presses. It actually comes from the American Society of Hematology Annual Meeting. This was actually presented just this past week in San Diego, California and provides a very, very recent data cut. And let me walk you through the data here. On this table, you'll see that these patients are patients with erythropoietin levels less than 500. Why did we present that? Because that indicates the majority of all patients with myelodysplastic syndrome.

You can see here those patients who achieved the primary endpoint, the RS-positive patients. We had more than 50% of patients experiencing or achieving the primary endpoint of transfusion independence of greater than or equal to 8 weeks and around 36% of patients with RS-negative disease. You could also see that these results are fairly comparable across low and high transfusion burden, really emphasizing the ability of elritercept to be an efficacious therapy across a broad population of patients with low-risk myelodysplastic syndrome.

This slide is also quite hot off the presses. It was also just presented at the annual meeting in San Diego, California. And it represents truly a very prolonged and durable transfusion independence that can be achievable in myelodysplastic syndrome patients who are treated with elritercept. This is a very impressive Kaplan-Meier curve because you can see among the responders, the median duration of transfusion independence was 134 weeks.

And among those patients, who had ongoing responses, 50% of them had high transfusion burden, reflecting the fact that elritercept is able to treat a typically very refractory population of patients with myelodysplastic syndrome. This curve further reinforces the benefit of elritercept across patient segments in myelodysplastic syndrome.

When we look at the safety profile of elritercept, the majority of the adverse events associated with this asset were mild to moderate, grade 1 to 2. There were no investigator or sponsor assessed fatal events associated with elritercept. And those patients who received or achieved transfusion independence of greater than or equal to 6 months showed greater improvement in quality of life, which makes sense given the fact that elritercept, therefore,

gives them a life away from the hospital, away from fatigue and away from risk of infection, hemorrhage and progression.

As a result of these encouraging results, we plan to begin a Phase III registrational study evaluating the efficacy of elritercept in patients with low-risk myelodysplastic syndrome. The primary endpoint is well validated. This is an endpoint related to transfusion independence at greater than or equal to 8 weeks, and the data will be stratified by patients with or without RS+ disease as well as for high and low transfusion burden. We are targeting a steady start in fiscal year 2024.

One major takeaway that I would like you to take from this presentation is the fact that we are building upon the preclinical understanding of this differentiated mechanism of action as well as the robust efficacy and safety data across the populations of myelodysplastic syndrome. It is to note that this drug can truly be a best-in-class therapy for patients with anemia-associated myelodysplastic syndrome agnostic of histology or transfusion burden. Its activity in both MDS and myelofibrosis really reinforce its status as a pipeline in a product, and we look forward to developing this very valuable asset and in harnessing its value with anemia-associated hematologic indications.

And with that, I'll transfer to Teresa.

Teresa Bitetti
President of Global Oncology Business Unit

Great. Thank you, P.K. Good afternoon. P.K. just shared with you what an excellent fit elritercept is to our pipeline of hematologic malignancies. And it builds really well on the historical legacy that we have in hematologic malignancies that started with VELCADE. And I think the most important thing is that this is a meaningful therapeutic option for patients. So let me give you a sense of the commercial opportunity that we have here.

Today, the market for MDS is $2 billion, and that is projected to grow to $6 billion by 2030. And I think that growth is, in large parts, reflective of the fact that there is a high incidence and a high prevalence. Taking a look here at the market map today, there's 50,000 patients in terms of incidents. And this is just looking at the U.S., Japan and your top EU4 countries.

I'll remind you, MDS is a very heterogeneous disease. Of that 50,000, 37,000 are categorized as low-risk MDS; and of the 37,000, 25,000 of those are transfusion dependent. This is the population that elritercept will serve. When we look at the medicines that are available across lines of therapy, there are a few that are out there in the market today. But I will tell you, the unmet need remains significant. RS- patients are extremely difficult to treat. They represent 70% of the marketplace. We also look at high transfusion burden patients. They are also very hard to treat. There's a high unmet need there. They're 40% to 50% of the marketplace.

And when you look at patients that are starting therapy in first line today, in less than a year's time 40% of them will already have had to move on to the next set of therapy. To focus on that unmet need, I'll just talk about that a little bit. One, what do patients want? They want freedom from constant transfusions. That transfusion independence is critical, and they want it to work quickly. Two, they want to make sure that there's broader activity, particularly RS-. There's a very high unmet need today in the market around efficacy in RS- patients and of course, always tolerability.

This is something that really matters. This disease is exhausting and fatiguing enough. You don't want the medicine to make it even worse, which is the current case with many of the medicines available today. And then convenient dosing and administration. That matters if you're not going in for an infusion every single week. And every single one of these parameters, elritercept has the potential to be best in class. This is the reason why we're very excited about this.

And to that end, we want to make sure that we deliver to as broad a patient population as possible, as fast as possible. The plan is that we will enter in second and third line, running in parallel very quickly a first-line study, so we can follow right after that. But I would like to remind you that elritercept has potential for life cycle management and other indications, and we are already planning through myelofibrosis, which P.K. mentioned.

I'll sum it up here. This has a very strong strategic fit when you look at our legacy, and the legacy exists by the fact that we have the development expertise, we have the research expertise. We know how to develop drugs in hematologic malignancy. And when you look at our commercial footprint, this is where we are in the market today. These are the physicians that we are talking to that we have relationships, long-standing relationships.

We know that elritercept is a different mechanism of action, which has parlayed into a very differentiated, best-in-class profile. And it's exciting when you're able to get a Phase III-ready asset, which is largely derisked that has potential not only in the initial indication but in multiple other indications that we can work through.

Last but not least, obviously, we're excited about the global peak revenue potential of $2 billion to $3 billion. This has been a wonderful deal. We're very excited. We believe that it really fortifies what we'll be doing in oncology. Without further due, I will turn it back over to Chris.

3) Questions and Answers

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

Thank you very much for your kind attention. We would like to move on to Q&A. You can ask 2 questions at most. Please go ahead. Mr. Wakao, please.

Seiji Wakao
JPMorgan Chase & Co, Research Division

Hello, this is Seiji Wakao from JP Morgan. I have 2 questions, firstly about the zasocitinib competitive landscape. I think zasocitinib will be a better drug than SOTYKTU. But it seems to be difficult compared to J&J's oral IL-23 receptor antagonist because based on J&J's Phase III data and the IL-23 is standard care and very familiar with physicians, so I'd like to know your view on zasocitinib compared to oral IL-23.

And the second question is about mezagitamab. I'd like to know the potential of IgAN. The incidence rate of infections is high with the mezagitamab compared to APRIL targeting antibodies. Do you believe this is due to the targeting of B cells? And do you see this as a disadvantage for mezagitamab comparing with the APRIL targeting antibodies? And also, could you comment on the Phase III dosing schedule in IgAN for mezagitamab? Will it be similar to that of ITP? What duration of dosing for the period are you considering? That's it.

Andrew S. Plump
President of Research & Development

All right. Great. I'll repeat the question and then identify a speaker. I think, Chinwe, the first question was around zasocitinib's competitive landscape, particularly relative to oral IL-23. Maybe you could start and Ramona you can add some comments.

And then there are 2 questions on mezagitamab. How do we compare to the APRIL and APRIL/BLyS agents? And then secondly, the Phase III dosing schedule. So maybe you could take that question as well.

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

All right. Thank you very much for the question. I cannot really comment on somebody's else drug, but I can tell you what our drug has done and why we are excited about the potential for zasocitinib to really offer something unique for patients with psoriasis. First, the study I showed you today was only 12 weeks long. The data for most of our competitors in this space is 16 weeks at the same phase. And we already have compelling efficacy over 12 weeks. I think we will continue to see that increase as we go into Phase III, a longer study with a primary endpoint of 16 weeks at the moment.

The other thing about this drug that makes it really appealing, is that it's a once-a-day oral drug. You can take it with or without food. We feel convenience and compliance will play a role. I shared the data with you on the selectivity of JAKs at this point. We have not seen anything to make us worry that we would have any adverse events related to that. With regards to what we have, we think the data will rule the day. And we are going to have Phase III readout 12 months from now that will show whether we're right or not. And we believe that this data will be fantastic.

Ramona Sequeira
President of Global Portfolio Division

I can add a little bit from the commercial perspective, Chinwe. Thank you. First of all, we're assuming that there is more than one oral coming into this market, so we're assuming the launch of the J&J as well as ours. And honestly, that helps us because what we want to do is change the treatment paradigm where orals are seen as a better first-line advanced therapy. And therefore, more companies helping to have physicians see the benefit and possibility in oral medication is going to actually be good for us to more than double the use of oral therapies.

But then within oral therapies, I know we're going to see the results of the Phase III trial. We have excellent results in Phase II. I will just say that what we know is, in the real-world setting, the way people can take our medication will not impact the absorption and the efficacy. We believe in real life and clinical practice, the results are going to be as good as we're seeing in a clinical trial because no matter when or how they take it, the absorption isn't impacted and they're going to get that level of efficacy. We're excited to be able to bring that to market and to be able to show that.

Maybe the last thing I'll add is that we spent a lot of time with key opinion leaders, clinicians and investigators in this space as we've been mapping out our Phase II and our Phase III trials. And I would say the feedback we're getting from them is a high level of excitement, and I think that plays out in how quickly we were actually able to recruit these trials. In a space that's relatively new to us, we were able to go in, build these relationships very quickly and recruit these trials significantly ahead of schedule. And on the commercial side, we always see that as a good indicator of the level of excitement for the assets.

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

The other question was about mezagitamab, and there are 2 parts. First was the risk of infection and how it compares to the other B cell agents that are in development. And then the second part was the Phase III dosing schedule for IgAN. I'll start with the first.

As in the first question, no direct competition, but I can tell you what we've seen. We haven't seen any increased risk of infections in the studies we have done. And I think you're right that there is a biologic reason to believe that the selectivity for plasma cells might actually be a bonus with regards to infects. In a sense, we are not disrupting B-cell maturation across the board. We still have, say, memory B cells that respond to things like vaccination and protect you from infections, very much in play. There is a theoretical reason to believe that the selectivity for CD38, in this case, might provide a safety advantage. Obviously, we're doing studies and accumulate more and more safety data, and that would be the way to prove that.

And then with regards to IgAN Phase III, we are in the process of designing those studies and I cannot share the dosing schedule with you yet since it's not ready.

Seiji Wakao
JPMorgan Chase & Co, Research Division

I have one follow-up. So could you comment on the efficacy of mezagitamab in IgAN. So UPCR, 55% reduction at 36 weeks, seems to be lower than other drugs. Should we think clear advantage for mezagitamab with uniqueness for dosing schedule, not efficacy?

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

The question was that the 55% reduction in UPCR might be lower than, say, other agents. Here's how I'll address the question. The reason for us to treat this disease is actually to preserve renal function, and the best measurement of preservation of renal function is the maintenance of EGFR. On that basis, if the goal is to protect the kidney from failing downstream, the way to do that is to maintain renal functional loss. At 36 weeks, we are essentially flat. There is no decline in the slope of the EGFR. The advantage is not just the dosing schedule, it is what we are seeing right now, and we will continue to gather data as patients continue on the study is that the ultimate goal, which is to protect their kidneys that are failing. We are meeting that at this point.

Andrew S. Plump
President of Research & Development

Maybe, Chinwe, if I may, I just wanted to add to the timelines. We recognize the competitive landscape that we're facing. And while we haven't started the study yet, this is a top priority for us, and we're moving extremely quickly. Actually, the design that we've put in place is a very creative design and recognizes the fact that, while we're coming in a little bit later than some of the other agents, in some ways, there's an advantage in doing that because there's a much greater regulatory understanding. There's a much greater appreciation for the predictive value of the early biomarkers like urinary protein and creatinine ratio. And we're going to be doing everything we can in running the study to accelerate and move this more quickly.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

This is the slide that I would like you to remember.

Next question, please. Sogi-san, please?

Miki Sogi
Sanford C. Bernstein & Co., LLC., Research Division

I have 2 questions regarding fazirsiran. The first one is, I'd like to understand the delivery of this short interference RNA. Is it at the organ-specific delivery? Or it's more kind of broader? I'd like to understand what the kind of special feature is of that delivery.

And secondly, I understand that it's really critical to really identify the patients early because once the disease AATD progresses, then it's too late. And I understand that the early diagnosis is really not present today. And you have already mentioned it, but I'd like to a little bit better understand what needs to change from now on. And then is it going to take a little bit for a while after you launch the drug? Or it's something you can accelerate?

Andrew S. Plump
President of Research & Development

Great. Thank you. Maybe, Chinwe, if you could take on the fazirsiran targeting mechanism and Ramona, if you could talk a little bit about the diagnostic challenges and opportunities.

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

Yes. First question is, is it specific to a particular organ. Yes, it is to the liver and not just to the liver, but to the hepatocytes in the liver. Hepatocytes is where alpha-1 antitrypsin is synthesized before it's secreted in the normal setting. In this case, it accumulates because of the mutation. And the siRNA is a GalNAc that targets hepatocytes, so it's specific to hepatocytes.

Ramona Sequeira
President of Global Portfolio Division

I can take the next question around the diagnosis. And what I would say is the diagnosis for alpha-1 antitrypsin-deficient liver disease needs to be done through genetic testing. Hence, our goal is to incorporate genetic screening into the liver screening that's happening today. We know in health care systems around the world, there is an increase in liver screening with the advent of more products treating MASH and obesity and fibrosis. And really, these patients are a subset within there that need a very specific treatment.

We believe we can work with health care systems because it's a very simple and inexpensive test. It's a blood test to do the genetic screening. We believe we can work with health care systems to incorporate genetic screening into the liver screening, so we can find these patients earlier, put them on some monitoring and then decide when to intervene in their disease.

I wouldn't say that would happen right away. But certainly, we're working now – even prior to bringing the drug to market – to say how we prepare to be able to identify these patients. The real urgency to identify them will come when we have a treatment because, today, even identifying them, there's nothing to treat them as they progress. So that is something that we're very focused on at launch. It won't happen at launch, but it will happen as we launch, I would say.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

Okay. Next question, please. Tony.

Tony Ren
Macquarie Research

Tony Ren from Macquarie. I would like to follow up on TYK2, zasocitinib. So, it's great to see that you guys are conducting head-to-head trial against SOTYKTU, deucravacitinib, certainly shows the level of confidence in this asset. So Wakao-san already asked you about the psoriasis where the current standard of care is IL-23, right? Would you in psoriatic arthritis consider doing a head-to-head trial against the standard of care in that space, which is IL-17 and TNF-alpha? TNF-alpha, I assume, would not be that difficult of an opponent, whereas IL-23 in psoriasis is a very competent rival.

Also, just to go to Slide 69 if I may, it looks like in the psoriatic arthritis trial, you guys are heading into the Phase III with 2 different doses, 15-milligram QD and 30-milligram QD. Just want to see what's the thinking there taking 2 different doses into the psoriatic arthritis study, whereas it looks like you fixed on a single dose heading to the psoriasis. So that will be my first question.

Andrew S. Plump
President of Research & Development

That sounded like 2 questions. That's okay. Go ahead.

Tony Ren
Macquarie Research

Actually, why don't you just answer that one. Otherwise, become a memory test, right?

Andrew S. Plump
President of Research & Development

That's okay. Please, you can finish the questions.

Tony Ren
Macquarie Research

Okay. Sure. If I may, then the orexin program, oveporexton, TAK-861. On Slide 30, 1 of the higher response doses there is 2 milligrams followed by 5 milligram 3 hours apart. That doesn't appear to be a very easily compliant dosing regimen to me. I just want to see what's your experience in trials or real patient setting. People are complaining about BID doses, right? I mean this doesn't look like it's particularly easy regimen to follow.

And also, you guys alluded to the fact that the pathophysiology of narcolepsy type 2 and idiopathic hypersomnia is not yet fully elucidated. In this situation, would you say it's a bit of a more risky proposition taking orexin 2 agonist approach in these disease areas versus type 1?

Andrew S. Plump
President of Research & Development

Right. Tony, thanks. I'm glad I was taking notes. So, 4 questions. Chinwe, perhaps you can take the first 2, which is head-to-head plans in psoriatic arthritis for zasocitinib. The second is why we chose to move forward with 2 doses in Phase III for zasocitinib in the psoriatic arthritis trial. And then maybe, Ramona, on oveporexton, you can comment on the potential for a BID dosing regimen. And then, Sarah, if you could talk a bit about, on oveporexton, the differences between NT1 development and then NT2 and IH.

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

Okay. First question was for me. Are we contemplating a head-to-head against IL-17 or TNF-alpha for psoriatic arthritis? We have no plans at this moment to do that. That can always change, but at the moment, we are not planning a head-to-head against those 2 assets.

The second question is an interesting one. You nicely noted that we took 1 dose to Phase III for psoriasis, and you're asking why we're taking 2 for psoriatic arthritis. If you look at the psoriasis doses predeclared, 30 milligrams, it's superior. But if you look at the psoriatic arthritis, there's a plateau between 15 and 30. Although when you include the skin, which is a part of this disease, the 30 is superior to the 15. But because what we are studying here is joint disease, we are taking 2 doses into Phase III just to be sure we have the right dose for the patients who have a joint disease.

Ramona Sequeira
President of Global Portfolio Division

So maybe I'll briefly comment on psoriatic arthritis and then talk about oveporexton and turn it over to Sarah. So just to let you know, certainly, we are working with the rheumatology community looking at overall evidence generation in psoriatic arthritis. We believe the sweet spot for zaso is going to be in patients that have comorbid psoriasis and psoriatic arthritis. But we also recognize psoriatic arthritis is a more complex disease, and there's a lot of things that we would like to look at and our opinion leaders would like us to look at. So really, we're looking at more Phase IV evidence generation for psoriatic arthritis and working with the thought leader community to design a plan that will help give them the type of insights they need when selecting treatment. So more to come on that.

And then thinking about oveporexton and the BID dosing, which is a little bit of a misnomer because BID dosing might be further apart, kind of morning and evening or something. The purpose of the dosing is to mimic the diurnal tone of orexin in the body. And as we talk to our thought leaders, the value of the dosing 3 hours apart or however apart we have it in our trials, in our Phase III trials will be that actually it mimics the natural diurnal tone of orexin, and this is what helps these patients be like healthy and into the normative ranges. And so there might even be a possibility for tailoring the dose depending on the individual's diurnal tone as they start taking it in real life.

We think this is going to be helpful for people to actually have full return to normalcy with narcolepsy type 1. It's a different way to think about treating narcolepsy. It's not the way how people have thought about it before. But because we know so much more now about orexin deficiency about the ebbs and flows of diurnal tones for orexin in the body and about the kind of efficacy and functionality you can get by dosing appropriately, we think actually the benefits are going to far outweigh the negatives in that dosing. It's actually going to help us have a differential advantage. And maybe, Sarah, you can talk a little bit about the trials and the patients in the trial themselves.

Sarah Sheikh
Head of Neuroscience Therapeutic Area Unit and Head of Global Development

I would be happy to do so. In addition to mimicking the natural orexin tone, the benefit risk that you see with the BID dosing is very compelling across all symptoms and maintained for the long term. That's an important one. Patients have been adhering in the trial. And as you heard, more than 90% are still ongoing in the long-term extension of the Phase II study, and patients are lining up to enroll into Phase III. So, I don't think that's an issue there either.

There are a few things I also wanted to just emphasize, and that's the flexibility in dosing. Patients wane in their ability to function later in the day, so around 2, 3, 4 p.m. That flexibility in dosing is huge, and it allows a tailored approach to individual patient satisfaction.

And then just a last point to make is that the current standard of care is multi-therapy dosed multiple times a day or multiple times at night. This is a huge step towards a single therapy that addresses all symptoms holistically. And we're very excited that we'll have that Phase III readout in 2025.

So NT2 and IH, orexin normal population. You're absolutely right. Those populations are more heterogeneous. And the question was does orexin help. And we believe it does. Actually, in our hands with earlier molecules, we have proof of concept in patients, that orexin normal populations like NT2 and IH can benefit from the orexin mechanism.

The trials we're going to conduct have to take the more heterogeneous patient population into account and be designed accordingly. And similarly, the molecules we choose have to be tailored to that population, and that's exactly what we're doing. We're very confident in our ability to deliver in these populations and look forward to the Phase II starts in the very near future.

Tony Ren
Macquarie Research

If I may just add a very quick one. The North Star slide Andy showed a few times, right, so on there, you have a number of $10 billion to $20 billion. Is that risk unadjusted, right, without risk adjustment?

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

Correct.

Sawada-san, please.

Nobuaki Sawada
JP Morgan Asset management

This is Sawada from JP Morgan. I have 2 questions. First is rusfertide. Just at ASH, Protagonist provided this Phase II extension data of rusfertide. I think that long-term data the focus is a risk for secondary cancer and myelosuppression. Currently, the standard therapy, hydroxyurea, has a risk for these diseases.

And the Phase II extension data showed the 11 malignancies, but the Protagonist analysts provided that there is no relationship between rusfertide and these malignancies. Frankly, I evaluate Phase IIb extension data of rusfertide. And next quarter, the Phase III data will be available, and the Phase III hurdle looks very low, only showed response rate, so this means FDA set a very easy hurdle for it, I think, what do you think of it? This is on rusfertide.

And second is mezagitamab, CD38 antibody is a very old drug. DARZALEX is a typical first generation CD38 antibody. But it has a risk for anemia or thrombocytopenia, because generally speaking, CD38 expresses at red blood cells or platelet cells. So generally speaking, the CD38 has a risk for them, but your mezagitamab has no risk for all that. At this stage, it is very difficult for us to analyze them, but do you have any hypothesis on why that has no impact on these cells? That's it.

Andrew S. Plump
President of Research & Development

Great. Thank you. If I understand the first question, because you really did a nice job laying out a lot of details of the program, are you asking our perception of the regulatory bar for approval for rusfertide? Is that the question? Okay. Great. If you can take that Chinwe. And then the second question was why mezagitamab doesn't have effects on anemia and thrombocytopenia.

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

Okay. I'm going to just rephrase how I understood the first question. You're saying that in the open label extension, our partners saw 11 skin cancers and you are asking, are we worried about the risk of secondary cancers using this drug, is that correct? I think that's what you asked. Okay. I think we have to go back. This is a disease itself, polycythemia vera, that has an association both with hematologic malignancies like leukemia and non-hematologic malignancies, particularly skin cancer. And then on top of that, some of the patients who have this drug, take hydroxy urea, which by itself, also has a risk. My understanding of the data that our partners presented that the 11 skin cancers were not felt attributable to the drug. They rather occurred in patients who had risk factors for developing skin cancer.

What it means to me is that we are treating a disease where the natural tendency and progression is to have other cancers. And there are multiple ways we can go about trying to unravel whether our drug is adding to that or not. One is just data, over time, treating a lot of patients to see if that. So far, in humans, we haven't seen any evidence to make that point. We also recently finished a 2-year rat carcinogenesis study. We don't have the final report yet, but we will be getting that. And that could also lend out some insight into what is going on in this case.

Next question, which is intriguing, it's whether or not we should be seeing some adverse effect on platelets and red blood cells with mezagitamab, because in DARZALEX, which is used in treating the cancer mostly, it appears, you're saying, that it's a side effect. What I can say is that in our studies, we have definitely not seen any risk of thrombocytopenia, quite the contrary. The data I showed you was that the platelets went up, not down. We have not seen that. We have not seen any risk of anemia. I don't know mechanistically why the other monoclonal antibody has that effect, but 1 potential possibility could either be dose or the underlying condition itself which is a cancer and a blood cancer. But in our studies so far, no evidence of thrombocytopenia and no evidence of anemia. And obviously, we'll continue to gather more safety information.

Andrew S. Plump
President of Research & Development

Maybe just to add quickly, Chinwe, it's important to recognize that mezagitamab is a different molecule and it binds a different epitope on CD38 than the other anti-CD38s. That alone doesn't explain why we're not seeing these effects on red blood cells or platelets, but it probably speaks to an underlying difference in the pharmacology and the molecule.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

Next is Sakai-san, please.

Fumiyoshi Sakai
UBS Investment Bank, Research Division

Hello, this is Sakai from UBS. Last year you spent JPY 5.3 trillion in R&D. If you take the last 5 years, it still comes up JPY 2.7 trillion, which is about double the size of the Astellas and Daiichi Sankyo. Now I'm not going to ask the past productivity, but you gave us this USD 10 billion, USD 20 billion potential. My question is, are you going to spend same way for next 5, 10 years with current R&D productivity? I know from the way you took over Takeda pipeline 10 years ago, I know things are collapsing or have already collapsed. You have managed the situation better, I think. But for the next 5, 10 years, resources are limited, I guess. What you're thinking going forward? That's my first question.

And second question is on Ramona-san's presentation, Page 47, the patient journey for narcolepsy, which is quite interesting, but it said diagnostic part could be crucial. Once you launch the product, whatever narcolepsy you're aiming at, you have to go through probably the same path. So that means we should expect a slow ramp-up in each product, each product launch? Would you have any means to shorten this process? So that's my second question.

Andrew S. Plump
President of Research & Development

Great. Thank you, Sakai-san. Maybe Christophe, you can talk a bit about planned future R&D spend, our intent and then Ramona on the narcolepsy patient journey.

Christophe Weber
President & CEO

On the R&D productivity, Sakai-san, first, I will highlight that the 6 molecules that we have highlighted today are not the entire pipeline. We have many more programs more early stage. So, the value is not there yet. But R&D is always early-, mid- and late-stage. Otherwise, you have a problem later on. It's very clear that we need to increase our productivity. We know that, I mean, we have been working on it. It's very clear, not only because you want to generate more molecules for every yen or dollar you invest. But also, the environment is getting more and more stringent, more price control, access is more difficult. And it's very clear that we need to increase our productivity overall as a company. We are doing a lot in that regard. Data and technology and AI will help us a lot in R&D, in research and development, but also in manufacturing. We are very much focusing on that for the future. It's very crucial. It's vital if you want to be successful in the next 5 years or 10 years.

Ramona Sequeira
President of Global Portfolio Division

I can comment on the narcolepsy diagnosis. I would say 2 things: First of all, today in the marketplace and in the treatment centers, there are many patients that have been diagnosed with narcolepsy type 1, about 80% of them have some level of residual symptoms. 25% of them tend to stop or discontinue their treatments. And there's a huge unmet need today even with those patients that, over the past years, have been diagnosed and are treated with symptomatic treatment, polypharmacy and still having all of those residual symptoms and don't have their functionality restored, and we hear that a lot from patients with narcolepsy type 1, that's our immediate opportunity. But truly, to unlock the top end of the peak sales revenue forecast, we have to make sure we can do a good job at differentially diagnosing narcolepsy type 1 and more quickly diagnosing narcolepsy patients.

I would say we're going to be doing both things. The diagnosis work, we're starting now to identify some partners in the marketplace that have expertise, maybe in data or algorithms or digital or home monitoring, so that we can actually have those partnerships in place. And when we're ready to bring the molecule, we can start that diagnostic work. That will take a little bit longer but add to the potential upside. And then in the very short term at launch, there's actually a large number of patients today that are undertreated and mistreated and looking for a different solution for narcolepsy type 1. Both those things are very important to us.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

Next is Hashiguchi-san.

Kazuaki Hashiguchi
Daiwa Securities Co. Ltd., Research Division

I'm Kazuaki Hashiguchi from Daiwa. I have 2 questions, first question is on Orexin franchise, the treatments for narcolepsy type 1. In your previous R&D conference, you showed your sales forecast to be between $3 billion and $4 billion. Why do you cut your sales forecast to between $2 billion and $3 billion? Are the main factors patient numbers, diagnostic rate, treatment rate, pricing or market share? Compared to the previous forecast, the progress of development has been graded. On the other hand, the number of the competitor products has been increased.

Second question is about long-term portfolio management strategy. In 6 products, in my understanding, the Orexin agonist is the only in-house product. Almost all your products are M&A or a licensed product. In general, the margin of an in-house product is higher than licensed products. So in-house products contribute heavily to shareholders return. Of course, our in-house products or M&A products contribute to patient value. But considering shareholders' return, do you think the current portfolio status is healthy? How do you think about your long-term portfolio management strategy?

Andrew S. Plump
President of Research & Development

So maybe Ramona, you can talk a bit about the Orexin sales projections. And then Christophe, if you could talk about the value of our pipeline.

Ramona Sequeira
President of Global Portfolio Division

Yes. So maybe just to comment on the sales forecast. In general, our overall understanding and knowledge of this marketplace has really evolved. The earlier sales forecast that we had disclosed a number of years ago was based on our previous asset, and that asset we were planning on developing across narcolepsy type 1 and narcolepsy 2 and idiopathic hypersomnia. So that incorporated 3 indications at a different time in the market. So today, as we think about oveporexton it is really focused on narcolepsy type 1, which are the patients who have Orexin deficiency where we believe we can have a significant impact by getting to the root cause of the disease.

The forecast is really focused on narcolepsy type 1. And I would say our understanding of the market and the disease state has also evolved in the sense that we have a better understanding of how to identify those narcolepsy type 1 patients, how they might be misdiagnosed over time and kind of how big that market is. So actually, the opportunity for narcolepsy type 1, in our mind, has grown compared to the last forecast, but because the asset has a narrower focus, that's the reason that the peak sales revenue is different.

Christophe Weber
President & CEO

On the second question, what we are aiming for is to have a competitive pipeline in the therapy areas that we have selected. And you will always have a mix of in-house product and in-license product. Of the 6 we have presented, 2 are in-house, for example, with Orexin and mezagitamab and 4 are in-license. But make no mistake, we don't do any business development deal which does not create shareholder value. The return on invested capital is always very significant. We put the bar very high on what we buy or what we in-license. Without the research investment that we make and the development expertise that we have in the different therapy area, we'll not be able to assess external compounds anyway.

So obviously, internal is great. Let's make no mistake. But what is important is to have a competitive pipeline which can allow us to grow the company and again, don't think that any business development deal or in-license is not profitable. It's absolutely not true, especially when we do early deals where there is a lot of work still to be done, not only on the development side, but also often on the pharmaceutical side. Any BD deal we do creates shareholder return. There is no doubt in that.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

Yamaguchi-san, please.

Hidemaru Yamaguchi
Citigroup Inc., Research Division

So this is Yamaguchi for Citi. The first question is kind of a similar question which I have on TYK2. I think you used to say around $5 billion to $6 billion, so the range is getting bigger and also a little bit of a lower end. Can you give me the reason, is there any change on an assumption of the TYK2 inhibitor at the moment compared to when you bought the drug a few years ago? So that assumption change. That's the first question.

The second question: Those 6 assets, which we continue to look at today, can you explain, what is more on the blue ocean side or red ocean side compared to the competitive advantage? Don't say all blue, there might be some competition. So can you tell me which is more blue side or competition. It looks like there is only 1 product there. Also, there are some second-in-class products. So can you explain how the product competitive advantage is from your side on this one.

Andrew S. Plump
President of Research & Development

Okay. Great. Okay. I think I understand the second question. So maybe, Ramona, the evolution of our market forecast for zasocitinib from the deal until now. And then, Christophe, do you want to talk about the relative competition.

Christophe Weber
President & CEO

I can.

Ramona Sequeira
President of Global Portfolio Division

So when we originally did the deal, I believe the way we had assessed total value was looking at the initial indications that included UC and potentially also Crohn's disease. We were looking at psoriatic disease plus at least 1 indication in inflammatory bowel disease as well. I would say, since we've done that deal until now, our understanding and actually, presence in this market has changed significantly in the sense that we've learned a lot more. We actually have a lot of people with deep experience in this area at Takeda, but we've also gone out and hired some people that have been able to join us and really help us understand.

Now the focus is more on psoriatic disease and $3 billion to $6 billion. The levers in that have to do with, obviously, the data that we see from our Phase III trial. We're expecting that the data in our Phase III trial is going to be similar to what we've seen in Phase II and what we see in our analytical chemistry. Looking at the pace of growth of advanced therapies which, as I mentioned, has actually helped if you have more orals on the market, looking at the pace of growth of orals within that advanced therapy and growth of the overall market.

So, it's really some of those growth levers that affect the overall forecast and then something that we call preference share. So how many patients will be choosing zaso or physicians will be choosing zaso first line. And we always use range for that. There are a number of levers we use with the forecast that help us kind of identify things that we want to be doing to focus on to commercialize successfully and that gives us a range. And as we get closer to launch, we have more understanding, and we can be more deliberate at letting you know what those levers are. But that's the main evolution, I would say.

Today, we haven't given any revenue expectations yet for UC and Crohn's disease. But obviously, we feel very strongly about the potential for the molecule in those disease areas. This is a market we know really well, and we think there's a big opportunity here for Takeda. So that's something that we're working very hard on now.

Christophe Weber
President & CEO

For your second question, I think, behind, there is a question like, are we too optimistic? Or that's what I'm understanding. We get to know each other after so many years, right? Well, first, I would say we are very conscious about the market condition. And if you look at the 6 assets, there are some, like, oveporexton, for example, or

fazirsiran, I think there is not much competition. The standard of care is very poor. It's all about being successful with the development, the approval and then improving the management of that disease. It's often very underdiagnosed and undertreated. So that's on 1 side. I think it will be up us to really change the standard of care. And if they make it to approval and launch, it will certainly have a very strong market share, because it's all about market shaping and again, improving diagnosis. So that's on 1 side.

And then on the other side, you have a product like zasocitinib. It's very clear. It's a hypercompetitive market. So here, we need to be differentiated. We need to show that we have an efficacy profile for an oral, which can redefine that segment. We'll not be the only one. You mentioned J&J earlier, but we can be a new generation of oral product. The key here will be to double the size of the overall segment. And we don't need to have a huge market share. If you do the math, I think we have been conservative in our range overall. I think you have a different market situation, either market shaping or market share and differentiation in order to gain market share. And with that said, it will be more on the market share side, as there are already treatments. They are not perfect. We think we have a truly differentiated molecule here. And therefore, it can actually really change standard of care as well but there are already treatments available.

Hidemaru Yamaguchi
Citigroup Inc., Research Division

Sorry. You said that narcolepsy and antitrypsin is blue ocean, right? Did you say...

Christophe Weber
President & CEO

Narcolepsy and fazirsiran are really where there is not a lot of treatment, and we could be first and best-in-class. Zaso is really entering the market where the diagnosis is done, but it's all about coming with an improved treatment for example.

Hidemaru Yamaguchi
Citigroup Inc., Research Division

How about rusfertide? Is it on the blue side or red side?

Ramona Sequeira
President of Global Portfolio Division

I would say, with rusfertide, and we see this in a number of diseases, we're really competing with therapeutic phlebotomy and it's really working to eliminate phlebotomy. You can have the patients feel so much better while they're on this medicine. And that's not unusual for us, competing with the standard of care sometimes can be very difficult, actually, because the standard of care has become so entrenched. Physicians are so comfortable with them and so used to them. Sometimes, in a sense, competition helps us because it helps to change the treatment paradigm and it helps to stimulate growth in the class and in the marketplace.

Christophe Weber
President & CEO

And the access challenge is very different, depending on the market situation, actually.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

The next question, Ueda-san, please.

Akinori Ueda
Goldman Sachs Group, Inc., Research Division

I'm Akinori Ueda from Goldman Sachs Tokyo. I have 2 questions regarding your narcolepsy franchise. So, the first question is regarding 861. In the context of the narcolepsy treatments, the SOL (Sleep Onset Latency) in the MWT seems problematic if it's too long or too short. So, TAK-994 indicated a strong efficacy in terms of MWT, but what level do you think is ideal from a clinical perspective? And also, you indicated cognitive function-related data. So, are such data sets important for considering the clinical meaningfulness for the treatment? That is my first question.

And second question is regarding the TAK-360. So, what was the base behind the first indication for narcolepsy type 2 and IH rather than type 1? Do you think 360 will have a better profile in the narcolepsy type 2 rather than type 1 based on the preclinical data or something like that? Or is that mainly to separate 360 from the development of 861 in your portfolio?

Andrew S. Plump
President of Research & Development

That's great. Maybe, Sarah, the first question is about oveporexton, the effects that we're seeing on daytime sleepiness as measured by MWT. Perhaps you can comment on that, the importance of the cognition data that you shared? And secondly, why are we pursuing type 2 narcolepsy and IH with 360 and not type 1 narcolepsy?

Sarah Sheikh
Head of Neuroscience Therapeutic Area Unit and Head of Global Development

Thank you, Ueda-san, for the questions. So MWT is a really artificial construct, and it's just 1 symptom of many. What we see with TAK-861 is normalization of function, and that's maintained over the long term and it's consistent and correlates across multiple different endpoints. You can't really normalize more than normalizing a patient, right? So, if you've reached normal, you can't get more normal in a way. And so that, to me, is the most compelling argument that we have an efficacious dose that also shows a very promising safety and tolerability profile. So that's one.

Now how does cognitive function fit into this? When we think about a treatment for a condition, you think about: where is the unmet need in this condition? And we went through all the symptoms and cognitive symptoms come out loud and clear as distinct from excessive daytime sleepiness. If you can normalize cognitive function, imagine what that'll do for patients. It allows them to work, to be productive at school and to, essentially, get rid of some of the limitations they've had to set themselves in their daily lives at work and at home. I think this is really a key novel thing that we've been able to show with TAK-861 and it's going to help set the bar really high for this new standard of care. Did you want to add anything?

Ramona Sequeira
President of Global Portfolio Division

No, I just wrote down your line, "You can't get more normal than normal," because I think I'm going to use it in my marketing slides.

Sarah Sheikh
Head of Neuroscience Therapeutic Area Unit and Head of Global Development

That's great. Your second question was about why didn't we go into NT1 with our follow-on compound, which is a next-generation chemically distinct, highly potent Orexin 2 receptor agonist? And with TAK-861, oveporexton, we have such a compelling leading program in narcolepsy type 1. Let that horse run to the finish, those results come in 2025, and then let's file that very quickly and get that drug to patients expeditiously.

The follow-on molecule lends itself to exploration in other populations. And we chose to go into Orexin normal populations led by sleep-wake cycle disorders including NT2 and IH. That's the reason, focus on NT1 with TAK-861 and follow-on with additional indications with TAK-360.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

I'd like to take the final question. Just 1 question, please.

Stephen Barker
Jefferies LLC, Research Division

Yes, Steve Barker from Jefferies. I had a question about zaso and your development program in IBD. I don't think you can disclose the doses that are being tested. But maybe you could just help us understand what problem you're trying to solve for. You've got the mouse data. I mean, it looks like, at the high dose, it wasn't quite as good as a biologic. Is that what you're aiming for, something that's good, but doesn't need to be a biologic? Or are you more ambitious? Any comments about your thought process that went into deciding those doses would be really helpful.

Andrew S. Plump
President of Research & Development

I think it would be great to hear from both, you, Chinwe, and you, Ramona, on the rationale for how we designed the Phase IIb study and some sense of what the doses are. And then, Ramona, you can talk a little bit about the product profile and what we're looking to achieve.

Chinwe Ukomadu
Head of GI&I Therapeutic Area Unit

Okay. I think the way I'm going to answer your question is, why do we have faith that this will work in IBD, right? A number of reasons. I'll start with what I describe daily, scientifically very strongly. The problem, as I've seen it, is that there have been all those ahead of us who've had TYK2 assets that haven’t worked in IBD and that has created this feeling that TYK2 is not useful in this area. But my feeling is it's not the science that's the problem here. It seems to be the molecules that are the problem. And we happen to have a molecule that allows us to do something unique. We can give more.

But you might say, why do you need to give more? You've shown me that you have excellent coverage by using 30 milligrams a day. Why do you need to dose more than that? And my response to that would be that we are not treating a disease in the blood. We are treating a disease in a tissue that is inflamed, grossly under perfused and where there is likely a scientific reason to believe that you will be losing drug just because of the nature of tissue. So, you actually would need more drug in order to achieve that efficacy.

If one can do that, take a step back then what you've got. If it's successful, it's an oral once-a-day drug that can be used to treat IBD. And if the data is compelling, we won't know until we get the data, we can begin to imagine just

how hard you can treat this disease with a rather simple, easy-to-administer medicine that can make a change for patients. That's what we're hoping for.

Ramona Sequeira
President of Global Portfolio Division

And I would say, from a commercial perspective, Steve, I mean we obviously know this market really well because of ENTYVIO. And the main goal here is going to be efficacy for this product. We want to come into the UC and CD market with a product that works and that shows that efficacy. As Chinwe mentioned, it is also safe and easy to use. At the same time, we know that with all the new medicines, even in the IBD market today, that efficacy ceiling has really still not been broken. We see more and more physicians starting to turn to various types of combination therapies in different types of patients for different reasons.

And hence we need to see the efficacy in Phase II first. We need a molecule that is going to be efficacious on its own. But because of the safety and efficacy of the molecule, based on the natural mutation that occurs in a healthy population, there is also the potential for combination therapy with this asset and as we look at that data, that's something we're keeping our eye on to evaluate down the line as well.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

Okay. Thank you very much. So that brings the Q&A session to a close. Andy, anything you'd like to say at the end to close out the event?

Andrew S. Plump
President of Research & Development

Well, thank you for the opportunity. I just thank you all for spending 5 hours here. We're very much looking forward to having a chance to interact with you informally. And I'd just like to give a huge thanks to the team for the outstanding work that they did, and I think that really came across today. Thank you all very much.

Christopher David O'Reilly
Global Head of Investor Relations & Global Finance

So with this, we conclude this event. Once again, thank you very much for joining us despite your busy schedule. For those of you who are in this venue, on this same floor outside of the door, we have a reception. So please join us. And today's presenters will be there as well. Thank you.