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Operator Operator

Good morning and good afternoon, and welcome to the Novartis Immunology Portfolio Update Conference Call and Live Webcast. [Operator Instructions]

The conference is being recorded. [Operator Instructions] A recording of the conference call, including the Q&A session, will be available on our website shortly after the call ends. With that, I would like to hand over to Ms. Isabella Zinck, Investor Relations. Please go ahead, madam.

Isabella Zinck Executive

Thank you very much, Sharon, and hello, everyone. Thank you for joining our call, another Novartis call this week. With me in the room are our presenters, Shreeram Aradhye, President of Development and Chief Medical Officer; Victor Bulto, President of our U.S. Operations; and Angelika Jahreis, who's the Global Head for the Immunology Development Unit.

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

Over to you, Shreeram.

Shreeram Aradhye Executive

Thank you, Isabella. Thank you, everyone, for joining our immunology-focused call. I'm delighted to be here with Victor and Angelika. Angelika and I have just come back from a very, very

interesting and exciting American College of Rheumatology meeting in Chicago. Moving to Slide 4.

Immunology has been an area in which Novartis has had a long legacy. And if I think of my own journey at Novartis over the last 25 years, it began with getting involved in Simulect and Neoral. Gilenya, which we actually developed for MS. And it's been great to be back for the last 3.5 years as we became a pure-play medicine company and chose to double down on immunology as one of our key therapeutic areas, leveraging then, the development of Fabhalta across a number of indications. And in this particular moment in time, super excited about the recent approval of Rhapsido, Remibrutinib for chronic spontaneous urticaria in the United States, the positive data with ianalumab in Sjogren's disease, as we will discuss, as well as our ongoing efforts with the bold ambition of using our CAR-T therapy, YTB323, for the treatment of multiple autoimmune conditions on the back of positive Phase I/II data.

Moving to Slide 5. We have chosen to, of course, remain committed to immunology because immunological conditions present and continue to present a large and growing burden for patients and society. More than 10% of the global population suffers from immune-mediated conditions. These conditions are chronic. They have a progressive nature.

They have significant impact on patients and their quality of life with significant both physical and psychological burden. Diagnosis is often complicated. Patients have heterogeneous manifestations, and the patient journey is typically identified as taking a significant number of years before the right diagnosis are made. These diseases represent a significant financial and socioeconomic burden and therefore, offer a perfect opportunity for the type of innovation that we are committed to at Novartis. Moving to Slide 5 -- Slide 6.

We have now chosen as part of our focus to focus on the following core areas. So we look at conditions that are -- we consider immunodermatology like hidradenitis suppurativa, chronic spontaneous urticaria. These are T cell-driven diseases. We are focused on systemic autoimmunity in diseases like Sjogren's, lupus, lupus nephritis, systemic sclerosis, looking at allergic conditions as well as the various arthritides. On the right side, we talk about the multiple platforms that we have expertise in, starting with small molecules, monoclonal antibodies, Bi/Trispecific agents as well as the more advanced platforms like CAR-T therapies, with the primary principle being to use the appropriate modality to deliver what we believe is a meaningful difference from standard of care if some is available or in order to allow us to treat a disease that has previously been difficult to treat.

We aim to break the efficacy ceiling in many of these diseases that we are currently aiming to treat, and in our new ways of working, have complete clarity right from the start as to what is it going to take to have a product that's going to be meaningful for patients such that it can be commercially viable and brings us value both to patients as well as to our shareholders. Moving to Slide 7. We do this both with the significant efforts with internal innovation from our biomedical research teams, but equally by identifying meaningful external opportunities for us to acquire and integrate into our portfolio. A perfect example would be the recent acquisition of the anti-IL-15 and antibody from Calypso, which we now aim to advance in multiple T cell-driven skin diseases, starting with atopic dermatitis. Again, our key focus over the past years has been on speed, making sure that we're developing the most efficient development programs that are asset-centric and aim to generate the data that is most informative for us for making a decision on whether a product is likely to deliver the value that we expected to bring to patients.

On the right there with IFMDUE, Monte Rosa and Kyorin are good examples of where earlier stage deals are another way for us to complement our own internal efforts, but with agents that we believe have the scientific reason to believe to bring again a disruptive difference from what is the rest of the competition in this space.

Moving to Slide 8. For quite some time now at Novartis, we have followed this principle of deeply understanding a particular mechanism of -- and its implications in various disorders. But then once we have understood that mechanism and have an asset in hand and the pipeline in a pill, which in this case is, of course, within quotes because the compounds that we're going to talk about today or the programs we talk about today. Rhapsido is a pill, but the other 2 are not.

But the principle here really is that we are now making as a pure-play company, a considered effort to make sure that we are developing our assets in multiple indications in parallel programs with an attention to being able to maximize the value that we can bring to patients and to the company based on effectively utilizing and delivering on these evaluations. You'll see that play out in the conversations that we're going to have later in the day -- I mean, later in this hour.

I'm going to take a few minutes to just talk about our efforts in CAR-T with YTB323, which is our next-generation CD19 CAR-T program. If we move to Slide 9. Of course, as you all know, the premise here is that in diseases where B cells have an important role to play, effective depletion of the B cell compartment utilizing the CD19 targeting CAR-T therapy has the opportunity to reset autoimmunity. People have spoken about an immune reset, the premise there as is depicted in the graphic in the center, is the idea that with the help of a CAR-T therapy, attain deep depletion of B cells with the subsequent reconstitution of the B cell compartment with naive cells with the loss of the autoreactive B cells resulting in a modification of the disease that allows patients to now be managed without ongoing immunosuppression, or if necessary, with the use of drugs with a response that allows them to have a much better quality of life, but will have significantly reduced amount of additional treatment. We began our own efforts building upon our long experience in CAR-T, if we move to Slide 10, with our Phase I/II study that was conducted by our biomedical research teams in lupus and lupus nephritis.

We were pleased to report that in the 21 patient experience, we were able to demonstrate with up to 12 months of follow-up, a meaningful reduction in the SLEDAI score over time. The little residual disease that you see there with the SLEDAI around 2 is really driven by the fact that any presence of proteinuria from the kidneys results in the score being as such. But we need to keep in mind here, the important concept that the CAR-T therapy takes care of any disease activity but cannot effectively reverse already, damage that has already been accumulated. So if you think about somebody that has renal injury in the context of lupus, while the nephritic component, as we call it, might be taken care of chronic glomerulosclerosis that has occurred over many years and the proteinuria that comes from it is unlikely to return back to normal.

Based on our data and our experience, we made the concerted effort to create a CAR-T program in autoimmunity, covering multiple diseases, as you see on the right side, with now a large number of these studies, which are Phase II pivotal trials designed in close collaboration with the health authorities, having started now across a number of diseases. So lupus, lupus nephritis, systemic sclerosis, inflammatory myositis, ANCA-associated vasculitis, as well as early plans looking at RA and Sjogren's disease. Separately, we are also evaluating our CAR-T programs in neuroscience in relapsing and progressive MS, as well as in generalized myasthenia gravis. We're very excited about the fact that we have more than 50 centers now active, and we are making good progress with moving this forward and we'll be looking carefully at how we are

going to accelerate our plans for being able to assess benefit risk and then find the appropriate patients that can be treated with this meaningful CAR-T intervention. Moving to Slide 11.

As I said at the start, we are now super excited about the approval of Rhapsido. Another example of a pipeline in the pill, Remibrutinib designed and discovered in our biomedical research teams. A BTK inhibitor that is fifth in class, but best-in-class based on its very precise profile. Super excited that it has now been approved in the U.S.

And with that, I'll hand it over to Victor.

Victor Bulto Executive

Well, thank you very much, Shreeram, and good afternoon, good morning, everyone. Rhapsido was indeed approved by the FDA on September 30 as the only targeted BTK inhibitor for chronic spontaneous urticaria with what we would characterize as a broad and clean label. Rhapsido is indicated for the treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1 antihistamine treatment with a clean safety profile, meaning no box warning, no contraindications and no required routine lab monitoring. And as an oral administration, a 25-milligram tablet twice daily with or without food. It's important to note that the initial HCP feedback has been very positive, and that we believe that this label fully supports our intended positioning as an immediate treatment, post antihistamine failure and before biologic treatment.

Now we can move to Slide 13. I wanted to characterize the size of the market first. I mean roughly, the CSU market opportunity is about half the size of the psoriasis moderate to severe market. You can see on the left-hand side chart that if you combine U.S., EU5, China and Japan prevalence, we are talking about 10 million patients who are actively treated for CSU. And about 50% of them are on control on antihistamine.

And only a small proportion of them are treated with a biologic for a variety of reasons. Now as you can see, the positioning for Rhapsido, based on the label that I just described, is really the next oral option right after that antihistamine failure. Now I think it's important as well to note that chronic spontaneous urticaria is a highly symptomatic disease, right? It's a systemic, debilitating mast-cell driven autoimmune disease characterized by red, swollen and itchy hives. And I cannot emphasize enough the role that each plays in treatment decision and actually the urgency that patients have to seek either a new treatment or treatment for the first time.

About 60% of these patients experienced mental health disorders, mainly depression and anxiety, with a quality of life impairment comparable to moderate-to-severe psoriasis and AD, with disrupted sleep being reported as one of the most burdensome impacts and with each another driver of patient dissatisfaction as well. Now given this highly symptomatic profile, achieving symptom control as quickly as possible to improve quality of life, we've understood, is a key treatment goal for chronic spontaneous urticaria. Now if we move to Slide 14, I want to shift to the clinical profile. And you'll see that Rhapsido has demonstrated both long-term safety and efficacy in CSU with a fast onset of action, which based on what I just described on the prior slide, fits very nicely with what we see as the unmet need. You'll see in the REMIX-1 and REMIX-2 trials, we saw meaningful improvement in symptom control across all measures, with results observed as early as we Week 1 post-hoc analysis.

I'd like to note as well that 50% of the patients achieving well-controlled disease at Week 12 and that we saw efficacy regardless of prior biologic exposure, as well as consistent activity across all subtypes of the disease. It's important as well to note that we also saw a favorable safety

profile, which included balanced LFTs. The two quotes that we have on the right here on Slide 14 come to broadly represent the HCP sentiment across both dermatology and allergy, highlighting both the breadth of the indications, but also the fast process of action would really matches what they believe patients are looking for. Now if we move to Slide 15 and honing into this onset of action. To further characterize Rhapsido's onset of action and demonstrating our confidence on Rhapsido's profile, we started the Phase IIIb U.S.

head-to-head trial versus dupilumab, evaluating the speed of symptom control, which is of critical importance to these patients. This is the RECLAIM study. And the objective is to assess the superiority of Rhapsido with versus dupilumab in chronic spontaneous urticaria, inadequately controlled patients by H1 antihistamines with a primary endpoint of urticaria assessment score change from baseline at week 4. This is a study that is currently recruiting with an expected readout in 2027. Now moving on to Slide #16.

For the U.S. launch, we do expect an initial uptake mostly from allergists, followed then by dermatologists. Both specialties, we know really well, and where we have been successful launching products in the past. On the left-hand side, you can see the split of target CSU patients by specialty, starting by the fact that 75% of those patients are currently treated by allergists who, on average, have about 60 CSU patients per HCP. So you can see it's a highly relevant disease that they treat.

And dermatologists, about 5 CSU patients by HCP.

Now we believe this fleet is a reflection of the currently available options. But with the launch of Rhapsido, we expect this shift to evolve the specialty landscape, bringing more CSU care into dermatology over time. Now on the right-hand side, you can see how we are covering the specialty universe with our field force at launch. And you'll see that about 5,000 allergists in the U.S., about 20,000 dermatologists that trip, there's around 415,000 patients who are ready for a change and are not currently controlled with antihistamines. Our current Novartis field force covers about 70% of these HCP universe and about 100% of the high-volume HCPs, which are about 3,500 in allergy and 2,300 in dermatology and cover the majority of these patients.

Now moving on to Slide 17. I wanted to cover the early U.S. launch success patterns, right? The first one is obviously to engage the early prescribers. We are targeting those high-prescribing allergists and dermatologists who treat about 80% of the CSU patients after AH failure.

And in the first weeks of launch, we are actually seeing 80% of the prescription coming as predicted from prior biologic users in CSU and about 75% of those prescriptions coming from allergists. Now we are also prioritizing what we call Rhapsido-ready patients. We are, of course, focusing on those 400,000 CSU patients who are uncontrolled on antihistamines to drive early positive experiences. As I mentioned before, two key determinants of readiness for these patients are intensity of each and also sleep disruptances. Now it is important to note that prelaunch -- as part of our prelaunch efforts, we identified about 20,000 patients who were hand raisers and are now being activated and the new focus or mainly the focus of initial patient activation activities.

Now lastly, an important point is that particularly in this disease with a high degree of symptomatology and the urgency to treat, we see support a picture access as a critical success factor. Therefore, we are providing a simplified experience with robust bridge program or the free drug program with sampling as well, and we aim for rapid coverage expansion with payers. Now for the initial months while we secure our intended broad access, most of the utilization will

be through either bridge or sampling. And as access unfolds in the first half of 2026, we will focus on converting these patients into paid fields, and you will start seeing then the net sales uptake. So all in all, we expect a fast uptake once access is established positioning Rhapsido as the first-line treatment option of choice after antihistamine failure.

Now moving on to Slide 18. For this new launch, we are again leveraging the commercial capabilities that we have honed over the last 3 years with a U.S. commercial organization that has been successfully launching between 3 to 5 new drugs or indications per year. Now on the customer engagement side, we're very proud of a field team that has been increasing its effectiveness year after year and with customer-facing teams, both in dermatology and analogy, that have strong knowledge and expertise across these areas.

From a patient support standpoint, we have developed industry-leading bridge support to accelerate onboarding with a fully owned end-to-end Patient Support Program that usually result in 3 to 5 days to dispense on average once a physician has written either a script or a service request form. And then finally, from a market access perspective, we have secured about 70% access to label within 6 months for recent launches. And once we have secured that access, we have about 30 days average conversion from free to paid drug. And these are some of the compounding capabilities that we've developed through the multiple launches across key therapeutic areas over the last years that we are now bringing in full force for this launch. Now moving on to Slide 19.

We wanted to make an important point. It is that CSU for us represents the first of many potential futures for Rhapsido. This launch provides what we see as the foundation for future indication expansion and a path to multibillion-dollar potential across all indications. Now if I move to the left-hand chart, you will see that in CIndU, we are currently in Phase III with a readout expected for 2026. It's important to note that there's about 400,000 patients in the U.S.

alone that could benefit from this treatment, and that currently, there's no biologic approved. HS is a market that we know well. And based on the Phase II data that we already saw with HS, we see potential for biologic-like efficacy with a rapid onset of action. Now this Phase III with an expected readout in 2028. Now lastly, in immunology, food allergy that as we know, affects 3.4 million patients in G6 countries and where we are seeing early strong Xolair uptake, which we see speaking to the high unmet needs for patients who today besides Xolair, only have food avoidance as a baseline treatment.

Now as a reminder, we're also developing remibrutinib in both multiple sclerosis and myasthenia gravis with readouts expected in 2026 and 2028, respectively. Now important to note, if I move to the right-hand side, that these future potential launches will fully leverage both the existing infrastructure capabilities and knowledge that we already have in-house, with CIndU having a complete overlap with the CSU footprint, HS having a complete overlap with our current Cosentyx HS footprint as well, food allergy building on the CSU allergy footprint. And finally, with multiple sclerosis and myasthenia gravis could build on neuroscience on our neuroscience footprint. So you can expect not only compounding capabilities and infrastructure, but of course, important investment synergies as well. Now moving on to Slide 20.

Now we're going to move from Rhapsido, a pipeline in appeal to another asset with multibillion-dollar potential across several indications, ianalumab. And for that, I will now hand it over to Angelika.

Angelika Jahreis Executive

Thank you, Victor. On Slide 21, we depict Sj gren's, which is a severe, systemic, and heterogeneous prototypical B-cell-mediated autoimmune disease. And Sj gren's is also called the chameleon of rheumatic diseases because it can manifest with so many different organ manifestations as depicted on the right-hand side. Most of the patients have debilitating eye and mouth dryness. And just to highlight a little bit what that means for patients, it is as if you have sand in your eyes, and I think everyone has experienced that how this impacts our quality of life.

And these patients do have that every day of their life, and they also experience that. My apologies. They have debilitating dryness of their eyes and their mouth. With respect to mouth dryness, it is as if their tongue is stuck to their pallet. They have difficulty swallowing, difficulties speaking.

And often these patients then in addition, due to the lack of saliva have dental caries, candidiasis, periodontal disease and loss of teeth. But the more severe patients suffer as well from potentially irreversible organ and system damage, as you can see on the right-hand side. In particular, I want to share one example of a patient that had pulmonary involvement. And that patient was a young woman in her 30s who was very athletic, energetic, a physician and was in the middle of her life after the birth of her son, she had a flare. And with that, she developed constitutional symptoms, fever, about 30 pound weight loss, night sweats and debilitating fatigue as well as interstitial pneumonitis, which meant she could hardly walk up a flight of stairs.

So very -- it was a life-impacting symptoms of a patient that developed Sjogren's disease. And I really want you to keep that in mind. As a physician, I am most worried about the systemic organ manifestations and the increased mortality risk that is associated with patients -- that patients have with systemic manifestations of Sjogren's disease, including the 20x to 40x lifetime risk of lymphoma that means up to 1 in every 10 patients with Sjogren's disease will eventually develop lymphoma. With that, I wanted to also talk a little bit on Slide 22 about the pathway to getting diagnosed. Patients, as I have said before, often have oral symptoms and they go to the dentist for that, but they do not share their additional symptoms with the dentist.

They go to the ophthalmologist for their xerophthalmia and do not share additional symptoms to the neurologist for the polyneuropathy or to their pulmonologist to share their shortness of breath, and it is difficult for the specialty physicians to then understand that this is truly a chronic systemic autoimmune disease. As such, the referral pathway is very long to the rheumatologist, and we know from the latest data from the Sj gren's Foundation that it's typically 4 years before a patient gets diagnosed from the onset of symptoms. Now the diagnosis is not difficult. We can do serologic testing. We can do skin labial biopsies.

And then with that and the clinical symptoms, we can arrive at a diagnosis of Sjogren's disease, but it requires the expertise of the rheumatologists often to come to that diagnosis. I believe that also physicians do not always refer because currently, there is such a lack of treatment options. On Slide 23, we see that Sjogren's actually is a really prevalent disease. It's the second largest disease that rheumatologists treat after rheumatoid arthritis, and it represents truly a significant unmet need because to date, there are no approved treatment options. Estimate the prevalence at 4 million people, but it is very -- it is not very clear if there are not far more patients out there because of the lack of diagnosis and the slow -- the long time to diagnosis.

About 2 million patients are diagnosed with Sjogren's disease. These are the typical patients that I described, female between 30 and 50 years of age at the prime of their years. I want to talk a little bit of current treatment options because as a physician for 20 years, we have seen trial

after trial in Sj gren's disease and none of them met the primary endpoint in later-stage trials. So currently, we rely on off-label therapies and many of these off-label therapies are then associated with side effects. So it is now an eminence-based field, not an evidence-based treatment, and that is certainly something that least physicians with a lot of uncertainty about how to treat patients with Sjogren's disease.

I want to share on Slide 24, our gold standard to assess clinical disease activity in Sjogren's trials, which is the ESSDAI score. It measures disease activity. And on the right-hand side, you see the score. It has been developed by experts, and it measures all of these heterogeneous clinical and laboratory domains to come up to that overall score. While the score goes to up to 123 points, patients typically, even if they have severe disease, have 2 to 3 organ involvement, and it is typically a flaring disease.

I would like to point out that based on the scoring system that has been established and has been validated, patients with less than 5 points have low disease activity, 5 to 13 moderate and greater than 14 high. There have been some attempts to assess the minimal clinically important difference. And it is important, as was noted during the ACR presentation that the minimum clinical important difference that has been defined by the EULAR Sjogren's task force and published in 2016 refers to the different intra-patient difference from baseline to end of treatment. It does not describe a difference between treatment arms. With that, there are other endpoints as well in clinical trial, patient-reported outcomes.

Importantly, for patients who have systemic manifestations, global assessments by the patient and physician will capture the patient burden in a much broader way. So a patient with interstitial lung disease and the shortness of breath will be assessed by these global assessments, but not by specific PROs that capture fatigue, dryness or pain.

And lastly, clinical tests, just like glandular function assessment through stimulated salivary flow can objectivize some of these more -- some of these endpoints. Now let's go to Slide 25 because this is a critically important slide because this is depicting why ESSDAI and disease activity is such an important outcome. We know and based on literature and multiple studies that higher ESSDAI scores are associated with a higher risk of adverse outcome, damage accrual, a higher risk of developing lymphoma, interstitial lung disease, cardiovascular events, leading to higher mortality in patients. So achieving lower ESSDAI scores is critically important for patients with Sj gren's syndrome because they are linked to better quality of life, reduced work -- increased work productivity as well as improved long-term outcomes, including mortality. So critically important that we reduce the disease activity as measured by ESSDAI.

And with that, I'll share with you the very exciting data and really the data that were the buzz of the ACR that Shreeram and I just attended. It is the data of ianalumab in Sjogren's disease. And ianalumab is on Slide 26 is our afucosylated, fully human, monoclonal antibody targeting the BAFF receptor through a novel dual mechanism of action. And importantly, we have NK-mediated antibody-dependent cytotoxicity and killing of B cells. And I'll show you some data that includes killing of B cells in the tissue, not only peripherally, and then once B cells -- once there is a depletion of B cells, and that has been shown in Sj gren's as well as in lupus, they increase BAFF levels, which is the B cell activation and survival factor.

And that binding of BAFF to its BAFF receptor that pathway of B-cell activation and survival is also blocked with ianalumab. So we are targeting both B-cell depletion in the tissue as well as survival of the remaining B cells. And here, I can show you a slide from a mechanistic study that was also presented at the ACR just this week in Chicago, and it depicts on the left-hand side, the

salivary glandular tissue from a patient with Sjogren's. And what I want to highlight is that this is not normal. You see these ectopic lymphoid tissues that are hallmark of the disease that are not seen in healthy tissue.

They are stained in purple and in brown by purple CD20 is B cells and CD3 is T cells. And you see how much infiltration you have and how much destruction of glandular tissue you have in Sjogren's disease. On the right-hand side, after 25 weeks of treatment with ianalumab, you can see that we have an 84% reduction in salivary gland B cell density. So it's a clear sign that we deplete the tissues in the target -- the B cells in the target tissue. So a clear difference to prior B-cell depleted.

With that, on Slide 28, I want to share with you the 2 studies that we conducted. These are 2 adequate and well-controlled Phase III studies. NEPTUNUS-1 and 2, these are global studies conducted on background of standard of care for these patients and both of them 52 weeks in duration. We compared ianalumab 300-milligram monthly subcutaneous dosing versus placebo. And in NEPTUNUS 2, we also included a ianalumab quarterly dosing arm.

The primary endpoint was the SI change from baseline. We also looked at SI responders, so the proportion of patients with a greater than 5-point reduction and at those with low systemic disease activity and then patient and physician global outcome measures as well as importantly, safety and tolerability. We predefined a pooled analysis and a lot of the data I will share with you today are from this pooled analysis. But now let's go to Slide 29, where I can share with you the primary endpoint data of both of these studies. And you see 2 almost parallel graphs here on NEPTUNUS-1 and NEPTUNUS-2.

Importantly, we have an early separation of both graphs. In gray, you see Placebo, in blue ianalumab. And both studies met their primary endpoint change from baseline in SI as a disease activity measure at week 48. Now if you go to Slide 30, you can see the quarterly dosing in yellow, and you see that there was a nice dose response when -- between quarterly and monthly dosing and that only the monthly dosing, which was the dose that achieved full BAFF receptor blockade at trough levels truly led to a statistically significant outcome at week 48. With that, I will also share with you then as a next slide, Slide 31, the pooled data with a rapid and sustained reduction in disease activity compared to placebo.

On Slide 32, from the pooled analysis, you see now the continuous secondary endpoint. And I hope that you also see and agree with me that if you look at this slide, I mean, all of the endpoints clearly favor ianalumab. And that is important outcome. Two of them have nominal statistical significance. These are patient global assessment, which assess how a patient feels and on a global scale, and that is truly important for those patients who have such heterogeneous disease manifestations that we have included in the NEPTUNUS study.

Physician global assessment scores concur with what we have seen for patient global assessments. On the next slide, you see the binary outcomes from the pooled data. And again, consistently, you see that all the outcome measures favor ianalumab over Placebo. Importantly, as I talked about the intra-patient change from baseline to week 48, you see that patients -- more patients achieved a 5-point reduction in SI in disease activity. And I've highlighted to you how important it is to reduce disease activity over time.

And we have nominal significance with respect to a higher proportion of patients on ianalumab achieving low SI activity, low disease activity associated with better outcomes, better mortality outcomes, better morbidity outcomes as well as reduction of long-term damage over time. Now

let me dive a little bit deeper in the patient -- into the patient global assessment. This assessment, as you can see here, very similar to SI, achieved a fast and sustained symptom relief as early as week 8 and up to week 52. Consistent with these data, we have seen nominal significant difference also in the physician's assessment of disease burden, and there is a separation between the placebo and the ianalumab curves along the way. Now let me go to Slide 37 because that is a very intriguing finding from this study in those patients who still have maintained glandular functions with a stimulated salivary flow of greater than 4 and 0.4 mL per minute at baseline.

Those patients we were actually able to increase the stimulated salivary flow. This is quite remarkable, and it goes along with improvements in oral dryness in these patients. And our hypothesis is that those patients who have a stimulated salivary flow of less than 0.4 mL per minute likely already have damage in their gland and destructed glands and not salvageable glandular tissue. But this is incredibly exciting because it suggests that there is some disease modification. Next, I want to go over the safety slides with you here.

And ianalumab showed a favorable safety profile. It was comparable to placebo. We have the data here side by side. And as you can see, ianalumab across the endpoints did not lead to an increase in adverse events and serious adverse events. For B-cell depleters, typically, we first look at infections serious infections and opportunistic infections.

And as you can see on this slide, they were all well balanced. There was no suggestion of any safety finding. The only B-cell malignancy that we observed in this trial was in the placebo arm with the Waldenstrom macroglobulinemia. With that, let me briefly summarize the results. These results were really seen with lots of excitement in all the many discussions I had at ACR with the rheumatologists because these are, in my view, really watershed data because they are the first ever successful global Phase III studies in Sj gren's disease, a disease that we have tried to find a new treatment for now for decades.

They showed a statistically significant SI improvement consistently across both NEPTUNUS trials. rapid and sustained disease reduction of disease activity. We have consistent improvement across secondary endpoints. In particular, we achieved low ESSDAI disease activity, which is such an important outcome measure. We improved and reduced the overall patient global assessment of disease activity.

So patients also felt that the treatment really improved their quality of life. Physicians concurred with that, and we have numerical improvements in other patient-reported outcomes. I do think the data on the salivary function and oral dryness are very encouraging. They are thinking -- making us think about next studies to profile that more. And importantly, we have seen with respect to safety that the adverse event profile was comparable in general to placebo.

Now with these very exciting data on Slide 40, you see our plans. We already have FDA Fast Track designation since 2016, and now we are going to submit across all regional regions. We will be building on the NEPTUNUS studies. We have already extended our extension studies to now follow these patients for 6 years with respect to efficacy and safety. We are exploring for future studies, as I have indicated in different and diverse children's populations.

We've already had a lot of excitement with the physician community who also wants to conduct studies with us, and we will share the data more broadly in publications that are planned to start. Now with that, I hand it back to you, Victor.

Victor Bulto Executive

Thank you very much, Angelika. Now I'll dive into the U.S. market preparation perspective, right? The first thing we're doing is launching a disease state education campaign to increase recognition of Sjogren's disease as a serious systemic and autoimmune disease that goes well beyond the apparent symptoms of mouth and eye dryness, right? The context that I think is important for us to note as Angelika noted, there's a lack of approved therapies and there's low familiarity with clinical endpoints.

So we do see an opportunity to expand the understanding of the systemic nature and the burden of Sjogren's disease to provide a framework for physicians to identify moderate to severe patients and, of course, engage and empower Sjogren's disease patients.

Now if we move to Slide #43, I also wanted to provide some color on the expected initial adoption from rheumatologists, right? Currently, we have segmented rheumatologists, which, by the way, we know really well through our work with Cosentyx and Ilaris between early adopters and late adopters. You will see that we do expect that the early biologic users, those who are proactive today, the use of label biologics early to prevent disease progression will be amongst the first adopters where we are concentrating some of the initial efforts. We will be concentrating some of the initial efforts at launch. They represent about 15% of the HCPs, and they treat about 1/3 of Sjogren's patients.

Then we have the later biologic users who are more -- a little bit more reactive. They do rely on frameworks to identify what they call biologic-ready patients. That's another 20% of the HCPs and about another 1/3 of the Sjogren's disease patients. So I think it's important to note that about 70% of the patients then are treated by rheumatologists who have a clear understanding of the need to treat these patients with advanced therapies. Now about 65% of the HCPs will be characterized as more symptom-focused HCPs, right?

They focus more on the symptom relief and typically, as of today and up until now, have not used off-label biologics.

Now of course, most of our disease state education, patient activation and ianalumab approval is expected to shift more of the symptom-focused HCPs into biologic users over time. I think it's important to note from a launch perspective that more than 90% of overlap exists between these physicians and the Cosentyx and Ilaris field force and the rheumatologists treating Sjogren's disease with 100% coverage of the early adopters by our current teams. Now moving to Slide 44. I also wanted to note from a patient segmentation perspective that we are looking at the overall landscape, Sjogren's has an overall prevalence of about 660,000 patients in the U.S. About half of them are diagnosed today and about 175,000 are under active rheumatologist care, right?

And about 100,000 of those patients have current organ system involvement as described by Angelika, right, which are the patients that we believe will be initially most likely to receive this treatment. So at launch, we will be combining the targeting from an HCP perspective on those who have already been treating patients with biologics and targeting this 30% or 40% pool of diagnosed Sjogren's patients who have organ system involvement because we see higher urgency to treat a those. Of course, over time, we will work to continue to expand both the active treatment and also the diagnosis rate as part of our responsibility in this space.

Now moving on to Slide 45. I wanted to follow a little bit of the same exercise I followed with Rhapsido, showing that these positive Phase III studies in Sjogren's, which is a highly heterogeneous disease, actually do increase our confidence in other B-cell-driven diseases,

right? So in the same way that with CSU, we saw it as a foundational indication for Rhapsido. We see Sjogren's as the first foundational indication for ianalumab with a number of potential indications following. You will see that for SLE and lupus nephritis that affect about 0.5 million patients in the G7 countries, we expect readouts around 2027, same for systemic sclerosis.

Now on the hematology side, where we also have a significant expertise and presence, as you all know, we had positive readout in the Phase III in second-line ITP, and we do expect readouts in 2026 as well for first-line ITP and second-line wAIHA. Now I want to highlight as well that these future potential launches will also leverage existing infrastructure capabilities and expertise, right? The SLE launch will build on Cosentyx rheumatology experience. Lupus nephritis will build on both our rheumatology and our established nephrology expertise. Systemic sclerosis will have a high overlap with rheumatology.

And of course, ITP and wAIHA builds on our Promacta hematology footprint as well.

So in closing, and moving to Slide #46, I would like to highlight that we have a broad and deep immunology pipeline with multiple late-stage assets targeting areas of high unmet need. At Rhapsido, we are very excited about Rhapsido being poised for a strong CSU launch as the first oral option post-antihistamine failure and before biologic with multiple LCM readouts starting next year.

I also wanted to highlight that ianalumab has demonstrated a meaningful clinical benefit in Sjogren's disease with consistent -- which was consistent across studies over time and across patient and physician-reported outcomes that this positive Sjogren's data derisks in our mind, ianalumab's life cycle management across a number of B-cell diseases, supporting the multi-blockbuster potential we see for this asset and that we have, over time, compounded commercial capabilities that will drive launch excellence and maximize pipeline value across our portfolio. And with that, I would like to open it up for questions.

Operator Operator

[Operator Instructions]

And your first question today comes from the line of Simon Baker, Rothschild and Co Redburn.

Simon Baker Analyst

On ianalumab, typically, in Sjogren's studies, you see a plateauing of the placebo response at 48 weeks, whereas you saw a reduction in the placebo response at 48 weeks. So I just wonder if you could give us any thoughts on that, particularly in NEPTUNUS-1. But also -- and forgive me if this is a naive question, but we see this very strong placebo response across all Sjogren's studies and the level of response you saw is not wildly different from that which we've seen elsewhere. So I wonder if you could just give us some thoughts on why the placebo response is so high in these studies.

Shreeram Aradhye Executive

Thanks, Simon. I'll take a start and then hand it over to Angelika. I think when it comes to placebo [indiscernible] , one thing to keep in mind is that our trials were designed to allow patients not randomized to ianalumab to continue getting treatments that they were otherwise on. So there were a significant proportion of patients that were on other therapies that they were being given by their physicians. I think that typically, the placebo response in terms of being part of a trial

and being then being managed in a manner that actually, in some sense, alters the patient's perception of their symptoms and how they feel is one contributor.

These are large studies in a heterogeneous disease run across multiple centers across many countries. And therefore, the observation of how that response evolves over time and the change towards the end that others have called out as well is simply, in my mind, a reflection of sort of the conduct of a large -- 2 large trials across multiple geographies in what is a difficult heterogeneous disease. Angelika, do you want to add?

Angelika Jahreis Executive

Yes, Shreeram fully concur. And I wanted to call out that I think it's quite stable on NEPTUNUS-2, the placebo arm. On NEPTUNUS-1, we see a slight increase in placebo, but I would not make too much out of this. This is probably variability in the trial or maybe the realization from patients that placebo -- from physicians that placebo does not work that well, right? But I do think as we have longer-term studies ongoing, we will see how patients fare once we switch them over.

Shreeram Aradhye Executive

Yes. I mean I think, Simon, I also want to add and when we've spoken previously, we've discussed the fact that the team actually did a lot of work over the years in the conduct of the trial to actually assure the quality of trial conduct. And I recall telling all of you that I was super proud of the team as having made all the efforts we could to ensure that in this complex difficult disease, we had multiple outcomes being assessed, we paid attention to the quality of the data being collected, how investigators were being trained. And I think I do believe that, that's actually at the heart in addition to the tremendous -- we were able to actually discern, if you will, the benefits of the dual mechanism of action of ianalumab as a result of a well-conducted trial, resulting in this unprecedented 2 replicate positive Phase III studies in Sj gren's disease. Next question.

Operator Operator

Your next question comes from the line of Thibault Boutherin from Morgan Stanley.

Thibault Boutherin Analyst

My question is actually on [indiscernible] food allergy. Just if you could help us understand reimbursement in that market and how to think about it. I mean, as you mentioned, we saw a very strong uptake from Xolair in the U.S., 85,000 patients treated. So theoretical number of patients is very large, but presumably, we need to break down in terms of population of patients, in terms of disease severity. So how to think about how to break down the population, who can have access to treatment and reimbursement to basically be able to seize the opportunity?

Shreeram Aradhye Executive

Thank you, Thibault. I'll give this to Victor.

Victor Bulto Executive

Yes. Thank you very much, Thibault, for the question. I think it's important to note, as you say, that -- on food allergy, we see both a very substantial unmet need in terms of size, right, particularly in the U.S. market. And thank you for noting a very strong uptake on the Xolair side.

I think it's early days to discuss about access projections, particularly when we are these many years out. But right now, what we are seeing on the Xolair front is that when patients are in need

and are prescribed by the allergists, they tend to get their medicine, right? So I think that's a strong indicator that we can start thinking about how to further shape this development program, and we are starting to think about how a launch could look like. But all in all, as you point out, a very exciting opportunity potentially for this asset as well in food allergy.

Shreeram Aradhye Executive

Next question?

Operator Operator

Your next question comes from the line of Richard Vosser from JPMorgan.

Richard Vosser Analyst

I was just wondering whether you measured clinical ESSDAI at all in the study. Some other trials are measuring that. And I wondered if the data was stronger on clinical ESSDAI. And I also wanted to ask on the ESSPRI benefit that was a trend, but not statistically significant. My understanding, which could be wrong is that that's more of an endpoint for a European approval.

So I'm just wondering how the data looks from that point of view, given that endpoint wasn't statistically significant, how the Europeans will look at that.

Shreeram Aradhye Executive

Let me give that to Angelika. Angelika?

Angelika Jahreis Executive

Yes. So yes, we are looking at the data to also assess the clin ESSDAI. We certainly have an impact on the biologic domain, but we also have seen when we look at our domains that we have an improvement across most domains, biologic or clinical. When it comes to the ESSPRI, the ESSPRI is measuring dryness, fatigue and pain.

Yes, it is the primary -- let me say, the primary endpoint for the European submission is the mean change in ESSDAI, which we have met across both clinical trials. So we are very confident also when we submit our data to the European health authorities. This endpoint was discussed with both FDA as well as the European health authorities. ESSPRI is a patient-reported outcome that is focused more on glandular disease, whereas we will be focusing the significant data with respect to the patient global assessment because we believe this describes more the patient symptoms that occur in those patients with systemic manifestations in this very heterogeneous disease.

Shreeram Aradhye Executive

Thank you Angelika. Next question?

Operator Operator

Your next question comes from the line of Benjamin Jackson from Jefferies.

Benjamin Jackson Analyst

Look, one for Shreeram, if I may. On YTB323 at the start of the presentation, you described the MS cohorts as relapsing and progressive for those early trials, whereas for Rhapsido seems to follow more of the traditional MS wording that we've been using for some time. So is this

perhaps a shift in the way that patients are being either defined or recruited for the earlier trials that are now coming through, perhaps more reflecting a peer approach to that? And is this Novartis driven or regulator driven? And as a result, what does this mean for remibrutinib and remodel when we get that readout next year?

Could this ultimately be a label definition, which is independent of relapse activity? Any color or thoughts around that definition of recruitment would be great.

Shreeram Aradhye Executive

Yes. I mean I think, Benjamin, I wouldn't read too much into the implications of how I described you the CART programs for what -- how the remibrutinib programs have been designed. Those have been designed for a while, and they reflect the relapsing MS population as we -- that we have enrolled. The thinking behind the exploration of CAR-T in MS was around the principle that eventually we expect CAR-T to be evaluated for patients who are considered refractory in some sense, given the burden of the treatment, its nature. And to that end, picking people with relapsing MS who have had severe activity and continued persistent inflammation despite the use of multiple agents.

And then when it came to progressive MS, again, a bold exploration of whether a CAR-T offers the opportunity to impact what we now call progression, be it secondary or primary, but thinking of more a combined term for the lack of a better word, that aims to address progression independent of inflammatory activity is the thinking. Early days, again, those are trials where the initial [indiscernible] patients are now being done. There is a lot of interest, and we'll keep you posted on how things evolve. Next question?

Operator Operator

Your next question comes from the line of Sachin Jain from Bank of America.

Sachin Jain Analyst

Just first on data, just wondering if you could talk to the dose response you've seen and whether you considered investigating more frequent dosing or higher doses and whether the PK/PD that you saw in Phase II is actually replicated in Phase III. And then as we think about the midterm opportunity in Sjogren's, maybe just provide your perspectives on the FcRn potential competition?

Shreeram Aradhye Executive

Angelika, do you want to talk about the dose response and...

Angelika Jahreis Executive

Yes. I think we have -- we are looking at our PK/PD as we speak. We've just received these data and presented them now at ACR. But as I've alluded to during the presentation, we know that the 3 monthly dosing is a trough not inhibiting BAFF receptor signaling. So we see a clear dose response, and we think the most -- the monthly dosing is the appropriate dose to carry forward to the health authorities.

Shreeram Aradhye Executive

And then your commentary on the potential competition from FcRn.

Angelika Jahreis Executive

It is -- we have seen Phase II data from FcRn. And we are waiting for their Phase III data. I think it will be important to see not only efficacy, but also the safety as these molecules deplete immunoglobulins, and we need to see that these patients do have an adequate response versus an adequate vaccination response maintained. But I think the data will show. We are now very excited about having the first pivotal global Phase III studies in our hands that have read out positive and are really focused on bringing this to patients ianalumab to patients as quickly as possible so that they can benefit from ianalumab.

Shreeram Aradhye Executive

I mean I think, Sachin, Angelika and I both just spent time in Chicago, and I must have met, I don't know, 20 to 25 at least different rheumatologists as well as representatives from the patient community. And what was interesting to see and quite exciting was that, one, it's the fact that nothing has been available and approved as well as the nature of the disease itself has sort of created this deep pent-up unmet need demand where people have suffered with what they think is being treated with eye drops and maybe drinking a little bit of water and not quite having the right answers for what patients were suffering with.

And I met a community rheumatologist with a large practice as well as specialized centers. And it was reassuring to see that having delivered 2 positive trials that essentially control disease -- demonstrate control of disease activity. And it's the disease activity that is at the heart of what patients make feel what they do over time results in additional complications, as Angelika pointed out. I almost got the feeling that once we make this treatment available, pending regulatory approvals and discussions, the interest in people wanting to try this treatment for the lack of a better word, seemed pretty high. Next question?

Operator Operator

Your next question comes from the line of Peter Verdult from BNP Paribas.

Peter Verdult Analyst

Peter Verdult here, BNP Paribas. If you forgive me maybe one commercial and one clinical. Shreeram, you said you spoke to 25 docs we spoke to 3 overnight who have been at ACR. The message was pretty uniform. They're going to put 50% of their patients on this -- on ianalumab, assuming approval and access is not an issue.

It's a question that I know you're not going to answer, but I've got to ask it, because I think the willingness to use is clearly there. How should we think about pricing? Is this a classic immunology drug? Or -- we know that there's nothing out there of the first systemic therapy approved FcRns that are being developed, their price point is $200,000 net. So I know you're not going to give me an answer, but just qualitatively, should we be thinking about this as a standard immunology priced asset?

And then if I may, on the clinical side, Angelika or Shreeram as well. You talked about following the NEPTUNUS patients up to 6 years. When you think about other plans, and I know it's only 24 hours since you've presented, but you have had the data in-house for a bit longer. Should we anticipate that you'll be doing trials where you will be enrolling patients with that baseline salivary function above 0.4 to see how that goes?

Shreeram Aradhye Executive

Well, maybe I'll take the second part of your question first, Peter. Look, our standard practice now, of course, is having completed the Phase III studies, there's already been a lot of conversations going on about what is the additional evidence that's going to contribute to accelerated adoption into clinical practice for the appropriate patients. So our process of what we call integrated evidence planning to provide additional data has been going on for some time. Angelika, I don't know if you want to add any specifics around it, but there will certainly be additional plans for additional data generation. She doesn't have much to add.

But I think -- and on this meeting, since I also have Victor here, Victor, let me give it to you to discuss whether it's too early to talk about price.

Victor Bulto Executive

Well, it is certainly too early to talk about pricing. But what I wanted to reinforce is what Shreeram and Angelika have brought up in our discussions with rheumatologists that as I mentioned, we know really well through our work on Cosentyx and Ilaris. We do see that very consistent value perception on both the unmet need, but also on the potential tool that they can gain with ianalumab, and we will certainly bring that up to payers as we discuss. As you know, one of the main drivers of adoption and then access will be actually that precise experience that physicians and patients gain as they utilize the drug, right?

And that's exactly what we expect. And of course, that will be our job at launch is to foster that utilization and the patients I described and the physicians that I described will be a priority. And based on, first, the safety profile, but also the overall efficacy profile, we do expect that to happen and to happen fast at launch. I want to stop just for a second on the safety profile because I think it's of extreme importance here on that trial, right? So physicians, the initial reports were very reassured, as Angelika mentioned, by that safety.

And we believe that's a prerequisite for trial, right, particularly in a disease that does not have anything else approved.

So I'm very excited to get to work and continue to prepare the market and this potential launch as well once approved.

Operator Operator

Your next question comes from the line of Graham Parry from Citi.

Graham Parry Analyst

Just I think a skeptic in the market would say that the biologic therapies that are used out there are effective, but they just didn't have decent trials run for them and that ianalumab is only as effective but run a better study. And of course, you haven't been able to compare versus biologic therapy because they're not approved and so you've got a placebo-controlled study. So how would you -- how do you plan to sort of get around that perception if it crops up in your marketing?

Shreeram Aradhye Executive

Graham, well, I think that just running a better study seems like a relatively odd way to represent 2 pivotal Phase III studies designed carefully, run across the world and delivering to positive results that actually allow for a drug to be taken to the regulators and potentially get it approved with a label. So I think to the skeptics that I say that, I'm just going to say that, well, the drug -- we

have studied the drug in the way that we -- in a meaningful way. And the consistency across 2 trials, the -- as you said, the overall data sets, especially the way patients feel their disease and the physicians see it. So we -- I see that as a really, really strong position to be in.

I'm going to hand it to Angelika because having been the one that actually the units that run the 2 trials, Angelika, how would you answer the skeptics?

Angelika Jahreis Executive

Yes. I would also add that some of these trials, I think, were run quite well as well and did just not show any evidence of effectiveness. So I would not just negate I know I think right now, physicians are using some of the therapies like hydroxychloroquine or rituximab. But I do think it is out of the spear that they don't have other treatment options. We do know that rituximab does not affect tissue B cells in the tissue, which is where the insult happens to the tissue.

So I would not concur with that.

And secondly, if you look at our studies and our trial size, these are not hugely overpowered studies, but these are reasonably sized studies that have shown a very good effect size and consistent across endpoints across all patient and physician-reported endpoints as well as over time, fast onset of action. If you look at the lines, they are really beautiful. So I would respectfully disagree with you, Graham.

Shreeram Aradhye Executive

With the skeptics.Next question?

Operator Operator

[Operator Instructions]

And your next question comes from the line of James Quigley from Goldman Sachs.

James Quigley Analyst

How are you thinking about sort of the label? And what are you going to look for in terms of the label indication? Is there a trend in any of the domains that could lead to leaning more towards one domain or the others or sort of narrow the label from a domain perspective? And how confident are you that this salivary flow or fatigue data can get on the label given the lack of statistical significance there? Or are those benefits covered in the physician global assessment?

And also a very quick sort of second one. Was there any reduction in steroid use or [indiscernible] use in the trial that you noted with ianalumab?

Shreeram Aradhye Executive

James, I'll give the steroid question to Angelika in a second. But I think on the label, I'm just going to say that, look, it's a little bit too early to start commenting on the label. We now have the data. Our core incoming position is that we have a rich data set in 2 well-done trials with consistent effects across multiple endpoints. We believe that we want to make this drug available to all the patients that can benefit from it.

And to that end, we'll be making the case for a label that allows us to accomplish that. But it will be too early to start commenting on precise elements of the label. Angelika on the steroid use?

Angelika Jahreis Executive

Yes, we are looking at the steroid use as we speak. So I unfortunately can't answer that question yet.

Shreeram Aradhye Executive

Next question?

Operator Operator

We will now take our final question for today. And your final question is a follow-up from Thibault Boutherin from Morgan Stanley.

Thibault Boutherin Analyst

Just a couple of follow-up on Rhapsido pipeline. So next year, the CIndU trial, Phase III trial has different primary endpoints by type of induced urticaria. So just if the trial doesn't hit primarily for all the subtypes, but some of them, can you still get approval by subtype? Or do you need to hit everything to get CIndU indication? And just you previously had interesting Phase II data for ESSPRI Sjogren.

Did not to move into Phase III now that you have all the data and more experience from a clinical perspective, could you all consider running a Phase III for remibrutinib in Sjogren?

Shreeram Aradhye Executive

Angelika?

Angelika Jahreis Executive

Yes. So maybe I can talk about CSU and pediatric development. We have an adolescent study ongoing, and we are certainly looking to also go into pediatric patients, but we will do that a little bit sequentially. But we have an adolescent study that is enrolling very well. Now with respect to CIndU, we are studying the CIndU, obviously, across 3 different manifestations of inducible urticaria forms.

I think it is too early to speculate. We are positive that the 3 forms will read out positive. But if not, we will have the adequate discussions with the health authorities to define what is the path forward. As we know to date, there are no treatments approved for CIndU. Xolair is not approved for CIndU and no other treatment.

So there is a real big need for those patients with inducible urticaria to have a first targeted therapy.

Shreeram Aradhye Executive