Pharming Group N.V. 4Q/FY 2023 Results Call

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Operator: Good day and thank you for standing by. Welcome to the Pharming Group N.V. Full-Year 2023 Results Conference Call and Webcast. At this time, all participants are in a listen-only mode. After the speaker's presentation, there'll be a question-and-answer session. As a reminder, the company will only take questions from dial-in participants. To ask a question during the session, you will need to press star one-one on your telephone. You will then hear an automated message advising your hand is raised. To withdraw your question, please press star one and one again. Please be advised that today's conference is being recorded.

I would now like to hand the conference over to your first speaker today, Sijmen de Vries, CEO of Pharming Group. Please go ahead, sir.

Sijmen de Vries, MD – Chief Executive Officer:
Thank you very much, Operator.
Welcome, ladies and gentlemen. Good morning, good afternoon, wherever you are, to our conference.

Please, next slide. And we're very happy to take you through the full-year results. And you can give me the next slide, because before I do that, I would like to point to the forward-looking statements slide that you now see, where we will be making forward-looking statements that are based upon our current beliefs and expectations, which may, of course, differ from what we expect.

So, having said that, I would like to now go to the next slide where you can see my face, and then move on immediately to the next slide.

We are indeed looking back to 2023 as a very successful year, whereby delivering strong growth, we built the foundation for that global rare disease company that we are setting out to build. And that, we can build that. We can all finance that by, of course, the cash flows that come from the marketing of RUCONEST®, which delivers considerable positive cash flows that can help us to build that foundation further.

We're very pleased that we delivered more than $227 million of revenue, which is a 10% growth, versus last year, which exceeded significantly the expected single-digit growth for RUCONEST®. And we saw that because we had some very good parameters, forward-looking parameters that were

really working. The number of patients increased and numbers of prescribers increased. And basically, it means that patients continue to be reliant on RUCONEST® despite increased therapy options that are available in the market, which, of course, are good for patients. But you can see that RUCONEST® continues to be that reliable cornerstone. And my colleague, Stephen Toor, will elaborate a little bit further on that.

Now, the next exciting bit, of course, that we could therefore, and start to execute on, was the launch in the United States for Joenja® (leniolisib), which is a product we in-licensed from Novartis in 2019. And we were very proud to actually, almost immediately after FDA approval, in April bring that product to the market and immediately get commercial coverage for that product and bring in more than $18 million of sales during those first nine months in the market.

In addition to that, Joenja® has been filed with a number of regulatory authorities in Europe, Canada, Australia, Israel, and as of two days ago, in the United Kingdom. And we are awaiting, of course, and we're working with all these regulatory authorities, and we are awaiting the next steps and necessary approvals in the not-too-distant future.

Then, of course, very important, the label of Joenja® is for 12 years and older, we have a number of pediatric trials that are ongoing, which are, of course, important. And last but not least, we also have completed enrollment for a small Japanese clinical trial. We are preparing for submission to the Japanese authorities by the end of this year. And my colleague Anurag Relan, our Chief Medical Officer, will talk more about that. And as it is an ultra-rare disease and a very new disease that was only described ten years ago, we have a very strong focus on patient finding. And again, Dr. Anurag Relan, will talk about that later.

And then I move to the right-hand side, which of course is even more exciting going forward towards the future because we strongly believe that leniolisib has vast additional potential for further development. And hence, we have basically set out to start a Phase II study in the second quarter of this year for the subsequent indication, which is significantly larger than APDS in patient numbers, PID with immune dysregulation. And again, Anurag Relan will talk about that in more detail a little bit later in this presentation.

And last but not least, we are very, very active. We continue to be very active to in-license or acquire clinical stage programs in rare diseases, preferably in immunology, hematology, respiratory and gastroenterology, to further leverage our commercialization structure that we have been building up and are building up as we speak.

And then on the bottom of the slide, you see that for the first time in our history, we gave total revenue guidance, and that will be between $280 million and $295 million, which is driven, of course, by Joenja®, but strongly supported by RUCONEST® during 2024.

And then I would like to go to the next slide, please, where you see then a depiction of the pipeline that we have. RUCONEST® obviously in the market, Joenja® in the US market. And you see then subsequently under regulatory review by many of the regulatory authorities and the pediatric program that's ongoing and the Japan program that's ongoing. And then the very exciting fact that

we are going to do the Phase II study for leniolisib for the subsequent indication; and last but not least, our very early-stage program, the HAE gene therapy that is in early clinical – preclinical stage. With that said, I would like to turn over to my colleague Stephen Toor, our Chief Commercial Officer, to take you through the commercial update. Thank you.

Stephen Toor – Chief Commercial Officer:
Thank you, Sijmen. Good morning. Good afternoon, everybody.

This is a slide I think you'll be largely familiar with. And I think the key thing to take away from this is that the key features of RUCONEST®, so namely the only recombinant C1 treating the root cause of the disease and 97% efficacy in one dose, is what continues to fuel the RUCONEST® growth and our success over the last nine years. These product features align to the excellent workout commercial medical and patient services teams deliver for customers and patients and their carers, is also why RUCONEST® remains a highly relevant part of the conversation in the US HAE community and globally.

That's remained the case despite three prophylactic launches over the last few years, leading to generally better-controlled patients and the genericization of icatibant. And I fully expect it to remain the case even in the face of acute competition in the future. And that's because HAE patients using RUCONEST® tend to have generally a more severe course of disease. And in that instance, the need for virtually guaranteed and fast efficacy that stops the attack in its tracks is critical, and it's typically the patient's only real objective. In most cases, that overriding need for efficacy won't be replaced by a convenience play.

So, looking at 2023, RUCONEST® performance was characterized by the continued growth in both prescribers and new patient enrolments. And it was also successful despite that market-wide event we saw in Q1 last year related to government reimbursed patients. Now, we have seen some disruption from that this year, but it's been muted by the almost halving of those patients' out-of-pocket costs in the US. And moving into '24, we've also seen that the strength of our leading indicators has continued into this year, namely new prescribers and continued support from existing prescribers and new patient enrolments. So despite some continued disruption in that government segment, we're still on track for where we expect to be in Q1.
Next slide, please.

This is, again, something you're very familiar with. Pharming has been in this space and committed to this community for over 20 years now. And it's really that commitment combined with the product itself, RUCONEST®, our people and the excellence they deliver, which is why you see on the right-hand side there, our prescriber base continues to grow and, as a result, our patient base continues to grow. And it's why, as I said, we remain enthused and confident in the continued growth of RUCONEST®, both this year and in the years ahead. Next slide, please.

Switching gears to Joenja®. We had, as you know, a strong first year, and as we close out that first year, at the end of this month, I'd just like to reinforce what a great launch the team here at Pharming delivered for us.

The launch preparation, as you've heard me say in the past, was first-class. And I think I wouldn't underplay there, what Sijmen said earlier, which is that within one week of approval, we had commercially covered patients with product in hand, which is outstanding.

The patient base steadily grew throughout the year, and we exited, as you know, at the end of the year with 81 patients on paid Joenja® therapy. In that time, importantly, we've seen very few discontinuations, and we have adherence rates close to 90%. So as we convert that caseload that we'd already identified at launch, our focus, unsurprisingly, moving forward, remains finding those new patients for this rare disease and then, given that APDS is an autosomal dominant condition, testing their families to uncover additional patients so that they too can benefit from the management of treatment with Joenja®, which, as you know, is the only indicated product with which you can treat APDS.

And then the other important factor to talk about here, in addition to the US, is of course alongside that launch, we continue to build out our ex-US capabilities in preparation for launches in the European Union, the United Kingdom, Japan, Australia and other countries in the Asia-Pacific region and also in the Middle East and here in North America and Canada.

With that, I'd like to pass over now to Dr. Relan, who's our Chief Medical Officer, for a medical update.

Anurag Relan, MD – Chief Medical Officer:
Thanks, Steve.
What I'm going to do today is talk a little bit about APDS and then provide an update on Joenja®, as well as where we see some additional possibilities for applying leniolisib in this second indication.

On this slide, you can see a little bit of information about APDS, which is a rare primary immune deficiency that, as Sijmen said, was only characterized in 2013. We estimate the prevalence of APDS at approximately 1.5 patients per million. And to that end, we have already identified more than 840 patients across the world in key global markets.

As with many rare diseases, the signs and symptoms of APDS can vary across patients, even within family members who have the same variant. This, unfortunately, leads to many potential delays in diagnosis and care and a lot of frustration amongst clinicians and patients as they try to treat these patients. Fortunately, a simple genetic test can provide a definitive diagnosis of APDS, and until the availability of Joenja® in the United States recently, treatments for APDS have really only been limited to addressing the symptoms of the disease. Again, these symptoms manifest early in childhood because these patients have this genetic condition that they're born with. But these treatments do not address the root cause of APDS, and without a specific indicated treatment, this was quite complicated for these patients to manage their condition and physicians to be able to treat them effectively. Next slide.

And you can see now with the launch of Joenja®, APDS patients have a choice now, specifically patients who are adult and pediatric patients, ages twelve years of age and older. And we've been able to demonstrate this by a randomized, placebo-controlled study where Joenja® met both primary and secondary endpoints with significant efficacy results. We also saw positive benefits in other key secondary parameters as well as exploratory measures.

On the safety side, we saw no drug-related serious adverse events or study withdrawals in the Joenja® studies. And we've also collected quite a bit of data now on long-term use of Joenja® from the open-label extension studies. And we provided some of this data, including reductions and discontinuations in immunoglobulin replacement therapy, or IVIG. We've also shown reductions in infection rates over time, and we've also seen that the safety is consistent with what we see in the short term.

When these patients are on therapy in the open-label extension study for several years, in many cases, we see the same types of safety profile that we saw in the short term in the randomized-control study.

We continue to collect this data, including showing sustained benefits in the size of their lymph nodes, the size of their spleen, some of their immune parameters, including their levels of IgM, and we presented some of this data at some medical conferences throughout 2023. And we expect to continue to present more data from these long-term studies in the coming year.

On the next slide, we can see what we're looking at beyond the FDA approval. So, as we mentioned in the press release, we are working closely with CHMP to address remaining outstanding issues. And we are now awaiting the CHMP's opinion on the leniolisib MAA. We, in fact, expect that leniolisib will be on the CHMP meeting agenda next week, but we are awaiting CHMP confirmation for this. As Sijmen mentioned also, the Japan clinical study, the enrolment is completed there now, and we are finishing the remaining studies to be able to file in Japan, hopefully toward the end of this year, beginning of next year.

Just earlier this week, we filed our application for the MAA in the UK with the MHRA, and we also have several applications already under review in Canada, Australia and Israel, and we expect regulatory action on these throughout the course of 2024.

On the pediatric side, we have two studies that are ongoing. The first is in children ages 4 to 11, and this study is expected to complete enrolment very soon. And then the other study, which we just started with the first patient dosed in November 2023, is continuing as planned.

On top of that, we mentioned that we have a number of patients in expanded access programs across the world, and as well as some new patients that are getting access to therapy through named patient programs. And I'll talk a little bit more in the next couple of slides about some work that we're doing for the second indication, and that progress is on target with the initiation of the development for this second indication. Next slide.

Let's talk a little bit about the patient finding because I think this is critical for any rare disease, but also for one of these newer rare diseases such as APDS. One key pillar of that is medical education, and we're doing a number of activities to support this education. Obviously, we attend numerous conferences and congresses. We present abstracts both on APDS and the seriousness of APDS, as well as some of the emerging data that we have, and ongoing data that we have on the use of leniolisib in these patients. And we, of course, publish a number of these results, and we've done that throughout the course of this year.

You see a list of some of the conferences that we presented at during 2023, and there'll be a similarly long list for 2024. Because a simple genetic test can make the diagnosis of APDS quite easy, we have a sponsored no cost testing program in place with genetic counsellors available to help review test results with patients as – and physicians as well, as well as to provide pre-test and post-test guidance. We've also partnered with a number of genetic testing companies to identify patients that have already been tested and diagnosed with APDS. So really reaching out in numerous ways on the genetic testing front.

And then, as Steve mentioned, APDS is an autosomal dominant condition. But we're finding through our work is that most family members haven't actually been tested for APDS. And this is due to a number of factors that we're trying to address, one by making genetic testing more widely available, but also education. We're doing a number of things to work with clinicians and patients to encourage family testing, and we have a program in place now that allows patients to directly request this through Genome Medical if they suspect APDS or if they have a family member that has APDS. Really, the goal here is to remove barriers to testing for patients that may have APDS.

On the next slide, you can see a little bit more about the activities that we're doing on what's called variants of uncertain significance. We previously mentioned that there are more than 1,100 patients that we're aware of in the United States alone that have this category of diagnosis, which is called a VUS. And what that means is that they have some symptoms that led them to get a genetic test done, but the genetic test result is inconclusive. And it's inconclusive primarily because that genetic variant hasn't been previously seen and hasn't been evaluated, whether it's disease causing or not.

We're doing a number of things here to help resolve this frustration for patients and clinicians. The first is we're working with experts, including those at ClinGen, to develop specific criteria for classifying variants. We're also partnering with a number of companies, including Genomenon, to make clearly available what variants are causing disease. We're trying to gather data, and these efforts that I'm mentioning here have already led to a number of patients getting correctly diagnosed with APDS.

On top of that, we're really trying to make functional testing more widely available, and we're doing a number of things here to support this type of activity, working with a number of research labs to try to make this test more widely available because ultimately, this is the way to resolve a variant of uncertain significance. And then it's not only one thing to test patients, but then also to share these results. And we're doing that through a number of databases, including the one sponsored by the NIH called ClinVar.

And then lastly, we are involved in a project with high throughput methods that will allow testing nearly all possible variants and creating a variant effect map, including variants that haven't been tested yet or haven't been observed yet. And this will allow us to eventually make it possible so that in the future there won't be any patient that has this type of diagnosis, or that has this inconclusive result. And those efforts are continuing on plan, and we expect later this year to be able to talk more about the results from that project.

And on the next slide, you can see some of the medical conferences that we presented at over the past year. These data talk about the seriousness of APDS, and you see the data on mortality that we presented, the data on lymphoma, but they also present data from the ongoing use of leniolisib in the APDS long-term results. We've seen data as well presented on the different manifestations, including manifestations in these patients' guts, in their lungs.

And then lastly, we presented just last month new data on the use of our navigateAPDS Sponsored Genetic Testing Program, and how that is uncovering patients and helping patients get the correct diagnosis.

As I said earlier, we're going to continue to present at a number of conferences this year, have a number of abstracts, a number of publications that are coming out where we can really educate the broader physician community and patient community, about APDS, about the seriousness of the condition, as well as the ongoing data that we're collecting.
Next slide.

Now turning a bit to the next indication that we're pursuing. Obviously, APDS is a primary immunodeficiency with immune dysregulation, but there are other immunodeficiencies with immune dysregulation, and they often have similar clinical phenotypes or clinical presentations, as you see with APDS.

Specifically, what we see is that these patients often get similar problems related to lymphoproliferation, or enlarged spleens and livers, excuse me, enlarged spleens and lymph nodes, but also they also have this problem of autoimmunity, where not only is their immune system not functioning properly, it's also attacking the body.

And what we're seeing is that there is a number of these PIDs, or primary immune deficiencies with immune dysregulation, that have a clinical phenotype that is similar to APDS, and often times are even managed before the availablibility of Joenja® for APDS in the same way. So there's a strong rationale to see what's going on here.

And I think if you see on the next slide, the clinical presentation of these diseases looks very similar to what we've seen with APDS. In fact, when you look at the right, you see all of the same types of things, or many of the same types of things, that we see with APDS. We also know that these patients have a high unmet need. And again, the standard of care immunosuppressive therapies, such as Sirolimus (rapamycin) that have been used, have a lot of limited concerns due to limited efficacy and tolerability.

So there's an unmet need here. And we know that these patients, based on work that's already been done in these various genetic disorders, have altered PI3K signaling. And we know that that altered signaling leads to the clinical symptoms that you see on the right. And as such, we think that leniolisib is well-suited to restore that signaling to normal, thereby helping these patients' clinical presentation also.

And to that end, on the next slide, what we're doing is advancing this with a clinical trial using leniolisib in this patient population. Again, the principle is that by reducing this PI3K-delta activity, we're trying to rebalance the immune dysregulation and improve their clinical symptoms.

We've been partnered with the NIH on this, and we're expecting to start a clinical trial soon. The data suggests that when we look at the patients with specific mutations that have this type of immune dysregulation, the prevalence is approximately five per million, which is a little bit more than what we've seen with APDS, in fact, three times more than we've seen with APDS. We have been engaged with FDA on this, and we've gotten feedback on the clinical trial plans. And we are underway now to begin that clinical trial shortly, which you can see on the next slide describing the study design for that.

It's a Phase II, proof of concept study, single-arm, with 12 patients, where we will ramp patients up, starting at 10 mg and progressing to 30 mg and 70 mg. This study will include patients where we know that the genetic defect, and you see some of the genetic defects listed there, ALPS, CTLA4 haploinsufficiency and PTEN deficiency, among others, where we will – where these patients have this altered PI3K-delta signaling. So we think that leniolisib is appropriately suited to be able to alter and restore that signaling back to normal.

The primary objective of the study, of course, is safety and tolerability. But we will be looking at PK and PD measures, efficacy measures, similar to the types of measures that we studied in the APDS population. And the goal really is to confirm the safety intolerability and then pick the best dose regimen for a Phase III study. And, as I mentioned earlier, we're partnered with the NIH on this, so look for more updates to come soon about the initiation of this study.

And with that, I'll turn it over to my colleague, Jeroen, to discuss the financials.

Jeroen Wakkerman – Chief Financial Officer:
Yeah, thank you very much, Anurag, and I'm very happy to take you through the financial highlights. To start off with Q4 2023 versus last year, we had a revenue growth in the quarter of 49%, and RUCONEST® grew by 34% in Q4 and had a record revenue of $73.3 million. You may remember that we were at a growth of 2% year-to-date at the end of Q3, so we're very happy with these Q4 sales results. And we saw strong performance in leading key revenue indicators in the US, including new physicians prescribing RUCONEST®, new patient enrolments, including high-frequency attack patients, and the total number of patients.

Joenja® revenue grew by 21% versus the previous quarter, so Q3 2023, and the revenue was $7.9 million. And by year-end, we had, as Steve also said, 92 APDS patients enrolled in the US and 81 patients on therapy, on Joenja®.

The gross profit in the fourth quarter of 2023 increased by $25.8 million compared to the fourth quarter last year, and this growth was driven by higher revenues and partially offset by increased RUCONEST® production cost and royalty payments on Joenja® sales.

The operating cost increased by $16 million in the fourth quarter compared to last year, and about half of this, $8.3 million, was directly related to R&D and marketing and sales expenses for leniolisib,

respectively Joenja®. And our expansion efforts, driven by preparation for the launch and further commercialization of Joenja®, led to a $7.1 million increase in payroll expenses.

An operating profit of $1.1 million was realized, in contrast to an operating loss of $10.2 million in the fourth quarter of 2022, and this improvement was primarily driven by the rise in gross profit and partially offset by the increase in operating expenses. The net loss was $2.7 million, and our cash position improved and grew from $209 million at the beginning of the year to $215 million at year-end.

If I then go to the next slide with the full-year results, our revenues grew by 19%, which was a result of higher RUCONEST® sales volumes and supported by a price increase which was below CPI in the US market.

The initial sales of Joenja® was $18.2 million in 2023 following the launch in April of the same year, and the revenues in Europe and the rest of the world increased by 12% to $6.2 million in 2023. The gross profit increased by $32 million, or 17%. And this development was broadly in line with revenue growth.

Our other income reflects for this year well, 2023, the sale of the priority review voucher to Novartis, which was for a pre-agreed price of $21.3 million and is a one-time payment. In 2022 Pharming reduced its minority stake in BioConnection and at the time we recognized a gain of $12.2 million. So that was in 2022.

The operating costs increased by $64.5 million, of which $10.4 million is attributed to milestone payments for Joenja® following the first commercial sale in the second quarter of last year. An additional $25.7 million of expenses is directly related to R&D expenses and marketing and sales expenses for leniolisib/Joenja®, and $24.2 million increase was from payroll expenses, driven by our expansion efforts in preparation for the launch and the further commercialization of Joenja®. And finally, we incurred impairment expenses related to our DSP facility, and that was for an amount of $4.7 million in 2023.

The operating profit decreased from $18.2 million to minus $5.4 million. And that was as a result of the increase in operating cost to build our Joenja® business. The total net loss in 2023 amounted to $10.1 million, compared to a net profit of $13.7 million in the year before. And the decrease was primarily caused by higher operating costs. And in addition, fluctuations in foreign exchange rates adversely impacted the foreign currency results in the statement of income.

On the next slide, we give an overview of the revenue in RUCONEST® over the last years, and obviously for last year you see also Joenja®. But RUCONEST® has grown by 10% in 2023, and we saw a record RUCONEST® revenue since the launch of the product in the US over nine years ago. Leniolisib is driving enhanced growth. We achieved overall 19% revenue growth in 2023, and we're very pleased with these results and with the continued growth of RUCONEST® from 2021.

On the next slide, you see the OpEx in cost category breakdown by quarter, and the message is that we continue to invest in Pharming's future growth. I've provided more detail on the growth of the operational cost earlier, and specific to Q4, the operating expenses increased by $16 million in the

fourth quarter compared to last year. And $8 million, so almost half of it was related to leniolisib and Joenja® in terms of marketing sales and R&D, and $7 million was related to payroll expenses to support the growth of the organization.

And for 2024, we expect quarterly OpEx to be less than the OpEx in Q4 2023.

Now, moving on to the next slide, to the cash flow. As I said before, it increased from $209 million to $215 million, and the graph shows the key changes in our cash position. The cash flow from operating activities was negative and offset by the cash from the sale of the earlier mentioned priority review voucher. And in addition, there were favorable currency exchange rate fluctuations with a positive impact on the cash, and that was amongst others on the cash that we hold in euros, and the euro-dollar exchange rate increased throughout the year.

Then going to the revenue guidance for 2024, on the next slide. We give a revenue guidance of between $280 million and $295 million for 2024. And that means a growth between 14% and 20%. We, as in earlier years, expect quarterly fluctuations, and Joenja® is a significant driver of this revenue growth. But also, we expect continued growth from RUCONEST®. And the RUCONEST® growth rate is higher than the guidance that we gave in 2023 because we expect some of the momentum from the second half of 2023 to continue.

Last year's guidance was low-single-digit, and we are confident to move that now to low- to mid-single-digit growth for RUCONEST®. The Joenja® assumptions are that we expect continued growth in patients on paid therapy and the pricing in the US is at an annual weighted average cost of $566,000 per year, per patient.

Now, moving on to the outlook for 2024. As I said, total revenue expected to be between $280 million and $295 million.

Joenja® in the US, we expect continued progress finding additional APDS patients, and that is supported by family testing and VUS validation efforts, as mentioned by Anurag, and subsequently converting patients to paid therapy.

For leniolisib outside of the US, we expect increasing revenues from commercial availability or through our named patient program and other funded early access programs in key global markets. We expect to complete leniolisib clinical trials to support the regulatory filings for approval in Japan and for the pediatric label expansion in key global markets, and we expect progress towards regulatory approvals for leniolisib in Europe, the UK, Canada, Australia and Israel.

We will initiate and advance a Phase II clinical trial for leniolisib in PIDs with immune dysregulation linked to PI3K-delta signaling to significantly expand the long-term commercial potential of leniolisib, and we continue to focus on potential acquisitions and in-licensing of clinical stage opportunities in rare diseases, in therapeutic areas like immunology, hematology, respiratory and gastroenterology. And that is to further leverage our commercial infrastructure globally.

Now with that, I would like to move on to the next slide and open up for Q&A and hand over to the Operator. Thank you.

Operator: Thank you. To ask a question, you will need to press star one and one on your telephone and wait for your name to be announced. To withdraw your question, please press star one and one again. We will now go to your first question. And your first question comes from the line of Christian Glennie from Stifel. Please go ahead.

Christian Glennie (Stifel): Hi, good afternoon, guys. Let's start off with RUCONEST®, I guess, just to get a bit more of a sense for these underlying drivers. Obviously, a very strong fourth quarter. You seem to be guiding for mid-single-digit growth in 2024 now. Is there a scenario in which it could get north of that and do another sort of 10%? Just trying to get a bit more sense for some of the drivers on RUCONEST® this year.

Sijmen de Vries: Yeah. Thanks, Christian. A very nice question. RUCONEST® indeed has some very strong, and Steve was already alluding to it, has some very strong underlying indicators in the market, which he says continue into the first quarter. We are, of course, aware of the fact that we are in a market which is has a lot of competition around. We continue to be optimistic, let's say it's year ten, right, that RUCONEST® in the market. So we can be optimistic by saying that we have the low- to mid-single-digit growth. And as and when we see indicators moving towards the north, obviously we will update guidance during the year, but for now, we would like to stick to that, in respect of RUCONEST®.

Christian Glennie: A natural follow-up to that. I mean, you touched on this, Stephen touched on this in the remarks around potential new entrants here on oral and convenience next year. Just to get a bit more insight, I guess, in terms of the patient profile here, and what your market intelligence tells you that you aren't going to lose patients effectively to that convenience option.

Sijmen de Vries: Yeah, I think Stephen alluded to it already, we see a very different patient profile that are using RUCONEST®. And basically speaking, when you look at the clinical results of those new acute options, you see that there is a necessity to a) have multiple doses, and b) still need rescue therapy. If you look at the RUCONEST® results, the word rescue therapy doesn't figure there because RUCONEST® is protein replacement therapy for that missing C1, or not functioning C1 inhibitor protein in patients with hereditary angioedema. Hence, why we believe that these products, in fact, serve a different segment of the population that suffers from hereditary angioedema.

We expect, therefore, that these oral acute products, if approved, of course, will serve that patient segment that is now currently, of course, using a lot of convenience products as well, such as subcutaneous injections that are, by the way, very stinging and painful, in which you have to give repeatedly, often to treat one attack, and that there the hurdle for those patients to actually step over into an oral would be fairly low. Whereas I think that patients that rely on RUCONEST®, that are not used to any convenience in therapy, but are relying on the reliability of efficacy of RUCONEST®, that hurdle will be a lot higher.

One can never totally exclude, of course, that patients will try it and may be successful. But on the other hand, we, like we said, we serve a very different patient profile with higher attack frequencies than we see in all those clinical trials that are being done by those new oncoming competitors.
I hope that answers your question. Sorry to be a little long-winded here, Christian.

Christian Glennie: No, that's very helpful, thank you. And then one final one on Joenja® and get back in the queue. I guess your guidance implying RUCONEST® 5% gets to about $240 million. So, Joenja®, the balance is somewhere between $40 million and $55 million for this year, if I'm understanding correctly. And therefore, what are your assumptions around the sales and markets that will contribute to that growth, and what gets you to the low and high end of that? So, is it mostly still US, or will there be reasonable contributions from other markets?

Sijmen de Vries: I think what we will see is, first and foremost, in the US, obviously. As you heard from Anurag, and from Stephen, a lot of activities are ongoing to find those patients in the US. However, the first numbers of patients that we had, of course, are on drug. We will see steady inflow in the United States during this year from, for instance, family testing efforts that will be systematically applied, as you heard.

The other thing is, of course, there will be initially small batches of VUS tested, and that will actually deliver, albeit in the beginning, a limited number of additional patients as well, whereas by the end of the year, but that's more for '25, of course, we expect that MAVE experiment, where Anurag talked about that combinatorial experiment, to deliver the bulk of the VUSs. And as soon as we have a bit more indication of what kind of percentage we actually have on VUSs, we will, update the market there as well, but it's a little bit early days for that at this point in time.

Now, that's for the US market. With respect to ex-US, we don't expect any significant sales from the European markets because obviously, as you know, reimbursement takes a lot of time. The European market sales will only cut in, in '25 and even further on, because some of those markets will take multiple years before you get an approval. The ex-US sales will mainly come from those paid early access programs in some of those markets, and from the name patients that are actually already being served. And that's what you can also expect, of course. For instance, in the Q1 results, you will see that there are some sales reported ex-US because that's ongoing as we speak.

In other words, the fluctuation in the Joenja® numbers, I think, depend on mainly, I think, on the numbers of patients that will come from the US market. I hope I answered that question, Christian.

Christian Glennie: Yep. Thank you. Thanks, Sijmen.

Operator: Thank you. We will now go to our next question. And your next question comes from the line of Alistair Campbell from Royal Bank of Canada. Please go ahead.

Alistair Campbell (RBC Capital Markets): Thanks, everyone. Thanks for taking my questions this morning. I have a couple on Joenja® if that's all right. First of all, obviously Joenja® is launching very well in the US, and you talked about, I think over 90% adherence rate, which is good. But just in the context of that, just sort of to confirm that what you're actually seeing in real-world use is kind of aligned with what you saw in clinical trials in terms of side effect profile and stuff like that, that'll be useful to get a sense of that.

And then secondly, just thinking about the second indication, the PIDs with immune dysregulation, obviously that's going to cover a variety of different genetic causes. And I guess what I'm trying to get for myself is a feeling of the risk around the profile of this program. I mean, basically, is your

expectation that all of those genetic dysfunction areas really biologically should respond, or do you think some of them will, or do you think they're all high-risk? I'm just trying to get a sense of what the risk profile looks like. My feeling is that at least some of those should probably come through, but just to get a sense of how you view it, that would be great. Thank you.

Sijmen de Vries: Yeah, I'm happy to hand that over to Anurag, of course, here in this case. Anurag, would you mind answering that question?

Anurag Relan: Sure. Maybe we'll start with the second question first, about the additional indication in primary immunodeficiencies with immune dysregulation. And you're right, we're looking at a number of specific genetic variants, genetic mutations that are causing this altered signaling, and that already has been described, right? So it's known that patients with ALPS, that patients with CTLA4, that patients with PTEN deficiency, have this abnormal signaling through that pathway. It's also known that they have immune dysregulation as a result of that. And then lastly, they're being treated with immunosuppressive therapies, such as rapamycin, to modulate that pathway.

We think it's quite logical to try to modulate the pathway with leniolisib in the same way that we did with APDS patients. I think, from our perspective, and really, this program came to us through our interactions with the immunology community. They, through all the work that we're doing on APDS, they kept on saying, look, there are other patients that they believe could benefit, and they listed all of these reasons that I just mentioned to you. And it was really on that basis that we partnered again with the NIH, who are leaders in these, and specifically in this area of ALPS and CTLA4 haploinsufficiency, to come up with this clinical trial program because they were so enthusiastic about being able to, 1) address the unmet need, but 2) to be able to use something that they were very comfortable using for APDS. And they had that confidence because they had been treating patients with APDS with leniolisib for several years.

And I think that comes to your first question, which was on, really, the real-world use of leniolisib, and how does that compare to what we've seen in the clinical trials. And I think what we're seeing is, 1) we're seeing that it continues to be generally safe and well tolerated. We're seeing nothing new from our pharmacovigilance efforts on the real-world use, suggesting a different safety or efficacy profile. But 2) I think what we're also hearing is a lot of the other benefits that we didn't even capture in the clinical trial program and we're trying to get all of that data.

In fact, we have a registry underway in the US where we're going to be following APDS patients longitudinally, and in the hope, actually, to try to capture a lot of the data that we didn't address in the original clinical trial because we weren't aware of all of the possible benefits that these patients experience. I think that's something else to look forward to as the year continues.

Alistair Campbell: Just a quick follow-up on that. When do you think, in the sense of timing, you might have something from the registry that be worth sharing with us, or, obviously, with physicians?

Anurag Relan: The registry is just underway, but we are continuing to collect and publish data for the use of expanded access. These are, again, this is essentially compassionate use patients in the

US, who don't qualify for commercial drug, or outside the US, who are on therapy. We are collecting that data, and we shared some of that last year. You'll see a lot more of that data from the expanded access program or case reports or case series of patients in the expanded access program. You'll see that at conferences this year. I think the registry because it's just started, I think that's more likely to be a '25 type of data, but I think that you're going to see through the expanded access program data coming out this year that reinforces what we saw in the clinical trial program and really extends even beyond that.

Alistair Campbell: Brilliant. Thank you.

Operator: Thank you. We will now go to the next question. And your next question comes from the line of Joe Pantginis from HC Wainwright. Please go ahead.

Joe Pantginis (HC Wainwright): Hello, gentlemen. Thank you for taking the question. I have a couple of questions on Joenja®. I'm going to start very specific and then just talk more to the broader disease, if you don't mind. So, first, Stephen earlier was talking about, and of course, you guys have great adherence rates. So, I was curious on the other end, what are some of the reasons you see for lack of adherence on the drug?

Sijmen de Vries: Thanks, Joe. Anurag, do you have any insights on that, that you can share with Joe?

Anurag Relan: Yeah, I think it's really just one-off cases, Joe, where, in fact, some of the cases where we've seen it, is that patients are underweight, and they need to be put on a lower dose, so that's not possible in the commercial program. So that's one example that comes to the top of my mind, but it's not anything we're seeing from a safety point of view that suggests any concern or something that we didn't see in the clinical trial program. So, I don't think there's anything substantive here.

Joe Pantginis: That's very helpful. Thanks. And then, I guess, Sijmen, if I heard you correctly earlier, it sounded like you might be disclosing in the future the role or the amount or proportion of VUS as part of your Joenja® revenue profile. First, was that correct? And then second, when do you anticipate, I know this is really forward-looking, that VUS could start to have a real impact on the revenue growth for Joenja®?

Sijmen de Vries: Yes, Joe, that is indeed forward-looking. Yeah, I said indeed, something like that. We're seeing, you see that slide from Anurag, you saw in the middle there that those individual VUS are now being evaluated, and that's actually starting and happening as we speak. The first small batches of those are expected to come through in the very near future, which may give us some early insights in that. Like I said earlier, it's not going to deliver bulks of patients, but it will deliver patients, and the bulk, I think, will be seen following the closure of the MAVE experiment, which is expected, as Anurag was alluding to, by the end of this year. I think '25 will be the year where the bulk of the VUS patients will become available for treatment. I think that's a reasonable forward-looking statement for now, Joe.

Joe Pantginis: Got it. No, that's fair. And my broader question about the disease sort of ties in with your recent data at AAAAI. Obviously, very intriguing data with regard to the molecular diagnostics. And I guess, I would ask Anurag, you know, the role that Joenja® could play with regard to, you know, multiple statements made in describing the disease where some patients do not have clinical actionability. So I'm just curious, first, can you, for all of us, help define why patients might not be actionable from a clinical standpoint or medical standpoint, and if Joenja® could have an impact on that?

Anurag Relan: Yes, I think it's a good question. It's something we're doing a lot of work on, is really educating patients and clinicians about APDS. I think it's a foregone conclusion amongst our team, of course, that this is a serious disease and that there's a significant mortality associated with it, that many of these patients, unfortunately, go on to develop lymphoma. And lymphoma is a key reason for the high mortality in these patients. The lymphoma that these patients develop is often not easy to treat, and the mortality rates are much higher than you would see in other lymphomas, for example, in other patients. I think there's a lot of education to talk about that.

I think it's also important to recognize that these patients do have different clinical manifestations. Some patients, it may be very obvious with a high infection rate, some patients' infections may not be the most predominant feature, but it could be the lymphadenopathy or the enlarged spleen. I think it's really educating clinicians also on what to look for in these patients, and to be able to monitor these patients. But really all of these patients, I think, have a serious condition, and they all are potentially eligible for Joenja®. I hope that answers your question.

Joe Pantginis: It certainly does. And my last question, and thank you for bearing with me, is more towards your continued strengthening balance sheet. And with that said, do you feel that your increased cash helps leverage additional business development discussions, and can you talk to the relative maturity of some of your ongoing discussions to in-license potential assets? Thanks.

Sijmen de Vries: Yeah, Joe. Yeah, thanks. Yeah. Of course, it always helps to have a bit more cash at hand in case one wants to do an in-licensing – pursue an in-licensing opportunity, which of course, as we said before, is our preferred modus operandi because that's much easier to deal with than merger and acquisitions. Having said that, I think with the arrival of Alexander Breidenbach, our Chief Business Officer, he's been really proactively working, and we got a very nice pipeline, and we are in advanced stage of discussions with a couple of possibilities. So we have a nice line-of-sight, as we call it, for opportunities that we are evaluating.

However, as you know, in business development, and I said this before, it doesn't count until you have a deal. So, yes, but we remain very active. And I think what also is – what we see is with our commercial success and with the ongoing ability that we are very successful in being able to market against competition in the HAE market, and that we are basically – know how to develop a new market, even in a new disease, we get a lot more visibility now that we are a company that is potentially an interesting partner of choice for those companies that should not go into commercialization because they will become single product companies. And commercialization is very expensive and very risky. And we therefore, like I said, because we have now got this under our belt, become more and more we see that on the radar screen, and we're getting a lot more inbound than we used to get.

So we are continuing to be optimistic that we get some opportunity this year to update you on a deal that we have clinched, and that we have actually expanded our pipeline.

Joe Pantginis: Very helpful. Thank you for all the answers, guys.

Sijmen de Vries: Pleasure, Joe.

Operator: Thank you. We'll now take your next question. And your next question comes from the line of Hartaj Singh from Oppenheimer. Please go ahead.

Fanyi Zhong (Oppenheimer): Hey everyone, this is Fanyi Zhong, on for Hartaj. Thanks for the question. Two questions from our end. So, first one for RUCONEST®. Can we still expect seasonality for RUCONEST® in first quarter sales as previous year? Any color on that? The second one for Joenja®. Can you provide any color on the duration of the patients for Joenja® so far, since Joenja® was launched around like three quarters, nine months, and your estimates on the APDS patient number growth in 2024? Thank you.

Sijmen de Vries: Yeah. Could I hand it over to you, Stephen, those questions, is that all right?

Stephen Toor: Could you repeat the questions? Because they weren't completely clear from my end.

Fanyi Zhong: Sure. The first one for RUCONEST®. So, can we still expect seasonality for RUCONEST® in first quarter sales as previous year?

Stephen Toor: Yes. Thank you for clarifying. Yes, I think you can broadly expect to see similar patterns to those which you saw last year, because the same types of events are happening in the quarter. So, for example, Q1 is the prior authorization season, and as we indicated last year, there is some disruption to government patients. As I said, we remain on track for what we expect to do this quarter. The leading indicators and the performance are where I expect it to be. But you should expect to see the same overall pattern through the year, I imagine. Certainly, in the first half.

Fanyi Zhong: Thank you.

Stephen Toor: And the second question?

Fanyi Zhong: For Joenja®. So, can we know some color on the duration of the patients on Joenja® so far, since it was launched around three quarters, like nine months ago?
Stephen Toor: The duration of the patients?

Fanyi Zhong: Patients on Joenja®. So, you know, I don't know if the physicians, these prescripts are like 30 days for each patient, or how long are the patients on the treatment?

Stephen Toor: I've got you now. As we mentioned earlier, patients are adhering well, unless there's either a weight issue or some such. So they're typically being prescribed on a monthly basis and dispensed on a monthly basis. And we see that cadence with patients.

Fanyi Zhong: Thanks. So, any estimates or projection on the APDS patient numbers growth in 2024, more specifically?

Sijmen de Vries: Yes. Like I said before, we will continue to get new patients on product in the USA, right? The adherence rate is very high. It's of course a chronic therapy. And 'we will update the numbers of patients towards the future on a quarterly basis, right, when we get these results. Did that answer your question?

Fanyi Zhong: Yeah. Understood? Yeah. Thank you so much.

Sijmen de Vries: All right.

Operator: Thank you. We will now take our final question for today. And your final question comes from the line of Simon Scholes from first Berlin. Please go ahead.

Simon Scholes (First Berlin): Hello. Thanks for taking my question.

Sijmen de Vries: Hi, Simon.

Simon Scholes: So, the exclusivity on RUCONEST® in the US expires in two years' time, a bit more than two years' time. I was just wondering what kind of impact, if any, you expect that to have on RUCONEST®?

Sijmen de Vries: Yeah, we expect no impact whatsoever on RUCONEST® in that respect because we believe that there is nobody that actually is working on or has any appetite to develop a transgenic platform to make a biosimilar for this product. Given also that it is of course a great product, but it has, in the greater context, it's not a huge commercial opportunity. So, therefore, no is the answer. No effect, no impact.

Simon Scholes: Okay. And just to follow-up from that, what's your current thinking on the likely timing of the first gene therapy in HAE, besides your own product, of course?

Sijmen de Vries: I think that will be still a lot of years away. Only the first patients are being tested now. Gene therapy is not the quickest development pathway forward, I would say, but maybe you can say something on that, Anurag?

Anurag Relan: No, I think that's it, Simon. That there are some initial results in a small number of patients, but I think this will require the typical development path, Phase II, Phase III, as well as long-term follow-up, which will take several years at the minimum.

Simon Scholes: Okay, thanks very much.

Sijmen de Vries: Thanks, Simon.

Operator: Thank you. I will now hand the call back for closing remarks.

Sijmen de Vries: Thank you very much. Yes, ladies and gentlemen, thank you for attending our full-year conference.

Like I said at the beginning, because of our very significant 19% growth in revenues, we laid in 2023 a foundation and the start of a long trajectory of growth which this company is now embarking on. And of course, that's why we guide this year for additional significant growth for the revenues, fueled by, of course, the continued growth expectations for RUCONEST® and the continued growth of Joenja®. And we feel very confident about the fact that we have started now all these systematic efforts to find those patients. The VUS validation efforts were mentioned, the family testing was mentioned, and of course, the increasing availability of leniolisib ex US, where through our name patient programs and other early access programs, we expect revenues, and of course, the completion of the clinical trials going forward that will support the approval in Japan in the future. This is of course not a 2024 story, as we all understand, because the file will only be ready to be submitted by the end of 2024.

We look forward to receiving the regulatory feedback from the various regulatory authorities and expect approvals during '24. And we are very, very excited, of course, that we can significantly enlarge the potential of leniolisib with that second indication, PIDs with immune dysregulation linked to the PI3 kinase-delta signaling to which Anurag alluded, which is a significantly larger opportunity going forward and where we believe there's a very strong scientific rationale underpinning the product. And, of course, not something that will report in 2024. But we will be very happy to update you, of course, once this trial has started and once this trial, of course, has the results and hopefully brings us to the next stage in development of leniolisib for that second indication .

And that is, my ladies and gentlemen, not even the beginning, because we are looking at additional opportunities to look, apply leniolisib in this, in adjacent areas. And more news that will be coming in the future about our efforts in that respect.

And last but not least, we have a very interesting line-of-sight of opportunities to in-license or do M&A activities for clinical-stage opportunities in rare diseases where we are feeling most comfortable to deal in immunology, hematology, respiratory and gastroenterology.
So thank you again for attending our conference, our full-year 2023 results conference, and we look forward to updating you on the next quarter results sometime in May.

Thank you very much. Goodbye.

Operator: Thank you. This concludes today's conference call. Thank you for participating. You may now disconnect.

[END OF TRANSCRIPT]