Pharming Group N.V. FY 2022 Results Call

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Joe Pantginis – H.C. Wainwright
Hartaj Singh – Oppenheimer & Co.
Christian Glennie – Stifel

Sijmen de Vries, MD – Chief Executive Officer:
Good morning or good afternoon, ladies and gentlemen to our 2022 results call. Before I start taking you through that. Please pay attention to the next slide, which contains a statement on forward-looking statements as we may be making forward looking statements in this conversation. They are statements based upon our expectations and assumptions and involve known and unknown risks and uncertainties that could cause actual results, performance, or events to differ materially from those expressed or implied in these statements. And you can read the rest for yourself, I assume.

I'm joined today by my colleagues, Dr. Anurag Relan, our Chief Medical Officer, and Jeroen Wakkerman our Chief Financial Officer. And we also have here, although not speaking on the conference, but to answer your questions, our Chief Commercial Officer Stephen Toor. And I would now like to start with the next slide please.

And then the next one. So, where are we? We have developed over the years a very strong base with potential for significant growth. And that is based upon the commercialized asset RUCONEST® recombinant humans C1- Esterase inhibitor for the treatment of acute hereditary angioedema attacks, which is commercialized by ourselves on both sides of the ocean, as you can see, in a lot of other markets as well as the U.S. and the European Union, and of course, the U.K.

The potential for growth is represented here initially by the anticipated approval and launch of leniolisib, a PI3Kδ inhibitor in development and regulatory review for APDS. We anticipate in the not-too-distant future the FDA approval, and later on during the year, the European approval. And we have morphed ourselves into a company that is focusing on development and commercialization of rare diseases. And the first thing that goes beyond the APDS indication for leniolisib will be that we are quite far along with investigating leniolisib for additional rare disease indications. We are based in Leiden in the Netherlands. And we are here actually in our U.S. headquarters in Warren, New Jersey, where we speak to you from. And of course, we are a public company since 1999, in Amsterdam, and since 2020 on the NASDAQ.

So, let's look at our business model on the next slide. We are really on our way to building a sustainable rare disease business. Whilst we are now commercializing RUCONEST® on both sides of the ocean, the vast majority of sales come from the United States. So, we're now a one product company with one geography, but that we expect to be changing very soon, with the anticipated approval of leniolisib for APDS, which will represent a not only a possibility for very significant growth of our U.S. commercial footprint and revenue base, but also a very significant revenue generator outside of the U.S. So, we're looking forward to this year being a transformative year, from which we transform from this one product, one geography company into multiple products,

multiple geographies company. And of course, like I said before, we are quite far on our way, and we'll update the market later in the year, to actually start additional development programs for leniolisib in additional diseases. And then last but not least, since we have a very scalable commercialization infrastructure in both Europe and in the U.S., we're actively hunting for additional products in rare diseases, to either in-license, that is our preferred mode of action, and if not, other possible mergers and acquisition transactions, to basically bolster that pipeline further, and really get a flywheel going, that we have here with our scalable commercialization operations on both sides of the oceans.

And in the next slide, you can see the pipeline, and you can see immediately what I mean with that. RUCONEST® is on the market and leniolisib very close to the market. And of course, if we start clinical trial programs in secondary indications for leniolisib, there is still a considerable gap between those two products, or those three products in the near future, and the preclinical assets that we have in the form of OTL-105, the HAE gene therapy and alpha a-Glucosidase from our transgenic platform, just like RUCONEST®, for Pompe disease.

So, let's look at RUCONEST® as being the strong foundation under our company. We returned it to growth again, after the COVID period, we returned to growth in 2022, as we were guiding single digit growth over 2021. And that is something we are very proud of. RUCONEST® was launched at the end of 2014, so it's already quite a mature asset and has found its unique place in the market. It is the only recombinant treatment that targets the root cause of hereditary angioedema by replacing the missing or dysfunctional C1 esterase inhibitor. And over the years, it has proven to be very well tolerated and effective and continues to be a very effective treatment for the treatment of acute hereditary angioedema attacks, including, and it becomes increasingly important, those breakthrough attacks that people suffer from when they use prophylactic treatments. And that is, indeed continues to be an issue that although prophylactic treatments have become an especially referring to the United States market, of course, where the vast majority of our sales come from. And although the prophylactic treatments have become a lot better, they all have the same issue that up to half of those patients suffer from breakthrough attacks. And breakthrough attacks can come very frequently or very rare, but they come always at a moment that you don't expect it. That's why it is always the case, it is good practice, in United States that when you are in prophylactic treatments, you always have acute medication at hand at home, to actually inject yourself in the case of RUCONEST® with the rescue therapy, and that becomes increasingly important. And that is also why we see increasingly that RUCONEST® is being used by more doctors and used by more patients to actually treat those breakthrough attacks. And it is - we can very proudly say - the second most prescribed product that is detailed for acute attacks.

And as you can see here, the FPC numbers speak for themselves on this slide. And we are finding that our patients feel very, very confident to administer the treatments to themselves. It's a slow IV injection, and the vast majority of patients do inject themselves in or by their loved ones in the privacy of their own homes. So RUCONEST® has been on the market for a long time and will continue to play a very important role supporting our business with sales and with important cash flows that enable us to invest in all those future programs that we are embarking on.

So, with that said, I would like to now switch over to that promise for a significant growth of the company in the very near future, leniolisib for APDS. And I would like to hand over to Dr. Anurag Relan, who sits here next to me to take you through the story of APDS and leniolisib. Anurag, over to you.

Anurag Relan, MD – Chief Medical Officer:
Thank you, Sijmen.

In the next few slides, what I'd like to do is review some information that we have on our understanding of the condition APDS, our understanding of the patient journey, and what we've done in terms of developing leniolisib for APDS. And then using all of this information to help identify patients. And then lastly provide an update on where we are in terms of regulatory status.

So, on the next slide, we can see a schematic here of how this genetic defect in one of these two genes leads to this hyperactivity of this pathway. You can see that within the cell there on the left, and that hyperactive pathway then leads to this dysregulated B and T cell development. So, these key components of the immune system do not develop properly. And as a result of not developing properly, patients suffer from a number of symptoms and conditions that you can see on the right. Most prominently these patients develop recurrent infections. They also, because of this abnormal development of their immune system, have what's called lymphoproliferation. So, they get swollen lymph nodes, their spleen is enlarged, they have problems with expansion of lymphoid tissue, especially in the gut, and that can lead to a condition called enteropathy. And not only do these immune system cells not fight infection, but they also actually lead to the opposite problem where they lead to a condition called autoimmunity. And this can lead to autoimmune anemias and cytopenias and other autoimmune disorders. But it's also important to note that APDS is a progressive condition. So, over time that disease worsens, and many of these patients, even at a young age, develop a condition called bronchiectasis, which is essentially scarring in the lungs. That is irreversible. And many of these patients unfortunately go on to develop lymphoma, again due to this unchecked lymphoproliferation and this abnormal development of their system.

On the next slide, you know, we can actually see what the consequences of this are on the patients themselves. Of course, we've talked about the physical consequences of recurrent infections. I mentioned bronchiectasis, and that can result in shortness of breath, coughing, just difficulty to do their normal activities. And you can see that that can impact their social wellbeing and as well as their mental wellbeing, but there's a significant treatment burden. These patients are frequently hospitalized to have numerous surgeries, many of them unnecessary, especially when they've not been properly diagnosed, numerous doctor visits. So, it's a condition that impacts many facets of these patients lives.

On the next slide, we see what is possible now in the current management of APDS. And that's really trying to address the consequences of the condition. So, not addressing the root cause. We're trying to address the symptoms. So, many of the symptoms and the manifestations are infections. So, these patients are frequently on antibiotics, either prophylactically or to treat their infections, most of these patients are on immunoglobulin replacement therapy. And then again, on the flip side, when they have autoimmune complications, or immune dysregulated complications, they're put on steroids, other immunosuppressants, or a class of drugs called mTOR inhibitors to try to modulate their immune system. None of these therapies of course, are FDA approved for this specific treatment of APDS. And again, the worst condition, the worst possible outcome for these patients is that they need a stem cell transplant. And unfortunately, even stem cell transplants, although potentially curative, has significant morbidity and mortality associated with them.

On the next slide, we can see the future now what we've -- and what we're developing is leniolisib, which is a targeted disease modifying treatment for APDS. And leniolisib specifically blocks the

PI3Kδ pathway and thereby modulating and trying to return to normal the activity in this pathway, a consequence then of that should be that we can actually develop the immune system properly and then again impact all the other things that are the downstream effects of that abnormal immune system development. And that's -- and we've gone on to study that together with Novartis and you can see in the next slide, the overall clinical development plan which includes a number of studies, dose finding studies, a placebo-controlled study, and at the bottom, a long-term extension study. There are patients now in that long term extension study that have been treated for a number of years, many patients, several patients over five years, one patient who has been in the study now for seven years. So, we have extensive data on the use of leniolisib, both in a long-term perspective, but also in a placebo-controlled fashion.

And in the next slide, we can see some of those results, we see that the study met, the randomized control study met both primary outcomes, which was number one to increase the number of naive B cells. Again, these are B cells that were not developing properly as a result of that underlying hyperactive pathway, we were also able to achieve decrease lymphadenopathy. Again, this was a primary manifestation of APDS. On top of that, when we look over in the randomized study, as well as over longer periods of time, these patients' spleen size shrinks, we see improvements in those autoimmune complications. We see in general that the drug was also well tolerated. In the data package that we submitted to FDA, for example, we have a median exposure of two years for the patient population. On top of that, when we start looking at the longer-term outcomes, we see that these patients are getting less infections and they're using less immunoglobulin replacement therapy. So, despite using less of the therapies that are needed to control infections they're actually getting less infections. So, it's actually very nice to see how impacting that pathway can impact the immune system and then could actually have an impact on all of these clinically relevant endpoints in terms of infections and also reduction of immunoglobulin replacement therapy.

On the next slide, we can see where we are now, in terms of safety. And what we see when we look at the randomized controlled trial data is a comparison of leniolisib on the left with placebo on the right, and you see a very similar profile in terms of the grade of adverse events that were experienced by these patients and that mimics what we see in the long-term extension data. So, in general leniolisib has been well tolerated. And again, as I mentioned earlier, we have some patients who are on the therapy in the studies for several years now.

On the next slide, we can see the activities that we've been conducting to help find patients. And there's a number of activities as we begin to understand the disease and this patient journey that help us inform how to go about finding these patients. We estimate that based on a prevalence of one to two per million, there's more than 1500 patients in the key markets where we intend to commercialize leniolisib first. We've already identified 500 patients in these markets. Much of this has been done through a partnership with Invitae, which involves a genetic testing program that is at no cost to patients that can make a definitive diagnosis for these patients. We also have a number of partnerships with medical organizations, patient organizations, and these are critical in helping us to uncover these patients who have this rare primary immune deficiency. And we've received tremendous support in these partnerships. Again, these patient organizations who are -- who really have the same goal that we do, which is to help improve the lives of these patients with these rare and ultra-rare diseases.

On the next slide, we can see where we are now with our regulatory status. As Sijmen, mentioned we have filed in the U.S., it's under review, with a priority review designation for patients who were

enrolled in the programs that I described, which were adults and adolescents aged 12 and over. We also have an ICD-10 code in place and we have a number of physicians already using that code, so that's also nice to see. And we have coming up at the end of this month, the expected decision from FDA on the 29th of March. And we expect that later this year, still in the second quarter of this year, we expect to be able to commercialize pending a positive decision from the FDA.

In Europe, we've also filed an application there, we also have a positive destination on our pediatric investigation plan, which of course is necessary to begin the filing process. We originally received accelerated assessment. This has now been switched to a standard assessment as EMA have requested additional data. We still, however, anticipate that CHMP will be able to provide an opinion later this year in the second half of this year, with an approval to follow proximately two months later. And with the U.K. regulators, we expect to be able to file soon after the CHMP.

And on the next slide you can see this over time, some of the key anticipated milestones. Earlier this year, we were able to begin the first of two pediatric studies. And again, we have the FDA regulatory decision coming later this month, with the U.S. commercial launch soon after that. We're also going to be starting a new study in Japan and we expect that to also occur in the first half of this year. And as I mentioned earlier, we're expecting a CHMP opinion as well as the U.K. filing in the second half of this year.

And I will now turn it over to Jeroen Wakkerman our CFO.

Jeroen Wakkerman – Chief Executive Officer:
Thank you very much, Anurag.

So, the financial highlights for 2022 versus last year related to the P&L. To start off with, our sales grew by 3.4 percent in 2022 to 5.6 million. And in Q4, sales were 54.6 million also a growth of three percent in line with the single digit growth guidance that we've given throughout the year. Gross Profit increased from 178 million to 188.1 million. That's an increase of 5.8 percent and therefore we improved our gross margin. Operating Costs grew from 167 million to 184.4 million, an increase of 10.5 percent. And the operating profit grew to 18.2 million, which is an increase from last year of 34.5 million. The net profit decreased from 16 to 13.7 million in 2022 which has a decline of 14.5 percent.

And in the next few slides, I'm going to give you a bit more color and detail on the results on what happens. And next slide, please.

The overall message is that we grew our sales, and we also grew our investments in the launch and the preparation of the launch in leniolisib. Revenue grew to another 5.6 and that was supported by a price increase which was well below the CPI level. But also, an increase in the number of doctors prescribing RUCONEST® and an increase in the number of patients. Regional split is that we had a growth in the U.S. of 3 percent, and the EU sales were flat over the two years.

Moving to gross profit, gross profit increased. And that was, amongst others, obviously, by the sales gross, but also by the improvement in gross margin from 89 percent to 91 percent. And that was driven by favorable production results, but also impairment on the inventory in 2021 of 2 million that we didn't need to take this year.

The other income is as you see a sharp increase from 2.6 million to 14.5 million. And that includes the transaction that we did with BioConnection our fill and finish partner, in which in Q2, we reduced our minority stake from 44 percent to 23 percent, that we had a gain on disposal of 12.2 million. The remainder of that other income is mainly grants that we received in the Netherlands on research and development.

The operating costs increased from 166.8 million to 184 million. And you see that overall, the costs were flat on a like for like basis, as I say, and you see the growth in leniolisib out of pocket expenses. So, we consider out of pocket expenses, namely third-party providers. And that almost doubled to from 18 million to 34 million. Please be reminded that in those normal operating costs, there are also leniolisib costs, for example, the 25 disease educators for leniolisib that started in on the 1st of August last year. So, the overall costs for leniolisib increase more than what you see here.

That goes into the costs category development R&D in this picture declines. But I'd like to remind you that last year, we had a one-off impact of 18.5 million, so we should deduct that from the 70 million to come to a like for like number. And that one off was related to OTL-105, the collaboration agreement with the Orchard Therapeutics and also an impairment of an intangible assets. So, on a like-for-like basis, the R&D costs were largely flat. G&A cost we increase and that was mainly because of payroll and IT costs just to strengthen the backbone of the organization with the growth that we foresee in the near future. And we see a growth in marketing and sales costs 26 million up from 59 million to 86 million, almost. And that was mainly in leniolisib. And mainly in categories like marketing and market access developments. The operating profits increased from 13.6 to 18.2. And that's the effect of the increase in the gross profit from the BioConnection gain on disposal and offset by the higher cost from our investments in leniolisib launch preparation. The net profits are reduced and that is mainly because of the financial results that reduced from 8.8 last year to minus 2.2 And that is mainly for an exchange driven.

There moving on to the next slide. Where you can see in a different way what happened to the profit before tax. Last year it was 23.1 million we had some one-off costs in 2021. Again, due to OTL-105. And some impairments. So, you could argue that the like-for-like profit before tax, last year was 43.1. So, what happened in 2022? Starting from that base, we grew, we grew the gross profit by 10.3 million, as I said the R&D expenditure was relatively flat, although within that path, there were quite some changes. So, we increased the investment in leniolisib. We increased the investment in OTL-105, we have more costs for AKI and cattle, the program that we have stopped by now. So, that will reduce in 2023. And we reduce the cost in 2022. On Pompe and on the COVID R&D. So, a mix of things and I think a good reflection of our strategic intents. The increased G&A expenditure was mainly as I said, because of payroll with additional people and it costs in marketing and sales was largely driven by leniolisib. See, again the BioConnection transaction results and a decrease in the financial results. And hence we come to a profit before tax of 15 million in 2022.

Not on this slide, but important for those who have modeling, you will see that we have a low tax rate, effective tax rate in 2022. It was only 9 percent versus 31 percent, the year before, so that's very positive. And the reason for that is that the gain on disposal on the BioConnection transaction was tax exempt. Then the cash flow development on the next slide please.

We started off the year with 192 million off cash. The operational cash flow was plus 22.9. With working capital almost flat during the year, so no cash outflow. The investment cash flow was largely related to two items CapEx in both PP&E and software but very limited was only 2 million in

total, and cash from the cash income and cash from the BioConnection transaction. The cash flow from financing activities was largely related to interest on the convertible and some regular lease costs. The negative exchange rate effects on the cash, we ended up with the cash and cash equivalents balance 50 million more than we started the year with at 207.3 finishing the year at two and 7.3. And we can confirm that we have full access to all of this cash, all our cash deposits.

To the next slide, the outlook for 2023. We continue to see low single digit growth for RUCONEST® revenues. The key event for 2023 is obviously developments on leniolisib. So, we expect a U.S. FDA approval in the first quarter. In fact it's 13 days from now the PDUFA date is the 29th of March and the U.S. launch and commercialization will start shortly after it in the first half of this year. For the EU we expect a positive CHMP opinion from EMA in the second half of this year, and a marketing authorization for Europe that will follow approximately two months later.

For the U.K. we will file afterwards, after the EU approval with the U.K.'s MHRA following the European decision. This decision relies on the EDCRP procedure. To accelerate future growth, our investments mainly in leniolisib will continue to impact profits in 2023. As you have seen in the previous slides that I've shown, we're working hard on lifecycle management for leniolisib. So, the new indications besides for APDS. And further details on our plans to develop leniolisib in additional indications will be provided in the second half of this year. And as Sijmen said, we continue to look for potential in-licensing and acquisition opportunities and focusing on late-stage development and assets in a rare disease. So, overall, we've had a good year: we've had sales growth, we've had an increase in operating profit. We've had good cash generation and cash in excess of $200 million and we are 13 days away from the PDUFA date for leniolisib.

With that, I would like to go to the next slide and open up for Q&A with my colleagues, Sijmen de Vries, Anurag Relan, and our CCO Stephen Toor, thank you very much.

Operator:
Thank you. If you would like to ask a question, please press star followed by one on your telephone keypad. If for any reason you would like to remove that question, please press star followed by two. Again, to ask a question, please press star followed by one. As a reminder, if you are using a speakerphone, please remember to pick up your handset before asking your question.

First question today comes from the line of Sushila Hernandez from Van Lanschot Kempen. Please go ahead. Your line is now open.

Sushila Hernandez- Van Lanschot Kempen
Thank you for taking my question. I just have a few questions. The first one on leniolisib. So, you have identified now more than 500 patients that have confirmed APDS diagnosis. Can you comment on what a realistic target is for the number of patients that you can identify? And is going to receive leniolisib once approved? And could you also provide an update on your reimbursement discussion? Thank you.

Sijmen de Vries, MD – Chief Executive Officer
First part, on the potential numbers? Well, I think you're referring to the label which is now 12 and up. All right, so we've started our first pediatric trial. And I'm looking here at Anurag, I think it's about 25 percent of patients are below 12 years of age. So, they would initially not qualify for treatment until such time that we have the pediatric approval in our hands. Furthermore, I think

we have not seen, so far, an APDS patient that would not qualify for treatment because the diagnosis is made by this genetic test. And that's pretty clear.

Anurag Relan, MD – Chief Medical Officer
And there's a small number of patients, of course that have already been transplanted some of those successfully. So, those also would not qualify. But again, the vast majority of the other patients that Sijmen mentioned would potentially be eligible for treatment.

Sijmen de Vries, MD – Chief Executive Officer
And then with regards to your second question about reimbursement, obviously, these discussions are mostly relevant for the European market, for outside of the U.S. Those have not started because we're not approved yet. And in Europe, normally speaking those discussions start after you have the approval for the product in the United States. We will be bringing your story; we will be bringing a shipment to the market as soon as possible after the due date. And we will of course inform the market about pricing in the United States as and when this happens.

Sushila Hernandez- Van Lanschot Kempen
Okay, thank you. And then just one more question on when can we expect to see additional assets entering your pipeline by internal projects or enlighten us on any acquisitions, next to a second indication for leniolisib or your gene therapy candidate?

Sijmen de Vries, MD – Chief Executive Officer
Yeah, so, basically, you know, the secondary indications leniolisib, second half of this year we will be informing the market about that. And with regards to in-licensing and acquisitions, we're very active. We have a small, very efficient business development group, turning over a lot of incoming assets that we get offered/that we find ourselves, we've had evaluation in several stages, we've done a few due diligence, even over the last year. And of course, as you can see, nothing had resulted in a deal. So, until such time, we keep working, beavering away at it, and trying to find those assets that fit our portfolio. And we're really looking for these rare diseases, I think leniolisib is very good case in point where we are very comfortable to take Phase III risk, because leniolisib we only could look at the first cohort of patients that had undergone the dose finding study and the Phase III study was ongoing. We're very comfortable with that, provided that we have a good clinical proof of concept in our hands, when we actually start to engage with the asset. Our preferred mode, obviously for this is, is in-licensing, as we are still a relatively small company. And of course, the licensing transaction is much easier to handle than mergers and acquisitions. Especially of course, when you are launching a product like leniolisib, that we are with leniolisib this year, which requires a lot of our focus. Hope that answers your questions.

Sushila Hernandez- Van Lanschot Kempen
Yes, that's clear. Thank you.

Operator:
Thank you. The next question today comes from the line of Joe Pantginis from H.C. Wainwright. Please go ahead. Your line is now open.

Joe Pantginis – H.C. Wainwright
Hey, guys, thanks for taking the questions. So, just looking at some of the internal workings of the company and the decisions that you're making. I've been covering you guys for a while. So, now I've

also been referring to sort of BC and AC, Before Cattle and After Cattle. But I guess I wanted to get into the continuum of that decision where, you know, obviously, you needed that potential capacity as RUCONEST® was looking to expand into, you know, pre-eclampsia and AKI, so I'm just wondering, what percentage of your decision factored into sort of the projected needs for RUCONEST® in HAE, with regard, you know, versus, your ability to expand your current rabbit populations for any other needs?

Sijmen de Vries, MD – Chief Executive Officer
Yeah, yeah. Thanks, Joe. So, the, the answer to that, is that there is more than sufficient production capacity, manufacturing capacity in the rabbit platform to serve Hereditary Angioedema. And even, you know, has significant growth possibilities. It is a very flexible system, it takes a while to upscale, but it is a very flexible system. And it has a very flexible manufacturing process. It takes also as a complex manufacturing system, but it is really, you know, has the capability and capacity to actually, you know, deliver a lot more products than we currently deliver. So, if we were to get a significant increase in market share in Hereditary Angioedema, we could actually master that.

Joe Pantginis – H.C. Wainwright
That's great. And then just curiosity with cattle, is there any potential here to monetize the platform that you already have in place?

Sijmen de Vries, MD – Chief Executive Officer
No, we unfortunately, we came to the conclusion that that's there's no significant possibility to actually monetize that. And therefore, we have halted all the activities there. I said, it's a different product.

Joe Pantginis – H.C. Wainwright
Yep. Absolutely. And I guess for your own, you know, obviously, you said, profits might be impacted further based on further investments in leniolisib. So, I'm just curious how much of that is, you know, the new indications that you'll give visibility on for the second half of this year versus, you know, where do you stand with regard to right sizing, the marketing and sales costs and investments that you still might have to do?

Jeroen Wakkerman – Chief Financial Officer
Yeah, exactly. We expect that the marketing and sales costs for leniolisib will further increase in 2023. And that's just to support the launch. In the EU, and in the U.S., obviously, on the lifecycle management, we hope to start with a clinical trial, for example, by the end of this year, but it will depend on the design of the trial, how much money we need to put into that and probably for 2023, that impact will be fairly limited. Because if it happens, it would be towards the end of this year anyway. So, the impact of that would be more in 2024. Then in 2023, that we foresee an increase again, in the marketing and sales cost in for leniolisib.

Joe Pantginis – H.C. Wainwright
Got it.

Sijmen de Vries, MD – Chief Executive Officer
Thanks.

Operator:
Thank you. The next question today comes from the line of Hartaj Singh from Oppenheimer. Please go ahead, your line is now open.

Hartaj Singh – Oppenheimer & Co.
Great, thank you. And thanks for the questions. Really nice update, we missed you all at our healthcare conference, but glad to be hearing your voices on the phone today. So, you know, maybe just talk a little bit about the 500 patients as a question before, I just want to build on that a little bit. You've estimated about 1500 patients as your market opportunity. You've already identified 500. You know, how do you think, Sijmen and Anurag, off the overall opportunity sort of, you know, of the prevalence of patients? I mean, do you think that 1500 is now a reasonable figure, or do you think it could be larger? And I just had a question on a follow up question.

Anurag Relan, MD – Chief Medical Officer
So, we when we look at the prevalence, and we have good data, for example, in some European countries where if we take France, for instance, where there's already 60 patients identified in a country, that's a population that's about 60 million, so we know the minimum prevalence, again, really without our involvement is, and without a therapy being available, is about one per million. So, we've conservatively estimated about one to two per million in terms of the prevalence, and that's where that 1500 number comes from. Now, as we've been out there talking about the condition, obviously, we're finding more and more patients, including in places like France and across Europe, as well as in the U.S. So, that number we expect to continue to increase. I think a big driver, also of diagnosis, though, is the availability of a potential therapy, a targeted therapy. So, I think, as you know, and hopefully we can have a therapy available for these patients soon. But once such a therapy is available, I think that will drive even further diagnosis. But I think for right now with the estimates that we're providing in terms of the prevalence, but certainly, you know, I don't think it would surprise any of us if the numbers were significantly higher.

Hartaj Singh – Oppenheimer & Co.
Yeah, that makes sense, just from being at ASH and talking to physicians and whatnot. That makes sense. Now, I've got to ask the obligatory regulatory question. I know, you're very close to the approval, but just where are you in terms of, you know, any FDA audits or facility inspections? And, you know, have you already had the labelling discussions? And thanks, for taking the questions.

Anurag Relan, MD – Chief Medical Officer
Sure. So, I can't comment on any specifics, other than to say we're engaged in regular contact with the FDA and that contact includes the routine types of things, including inspections, audits, as well as labeling discussions that have, that are occurring.

Hartaj Singh – Oppenheimer & Co.
Great. Thank you, everyone. Good luck, and we'll talk soon.

Operator:
Thank you. Thank you. As a reminder, if you would like to ask a question, please press star followed by one on your telephone keypad. The next question today comes from the line of Christian Glennie from Stifel. Please go ahead, your line is now open.

Christian Glennie - Stifel
Hi, good afternoon, guys. Thanks for taking the question. questions. First question on, start with RUCONEST® just to get an idea about 3 percent growth last year in the U.S. the price versus the volume mix in terms of what was driving that? And what are your expectations for 2023?

Sijmen de Vries, MD – Chief Executive Officer
Yeah, yeah, we stated that we took a price increase below the CPI, that's our normal modus operandi over there and has been our normal modus operandi over the years. So, I think the price, the price increase, of course, is the biggest driver of this growth. So, you can say that the underlying volume growth is more or less now flat to slightly, maybe going up or down. And there's some quarterly fluctuations there as well. But I think that's how you should see that. So, it means that RUCONEST® continues to basically be prescribed by a wider audience of physicians. We think that's important. As I was saying, in my earlier part of the presentation, also about more users, more patients and more prescribers, reflecting the fact that there is a continued need for this product, in terms of especially the breakthrough attacks that continue to occur under all the prophylactic treatments that are available in the market. And yes, some of them have improved significantly from the past, but no, patients will always need and always have acute treatment at hand to be able to treat the unexpected breakthrough attack. Do not forget this is a stress related disease. And people can be very nicely surprised by breakthrough attacks.

Christian Glennie - Stifel
Thanks, and then on leniolisib, a couple here. So, just on the 500 patients, you've already about 25 percent under 12.

Anurag Relan, MD – Chief Medical Officer
Yes.

Christian Glennie - Stifel
What's the rough sub split of the 500 in terms of the U.S. and Europe?

Sijmen de Vries, MD – Chief Executive Officer
Anurag, would you like to comment on that?

Christian Glennie - Stifel
I would take that one. So, I think there are about equally distributed now we have a starting gun. So, I will also comment that a lot of the work that was done in finding patients was actually initiated in Europe through this group called the European Society for Immune Deficiencies. So, they have done a lot of the work. And in the U.S., there wasn't such a coordinated effort. So, we're a little bit behind in terms of the process. But we're quickly catching up, I think, in the U.S. in terms of disease state education and finding patients.

Sijmen de Vries, MD – Chief Executive Officer
So, to say to say that European add stock right on this whole thing. Exactly. But we're getting we're getting in the U.S.

Christian Glennie - Stifel
Sorry, but just to clarify things, is the 500 just European and the U.S. - I think it included some other markets, maybe, or not?

Anurag Relan, MD – Chief Medical Officer
No, it does include other markets as well. I was saying that amongst the, if we look just at the U.S. and Europe alone, they are about an equal number.

Christian Glennie - Stifel
Okay, and then I'm on the EMA side, obviously, you had the initial shift from accelerated to standard review. The way you described at the time was obviously further data from the open label extension. Is that, you know, subsequent interaction with the AMA, is that still the case? I mean, there's anything additional thrown out there or has there's been no change there?

Anurag Relan, MD – Chief Medical Officer
We were collecting that additional year of data intend to provide it to EMA in our responses. And we're still expecting an opinion from the CHMP in the second half of this year.

Christian Glennie - Stifel
And finally, if I may, in terms of thinking about, you know, a bit of on the modeling side, I mean, obviously the nature of agreement with Novartis is probably confidential but an idea of the potential milestones that might be applicable to Novartis on FDA approval, and to what extent that might actually be offset by them exercising the option on the priority review voucher that they should get - just any insight you can give us there would be helpful.

Sijmen de Vries, MD – Chief Executive Officer
Yeah, happy to do that. And give you some guidance. I think, for modeling purposes, it's probably a pretty neutral operation.

Christian Glennie - Stifel
Okay, so the PRV offsets the milestone, yeah. Okay.

Sijmen de Vries, MD – Chief Executive Officer
Along those lines. Thank you. Okay.

Operator:
Thank you. There were no additional questions waiting at this time. So, I'd like to pass the conference back over to Sijmen de Vries for any closing remarks. Please go ahead.

Sijmen de Vries, MD – Chief Executive Officer
Thank you very much. Yes, gentlemen, as we were referring to, we had a very good year 2022, we laid a very good base for transferring our company from the one product, one geography company into two products, multiple geography company, we believe that leniolisib has a very significant commercial potential, significantly larger than the RUCONEST® franchise. And, of course, we're very proud of what we have achieved and continue to achieve with requests, which is of course, a very strong supporter and foundation and cashflow generator going forward. And we believe also that the high hurdle to enter the complex manufacturing of the recombinant C1-INH esterase inhibitor, by means of our transgenic platform will therefore mean that there will be for the significant period going forward. RUCONEST® will continue to create those generate those cash flows, that enable us to invest in all these plans, including leniolisib secondary indications, and also in-licensing of additional assets, to actually start launching products on a very regular basis going forward. Because the other nice thing is we are having a very nice, scalable commercialization operations on

both sides of the ocean. And therefore, we can easily handle additional assets for commercialization over the coming years.

So, we look forward to catching up with you later in the year when we have the next set of results available. And continue to embark on our journey into 2023, this important transformative year for the company. Thank you very much for attending this conference. And like I said, we look forward to updating you on the next occasion. Goodbye.

[end of transcript]