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PRESENTATION

Holly Manning - *Agios Pharmaceuticals, Inc. - Director of IR*

(technical difficulty) (Operator Instructions) And with that, Jackie, I will turn it over to you.

Jacquelyn A. Fouse - *Agios Pharmaceuticals, Inc. - CEO & Director*

Thank you, Holly. Good morning, everybody. Thank you for joining us this morning, as we're very excited to talk to you about how we're taking Agios into a future full of potential, with a lot of opportunities ahead of us as we reimagine our future. We've also this morning announced a transaction that will enable that future, and I'll talk a little bit more about that transaction as well.

Delivering excellence is something that has always been at the core of what we do at Agios, and we've done that over the course of our 12 years of existence, and we intend to continue to do that for a very, very long time as we try to bring the full potential of our science to the patients that we want to serve. Part of delivering excellence also includes being willing to evolve your strategy and your approach as the landscape around new changes. And so the -- one of the things that we're going to talk about today is the evolution of our strategy at Agios as we move forward into what we think is a very bright future.

Having trouble advancing the slides. Is there a trick to advancing the slides? Guys, sorry.

Holly Manning - *Agios Pharmaceuticals, Inc. - Director of IR*

I'd just want to make sure you're clicked into PowerPoint and not accidentally in the Webex?

Jacquelyn A. Fouse - *Agios Pharmaceuticals, Inc. - CEO & Director*

Here we go. So the first -- sorry about that. The first slide has some information for investors related to our transaction that we announced with Servier this morning.

The next slide has our forward-looking statements. Now, what has not changed with Agios? What's not ever going to change at Agios? As always, we are driven by a sense of urgency to bring truly transformative therapies to helping patients. We have done that by bringing the biology of IDH inhibition to cancer patients over the course of our 12 years of existence. Along the way, that same scientific platform in cellular metabolism has also brought forward the elucidation of the biology around PK activation and PKR activation within that. We've been studying that mechanism in our company for -- in humans for around 6 years. And our intent on a go-forward basis is to reach as many patients as we can with our differentiated science, with focus in genetically defined diseases as we take things forward to benefit patients like Tamara, who you see on the screen here, who has pyruvate kinase deficiency.

We're at an inflection point as a company. We have delivered differentiated therapies in the past to IDH mutant cancer patients, and we've continued to develop our science and see the evolution of our pipeline, both our clinical development as well as our research pipeline. And today, we are making the decision to move forward with our strategy with a singular focus on genetically defined diseases because we think that we see tremendous potential in that area and an opportunity to reach even more patients on a go-forward basis than we have in the past, with a relatively greater differentiated profile for the therapies that we're going to bring forward for those patients.

In order to enable this strategy, we also have announced that we are engaging in a transaction to divest our oncology assets to Servier, a global French pharmaceutical company. And in their hands, we believe that they will be able to take those assets forward and continue to maximize the value for patients from those assets. While today, we were able to capture terrific value for those assets and then reinvest that in our company as well as return some funds to shareholders and thoughtfully pursue capital markets independence as we've rightsized both the capital structure and the cost structure for Agios in line with where we're going in the future.

We've had a lot of developments over the course of the last year that give us great confidence in our genetically defined disease research capabilities and our pipeline. And as we evaluated the promise of our portfolio for both delivering great therapies for patients as well as allowing us to create relatively more value for shareholders over time. We came to the conclusion that the right thing to do is to focus singularly on these genetically defined diseases, including rare genetic diseases under that umbrella, and we'll talk a little bit more about that pipeline in some of the untapped potential that we think that we have, both in our PK activation platform as well as other mechanisms that we have coming out of our research team.

Don't get us wrong, we love our oncology assets. We think that we have terrific assets. The landscape in oncology has evolved over the last 12 years since we were founded as a company, and we think the best solution for the ongoing support of those assets, taking those assets to benefit the most patients possible, is for us to place those assets in the hand of a company who is going to take them forward, and we'll be able to singularly focus on genetically defined diseases where we think we can make a relatively brighter impact.

The deal that we announced with Servier today is allowing us today, capture the full value of our oncology portfolio and enable our future strategic focus and shift for Agios. It includes cash consideration of up to \$2 billion, of which \$1.8 billion is upfront cash. Then we have a \$200 million milestone payment -- potential of regulatory approval of vorasidenib. We also have rights to 2 sets of royalty streams, one on TIBSOVO and one on vorasidenib. So we continue to participate in the success of our oncology assets as they go forward.

Importantly, we are planning to return at least \$1.2 billion of that \$1.8 billion of upfront cash to our shareholders, most likely in the form of share repurchases. And with cash that we have on our balance sheet and the remaining proceeds, we can achieve capital markets independence to fund our company through the next wave of our major catalysts allows us potentially to expand our genetically defined disease portfolio efforts and takes us to cash profitability -- cash flow positivity in 2025.

This has been a very deliberate process for us. We've done this from a position of strength. I think all companies are constantly evaluating their strategy and their portfolio of assets. We have been (inaudible) over the course of 2020 as we saw a positive evolution in terms of the clinical data supporting our lead product, mitapivat, in a genetically defined disease area as well as the evolution of our research efforts and where we think we can take our portfolio in genetically defined diseases. We become even more confident in the value creation potential of those assets on a go-forward basis, and the need to focus so that we can bring our best efforts to those, be first, move fast and be the best across the indications that we want to bring forward in this area. To enable that strategy, we ran a broad process to evaluate the options for our oncology assets and that culminated in the announcement of the deal that we have with Servier that we have brought forward today.

We believe that the reimagined Agios of the future represents a very compelling story for our patients, for our employees, for the opportunity to bring our science forward in truly differentiated fashion in genetically defined diseases, and we think it represents a compelling investment opportunity for all the reasons that I've talked about up to this point in the presentation.

We're very excited about our near-term catalysts and all of the things that we've seen in terms of developments with mitapivat and its potential to play across a variety of hemolytic anemias. And then that has evolved over the course of 2020, and many of you have followed the evolution of

our data over time, including the recent announcement of the positive results from the ACTIVATE non-transfusion-dependent pyruvate kinase deficiency Phase III trial that will enable filing for that indication in 2021.

And we expect to include in that filing the results from our ACTIVATE-T transfusion-dependent patient population in pyruvate kinase deficiency that we expect to have in the first quarter of 2021 as well. We're also initiating pivotal development in mitapivat in thalassemia and sickle cell disease. You've heard about the thalassemia pivotal program. You will hear more about the sickle cell disease program. So all the things that are listed on this slide in the yellow/orange color are near-term catalysts for us as we're moving these programs forward, including our next-generation PKR activator 946 that's being studied in healthy volunteers.

When we look at 2025 and beyond, now with the shift in strategic focus and the enabling transaction that we're undertaking with our oncology assets, in 2025, and you'll remember that we talked about our vision at the beginning of this year for 2025. And that was before we had this evolving clinical dataset for mitapivat and before seeing how our genetically defined disease research efforts have been evolving.

Now when we look forward to 2025 and beyond with this shift, what we can tell you today is we expect mitapivat to be approved in 3 indications across hemolytic anemias. We also expect to have a broad pipeline with at least 5 compounds and at least the potential for treating 10 indications. The prior vision, as you may remember, included 6 compounds in clinical development with -- and at least 8 indications. You can now see the potential that we see in genetically defined diseases only and why so we're excited -- why we're so excited about the future and the focus on this.

We continue to expect a robust productivity out of our research team. And as we have said before, we're continuing to see ourselves as being cash flow positive in 2025. And now with the transaction we've announced, this morning, we're capital markets independent to that point in time.

I do want to take just a couple of minutes to talk a little bit about our legacy as a company and what we've built over the last 12 years. The first thing I want to do is thank every Agios employee who is with us today, every person who's been with us over the course of the 12-year journey for Agios because that -- all of you have contributed to building the company that we are in the fortunate position of being able to look at today and decide where we think the greatest potential for our science and patients is on a go-forward basis in the company that also is moving toward a sustainable business model to deliver long-term value for our shareholders. Every one of our employees has contributed to that.

This is a big announcement today for our company and our people. It's emotional for our teams and so I want to congratulate them and recognize the legacy of everybody who's contributed to Agios.

On this slide, we have highlighted some of our past achievements. I don't need to spend too much time on those, other than just to -- just to remind all of you that the things that have made Agios great are attributes that we retain within the company as we take it forward into the next wave of success in the coming decade. And that includes our core expertise in cancer metabolism and what we've learned about the treatment of genetically defined diseases over the course of our history in elucidating the biology of cancer metabolism and the potential for therapies coming from those roots in cancer metabolism to deliver great therapies for patients.

These are some of the accomplishments that our team has produced over 12 years. We're very proud of having brought IDHIFA and TIBSOVO to the treatment of IDH mutant cancers, and that's always going to be something that's part of our legacy and something that we can be very proud of. We think that where we're going today, with the strategic focus and the enabling of that strategy with the transaction that we've announced with Servier is going to allow us to accelerate the impact that we can have for patients and the value that we can create also for our shareholders.

When I think about how things are coming together to make me and all of us at Agios very excited about our future, as excited as we are -- have ever been. The intersection now of the potential of the science of cellular mechanism that's such a central part of our heritage and our scientific competency. We're clear leaders in this area. The intersection of that and how it has evolved over time with the insights that we now have in genetically defined diseases, combines to make for a very powerful position for Agios -- a position that we think is unique and is going to allow us to bring a differentiated proposition to the treatment of these diseases as we take the company forward. We have been the pioneers in PKR activation for quite some time now. We have a differentiating leadership role in this area.

We have been in the clinic, studying PKR activation for approximately of 6 years. We've already generated a lot of productivity across the different areas that you see on the slide here. And we've contributed to a number of firsts related to patient advocacy, related to interactions with the physicians who treat hemolytic anemias, and we've produced the first positive Phase III trial readout for pyruvate kinase deficiency and expect to have an approval of the first approved product for the treatment of that rare genetic disease. We see a lot of potential in PKR activation on a go-forward basis, and PK activation and other things coming out of our research. So we're already differentiating leaders in this area, and we're going to continue to lead and be the best and the fastest in this area.

What you see now is how we've evolved our clinical development strategy as well to run broader clinical programs to support molecules that we believe in. This is the pipeline overview for mitapivat, our lead pyruvate kinase-R activator. This is a drug that we believe easily has blockbuster potential across a range of hemolytic anemias. You're familiar with some of these. When you put it all together on one page, it's a very exciting story and an anchor product for our genetically defined disease platform that gives us a potential to have a peak revenue blockbuster product with our first drug that we're going to bring to market for the first approval for pyruvate kinase deficiency starting in 2022. And then the opportunity with label expansions over time to significantly increase the impact that we have on a greater number of patients with this mechanism.

But we're not only a mitapivat story. We love mitapivat. Mitapivat's going to be great. It's going to be an anchor in our platform, and we like what we see for that drug across pyruvate kinase deficiency, thalassemia, where we're the first company to generate clinical data for alpha thalassemia patients, and we like what we see for sickle cell disease, a complex disease that needs more treatment options. But we have a lot more going on. I mentioned earlier, we have 946 in healthy volunteers. On the right side of this slide, at least it's on my right, you can see a variety of indications that we think the drugs and the PK activation mechanism can play in. We have our PKR activators.

We have even more of those in the works behind 946. And we have others in the PK activation arena that go from PKR activation to PKM2. Again, you see the indications on the sides, and we've included patient -- estimated patient numbers for some of those. As we take things forward, we're going to be looking at those and thinking through the opportunities and prioritizing how we take some -- take these programs forward, but we have an opportunity to move very quickly with 2 PKR activators that are already in humans to do proof-of-concept work to see where we might be able to move fast in some of these other indications.

And over time, we'll be sharing more data with you, both preclinical data that supports the profile of these drugs as well as the ongoing evolution of our clinical data. We also have other mechanisms moving through our research platform and a very productive team pushing these forward with what we think can be best-in-class and first-in-class mechanisms to treat the indications that you see down there in green. The 2 mechanisms we've highlighted here include PAH, where we soon have a development candidate coming along for phenylketonuria, PKU, and we're also moving forward a novel mechanism called BCAT-II. And over time, Bruce is going to be more than happy to talk with you about how he sees the potential here. So terrific anchor product in mitapivat, great pipeline coming along behind it.

So we've seen the evolution of our portfolio. We're taking deliberate steps in order to be able to realize the full potential that we think we have here and deliver that for patients first, our employees and our shareholders. So the announcement that we're making today regarding the focus and our new strategy on a go-forward basis on genetically defined diseases, we think is absolutely the best way for us to reach more patients and be truly differentiated in the therapeutic areas that we are going to serve.

The transaction with Servier is a transaction that enables that while placing our oncology assets in the hands of a company that I think will absolutely do them justice and continue to do great things for patients with those assets.

The Agios of tomorrow is going to continue to leverage the core values and capabilities that have made us successful to this point. Some of those are listed on this slide. By bringing those, singularly focused on delivering terrific treatments for patients with genetically defined diseases, we think that we're going to create differentiated therapies for patients and do great things for our shareholders and all of our constituents. And some of those aspirations are listed on the right side of the slide here.

So we're extremely excited about where we're going today. The 2 things have come together, 3 key messages for you. We've made a strategic decision to accelerate and expand the difference that we can make for patients with genetically defined diseases by singularly focusing on that area. We believe we've captured full value and monetized that value today for our shareholders and in support of our business model, through the

transaction that we're undertaking with Servier. And we're going to use this opportunity to realign both our capital structure and our company footprint so that we're set up extremely well to deliver on the promise of tomorrow that our science holds for patients with genetically defined diseases.

So again, I want to thank all of our employees at Agios and everybody who's been supportive over the last 12 years for making us successful putting us where we are today, and we're extremely excited about where we're going in the future. We hope that you get excited about it as well and join us on that journey. So thank you very much, and I'm going to stop and let Holly start emceeding the Q&A. Thank you.

QUESTIONS AND ANSWERS

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

(Operator Instructions) So I will start with a question from Alethia Young at Cantor. "The value of this deal is almost the entire market cap, so do you think this indicates that the oncology platform was being undervalued or that that mitapivat was being undervalued?" And then as a follow-up, "Why is now the right time for this transaction?"

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

So let me take a stab at that. I think that it is -- I think all of it may have been undervalued from my perspective. It seems like there's been some challenges maybe with respect to trying to figure out where to best place of value, in terms of the intrinsic value of the company today, in line with the future opportunities associated with any of our assets.

And that ties into the second part of the question, which is why do this now? We remain in a position of strength. We could have continued to do what we're doing. We think we have terrific assets. At the same time, it -- we see incrementally -- significantly incremental relative value creation potential in the future coming out of our genetically defined disease efforts as compared to our oncology efforts. The landscape has changed over time in oncology. And so we -- when we think about how to focus our efforts on a go-forward basis, we think we're going to create relatively more value for both patients and for our shareholders with genetically defined diseases. And we feel like we've captured -- to the point about our intrinsic value as according to the stock market today, we think we've captured the full value on a risk-adjusted basis today and have in our hands a transaction that gives us a significant amount of cash upfront. So we can strike the right balance between supporting our future strategy and returning some funds to shareholders. So I think the focus on GDD is going to allow investors and analysts to really dig into those assets and try to assess what your views are on the full potential of those. We think they're underappreciated today.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

Great. Next question comes from Anupam Rama of JPMorgan. "When should we expect to hear more about the internal GDD pipeline? What are your thoughts on expanding beyond PKR?"

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

So I think we've got a few things in the works, and I hope, over the course of 2021, that we're going to be able to build out with substance. So we don't want to talk about things too early and make promises that we can't deliver on. But we've been doing a lot of work here. We're seeing a lot of evolution of the science, and I'm more than happy to let Bruce comment as he wishes, but we're going to be gradually unveiling and talking about our programs coming forward in that pipeline as we have substantive data to support that. You're also, over the course of 2021, going to see data updates for the thalassemia Phase II trial for mitapivat. You'll see the ACTIVATE-T top line results in Q1. We'll be filing for mitapivat in PK deficiency. You'll likely see updates on our sickle cell disease program. You'll hear something about 946 as we continue to run that healthy volunteer study. And then as we have data to support our research efforts, we're going to bring that forward as well.

So I intend for our team to create a nice flow of information over the course of 2021 to continue to build that out. We have a lot going on. The transaction today is going to enable us to move even faster on some of these things, potentially go even broader. As I said, we've got 2 compounds in humans now where we can take those and look at other opportunities for those compounds, potentially in other hemolytic anemias, some of which were listed or other indications that were listed on the slide that was included in the deck.

Bruce Car - *Agios Pharmaceuticals, Inc. - Chief Scientific Officer*

Okay. So Jackie, just to add to that, you've already mentioned that we've been studying the PKR mechanism for 6 years in patients now. Well -- so everybody should be aware we've been studying PK activation in detail in our labs for over 12 years now and supporting the study of this in other labs as well. And this has given us a tremendous scope of knowledge for understanding how that we can impact diseases in which PKR activation is important, but also PKM2 and potentially PKL. And a common theme that's underpinning this is a strength that we've built in a computational, synthetic, structural chemistry and biochemistry around allosteric activators and how that parlays then into cellular metabolism. And Jackie did mention an approach that we're working on in phenylketonuria. That's also an allosteric activator. And this is really a unique strength that we've built in this space that we realize -- we can really extend into multiple therapy -- genetically defined disease therapeutic areas.

Jacquelyn A. Fouse - *Agios Pharmaceuticals, Inc. - CEO & Director*

I'll just quickly maybe take the opportunity to remind everybody that when the company was founded in 2008, it was founded on the basis of a scientific platform in cellular metabolism and fully exploiting the science of cellular metabolism to bring it forward to the treatment of serious diseases. The -- one of the first insights that came out of it was related to these IDH mutations and these driver mutations in cancer. And then the company focused appropriately on that, very quickly brought those forward, got them into humans pretty fast in 2013, and then the first product approval in 2017.

It's a terrific, terrific outcome for patients and a very, by industry standards, rapid movement, but the founding of the company was not predicated only on serving cancer patients. It came back to the roots in cellular metabolism and some of the things that Bruce has been talking about. So we've been tuning this for 12 years. And we moved fast with IDH mutant cancers first and appropriately, but along the way, we've been continuing this other work. And now we see terrific opportunity associated with that in the midst of a changing cancer landscape, which over the last decade has evolved with checkpoint inhibitors and IO and cell-based therapies, combinatorial strategies. And this is one of the reasons why we see relatively greater differentiation for what we can bring to patients in genetically defined diseases on a go-forward basis. And that's a long comment and I'll stop now, Holly.

Holly Manning - *Agios Pharmaceuticals, Inc. - Director of IR*

No worries. Next question comes from Kennen MacKay of RBC. "How does this divestiture change the aspirations outlined at the beginning of the year for \$1 billion of revenue by 2025? And can you help us with the SG&A and R&D expense run rate moving forward after this?"

Jacquelyn A. Fouse - *Agios Pharmaceuticals, Inc. - CEO & Director*

So at some point, I'm going to stop talking and maybe let Jonathan talk, but I'll just say, you saw on one of the slides where we have updated the 2025 vision elements that we are able to update today and give you, so you saw that. Clearly, and we said it before, part of the \$1 billion revenue target in 2025 included TIBSOVO revenues. We're also seeing an evolution of the mix, and we talked about that. I think over the last few weeks or couple of months, we're seeing -- as we have more visibility to the potential approval time lines for mitapivat in thalassemia and sickle cell disease. We do have -- we are refining how we think about the mix of what our revenues could look like in 2025, but we're not ready to give you a number yet. We have seen that mix shifting over time, but TIBSOVO was still in there. So unlikely that we hit \$1 billion of revenue in 2025, but we're going to come back at some point with you when we have more visibility to what the mix of indications could look like in 2025 and where we would be in the revenue ramp trajectories.

I think the most exciting -- one of the very exciting things about this is you're going to have mitapivat moving into indications with a greater and greater number of patients and these will be early in the ramp trajectory for indications like thalassemia and sickle cell disease. And we could see those coming in late in that time frame, and then very strong growth post 2025 as those start to ramp up. And we'll see how the product profile evolves based on the totality of the clinical data that we have at that point in time. SG&A, Jonathan, do you want to talk about that?

Jonathan Biller - Agios Pharmaceuticals, Inc. - CFO and Head of Legal & Corporate Affairs

Sure. Thanks, Jackie. So as Jackie mentioned when she walked through the strategy that we're executing here -- and this transaction being a part of it. An important part is making sure that we're rightsizing both the capital structure of the company and also our cost base. So we're in that process. We'll be sharpening pencils, but 2021 will be a year that will be kind of a hybrid year for us because this transaction is likely not to close until sometime in Q2. We'll have some transition service obligations that we'll be providing to Servier, so they can make sure that the oncology business runs smoothly as it transitions over to them, but I think as you're thinking as we move into the end of next year and into 2022, you'll see a very rightsized, focused genetically defined disease business with meaningful (inaudible) be in overall OpEx. And so it will certainly be smaller than our -- where we're ending up on 2020. And I think what's important and what I will guide you to is our belief that this transaction, after the \$1.2 billion of return to shareholders will allow us to still be capital markets independent. So we can get and fund these programs, accelerate the excitement that we're seeing with PK activation and what Bruce was talking about and do that without the need to go back to the equity markets to raise funds and get ourselves to cash flow profitability in 2025.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

Great. So the next question comes from Tyler Van Buren of Piper. It says, "So for how long have you considered selling your oncology assets? And when did the talks with Servier begin? And how long did it take to consummate this transaction?" And sort of as a follow-up, "Why is Servier the best owner or the most qualified to maximize the value?"

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

Why don't I start with Servier and then maybe let Jonathan also come in on the process that we ran. So the first thing that I would say is this is driven by the strategic pivot to focus on genetically defined diseases. And that decision was supported over the course of time in 2020 as we saw data evolve in -- across the 3 indications for mitapivat as well as the productivity of our research team and the potential for the long-term additional compounds to come out of that platform. So strategy first, then the oncology asset sale process second. But with respect to Servier, I think we ended up with a very unique alignment of strategic interests that are complementary across the 2 companies. In Europe, Servier is a pretty well known company. They're now establishing their presence and growing it in the U.S. They have as from 2 or 3 years ago, began to prioritize oncology as a therapeutic area that they want to build out, and they also want to build out their presence in the U.S. They have deep respect for what we've built at Agios on the oncology side of things from both our assets and our people. And so that alignment of our desire to refocus our strategy on genetically defined diseases, their desire to prioritize oncology as well as increase their presence in the U.S. and they are also a company who put forth a very compelling value proposition for us with a significant amount of upfront cash for our assets. And Jonathan, do you want to...

Jonathan Biller - Agios Pharmaceuticals, Inc. - CFO and Head of Legal & Corporate Affairs

Sure. Sure, Jackie. So as Jackie mentioned, as we saw the emergence of the promise of mitapivat across these first few indications, and then the PK activation platform more generally, we already started, and we knew we were going to want to allocate more of our capital to that investment opportunity. So we began exploring different options to create the most value from our oncology assets. And that was a process that included -- as we started, we were very open-minded as to the form of the transaction or transactions that might ultimately evolve from that process. And so as we did that, working with our financial advisers and our internal team, it was a broad process that included, ultimately, I think 17, 18 companies that we had conversations with along the way, exploring how we could best extract the value both for patients going forward and for our company and our shareholders and the deal that evolved, ultimately was this one with Servier. And I think as Jackie noted, in addition to the financial consideration, which we viewed as capturing the full value, the importance of these assets to Servier and the importance of our people to Servier,

I think, was really critical for us because it was pretty clear in a deal like this, there's going to be some element of contingent consideration. And so having it be determined by a company that's fully committed and able to really advance it is really -- and with our people, giving us more confidence that we'll get there, and we'll actually see that potential value. For example, the vorasidenib milestone payment and royalties, which can be a very nice complementary source of cash flow for us going forward. You'll see more information. We're filing a proxy statement, so there'll be a very detailed description narrative of the process as well.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

Great. So the next question comes from Marc Frahm at Cowen. He says, "Press release says Agios will return at least \$1.2 billion to shareholders. What would cause this to increase? And would a similar ratio of the vorasidenib milestone be returned to shareholders if it is earned?"

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

So I think, again, Jonathan is probably going to want to come in and make my answer better because he always does. But the -- so what we're signaling to you today is what we think that we need between the cash that we have in our hand, the cash that we will retain after returning funds to shareholders, to fund our base case plan out to 2025 and allow us to focus, move fast with high quality, even continue to expand that research pipeline. And we've said at least \$1.2 billion because we think that we have tremendous value creation potential with these assets. We also want to reset our capital base. And we want to have -- we have some flexibility to toggle that. So it's going to be partly related to the evolution of our stock price and partly related to some of the other things that's included in your question around receipt of the milestone, how the royalties go, other things we may do with our portfolio if we see opportunities to partner either geographically for delivering the most value to patients globally and for our shareholders, with the potential that our drugs have across the different indications, which have very different mixes in terms of the geographic distribution of the patient population. And some of the indications that you saw on the research pipeline slide might be indications that we would not necessarily lead on ourselves, that we want partner on. So I think this gives us a lot of flexibility, and it's why we're comfortable with saying at least \$1.2 billion return to shareholders.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

Okay. Next question comes from Peter Lawson of Barclays. "When can we expect the second-gen PKR activator, AG-946 to enter the clinic? And when can we expect to see the next data from the Phase III Indigo trial for vorasidenib in glioma and the time line around commercialization?"

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

I think Chris could maybe address that?

Christopher J. Bowden - Agios Pharmaceuticals, Inc. - Chief Medical Officer

Yes. So AG-946 is in the clinic now. We're undergoing with our study in healthy volunteers, with single ascending dose and a multi-ascending dose cohorts underway and plan -- for their plan depending on how dose escalation and safety (inaudible) sickle cell cohort with that. For the INDIGO trial, we haven't guided yet to when we think we will have data. The study is in its early operational phases. And so we can't provide that information, and although we can tell you that the -- even in the phase of the (inaudible) issues that have been encountered with getting studies up and running, and clearly we've seen really good initial accrual of the study. We're very encouraged. And thanks to our team, who've been -- and the investigators and patients, things are moving along there. So hopefully, as that trial continues to accrue and we'll get a better sense of what the accrual kinetics -- stable accrual kinetics look like, we'll be able to guide further there.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

So the next question comes from -- well, we have 2 questions that are similar from George Farmer at BMO and -- sorry, my computer (inaudible). And Andy Berens at Leerink. So they ask, "Can you provide guidance on how this deal affects burn rate going forward? And how should we think about ongoing R&D expense?"

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

I'm looking at Jonathan to see who wants to start. So we had already included in our base case plan, where we talk about having cash runway to the end of 2022, the initiation of the pivotal plans for mitapivat in both thalassemia and sickle cell disease. So this transaction is one of the reasons why we can then go forward with capital markets independence because we'll be able to continue to fund all of those programs in 2023, 2024 and into 2025, the year that we expect to be cash flow positive. And we've also made some assumptions in our plan about the ongoing productivity coming out of our research group and funding the successful movement of molecules into IND and then through the early stages of clinical development. So that is included in our plan.

As Jonathan mentioned, and then maybe I'll stop, we are going to undergo a transition year in 2021, and then a bit of a reset. And I think he said that we expect our expense base, at least on the SG&A side, to be lower in 2022 than it is in 2020. And that creates some opportunity to move resources more into research and development, but at the stages that we are with some of these programs and it's including the PKR activators that are already in the clinic, we'll be able to very rapidly move into proof-of-concept trials in humans with those 2 PKR activator molecules for some of these other hemolytic anemias. And there are potentially accelerated paths to approval for some of those rare indications and things like that, and we just need a little bit more time to flesh out the prioritization of those so that we can move the fastest in the areas that hold the greatest opportunity. And I don't know if Bruce wants to comment about some of the things coming out of Research or Jonathan, you want to talk about the expense side of things, but we think everything is kind of lining up to take us in a very clear direction with respect to how we're allocating the resources across the different activities. And maybe Darrin can talk a little bit at some point about the commercial model for the PKD launch as compared to some of the commercial organization that we have today with the PKD approval coming in 2022.

Bruce Car - Agios Pharmaceuticals, Inc. - Chief Scientific Officer

Okay. Just very briefly, adding on to that, Jackie, identifying really considerable scope for expansion of the number of indications that we can hit with PKR alone, and then with PKR and PKM2, either combined or separately, in our preclinical labs we've instituted a variety of studies that are currently ongoing that are really starting to generate some very interesting results. So that will flow into the potential indications that we could have in hematologic and other indications in this coming year and subsequent years. And of course, if there is additional investment, I'd be very welcome to what we could do then to accelerate our broader portfolio of other inborn errors of metabolism and genetically defined disease approaches, of course.

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

And the transaction enables us moving quickly on those opportunities as we see them in accommodating that investment. Darrin, do you want to talk about the commercial model just a little bit or...

Darrin Miles - Agios Pharmaceuticals, Inc. - Senior VP of U.S. Commercial & Global Marketing

Sure, sure. So I think as we've shared previously, the -- we intend to have a small field team on the ground by the middle of this year, about a little more than half the size of the oncology sales team if you recall, we're -- we were spending a fair amount of time prior to the approval focused on conventional market development activities, but specifically on physician profiling, identification and patient identification where possible. So we can further understand the true prevalence of the disease across the major markets. So -- and also remind you that these physicians that we're going to be calling on for PKD are also going to be the same physicians who will treat thalassemia and will also treat sickle cell disease. So it will give the community several years of familiarity with mitapivat before they begin to expand the use of mitapivat into new indications.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

So next question comes from Michael Schmidt at Guggenheim. "What will this transaction mean for your cost structure going forward?" I think we kind of covered some of that, but...

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

Yes. I mean, just to summarize it, as Darrin and as Jonathan said, when we make our way through 2021, which will be a transition year and a hybrid year, and we get to 2022, we expect to have the SG&A part of the cost structure in 2022 be lower than it was in 2020 and by a meaningful amount. It's hard to give you an exact figure, but we're very focused on rightsizing the SG&A infrastructure for the opportunities ahead of us. And then evolving that over time as we take the products into additional indications as we move mitapivat from PKD to sickle cell to thalassemia, and we can gate that spend according to the opportunity. So that's one thing. Our base case plan assumes funding of all the pivotal programs that we see ahead of us today as well as our ongoing research efforts and funding an assumed number of successful candidates making it to IND and beyond, and that's where we want to be able to spend the money, but this is the transaction and the pivot in the strategy with the focus on genetically defined diseases is giving us a pretty significant opportunity to re-account -- reallocate our spending to the highest opportunity activities that we can pursue, and the mix of percentage of spend to R&D is going to go up versus percentage of spend in SG&A.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

So maybe a quick follow-up for Michael. "When will you file the next IND and in which disease/area?"

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

So I -- without overstepping my balance here, I think the next likely candidate will be our PAH mechanism candidate for PKU. We've talked about that some. I'm not sure that we're quite yet ready to declare on the timing for that one, but we're moving it as quickly as we can. And I think we'll give you some insight into that early next year when we can be a little bit more accurate about the time line, but suffice it to say that, hopefully, you see excitement in my eyes. I think we're making some great progress in terms of moving that along, and we hope to have some -- a little bit more concrete visibility on that to be able to tell you about it relatively soon.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

Great. And I've got this question from multiple people in multiple different ways, but "How did you come up with the \$1.2 billion as the appropriate amount of return to shareholders? And how will you return that to shareholders, in what form?"

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

Do you want to start, Jonathan, or...

Jonathan Biller - Agios Pharmaceuticals, Inc. - CFO and Head of Legal & Corporate Affairs

Sure, sure. So it's really -- we came at this in -- from many different angles. And ultimately, as Jackie suggested, I think a little bit earlier, it was a balancing act, right? And so it was both -- we want to realign our capital structure, have an outstanding number of shares that are more reflective of the stage of company that we will be now as a focused GDD company. When we close this transaction, we'll be a year-or-so-ish away from our first launch. We'll have 3 relaunches in the course of the 4 years that we're expecting. We wanted to make sure our capital structure and outstanding shares reflected that. And when we think about that historic equity capital that we've raised since our IPO, including that IPO, the public raise has been -- this is about 70%. I think return of that, that amount. And so that was certainly something that we thought about. And then the other side

of the ledger was wanting to retain capital to get us to cash flow positivity in 2025. And as Jackie noted, I think it's important to emphasize, this includes what we see to deliver that 2025 vision that Jackie talked about earlier. So it's the 5 molecules in the clinic for 10-plus indications. That's included, that's assumed in what we're saying we need to get to cash flow profitability. So it's really a balance of those things. That's how we triangulated it. And we feel it's a very meaningful amount. It's 2/3 of the upfront consideration. And so we think that that's quite appropriate. And in terms of how we're going to do it, we certainly feel that share repurchases are the most efficient way to accomplish that capital return, particularly in a case like ours, where we're very confident in the long-term shareholder value creation that we can generate from this focused GDD business. So that's our plan for the manner in which we'll return to capital. Over to you, Jackie, if you want to add anything else?

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

That was perfect.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

Great. Question from Mark Breidenbach of Oppenheimer. "As you expand your rare disease pipeline, will the new programs exclusively come from in-house discovery or are you looking to bolster the pipeline within in-licensing agreement?"

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

I mean I think -- I'm happy to let Bruce jump in as well. I think in the initial wave of things, what you see in terms of what we have going on internally today with wholly owned molecules for which we have the global rights. We've got a tremendous amount of opportunity. So our -- we're going to be prioritizing moving those programs as fast as we can and in the areas that hold the greatest potential for unique differentiation.

At the same time, and we've always done this, we do want to stay open to what's going on in scientific innovation and ideas that are out there. And we will be constantly canvassing that landscape to potentially complement our own efforts on the research side, but everything that we're outlining for you today and the vision and the potential that we see on a go-forward basis is coming out of the productivity that we already see with programs that we have in-house. And so I think that gives you a nice kind of risk/reward profile on a go-forward basis.

Bruce Car - Agios Pharmaceuticals, Inc. - Chief Scientific Officer

Not much to add to that, Jackie, but you saw the pipeline that's ahead of us today. We've got plenty to keep us busy. We also have a very rich and sustainable early validated target pipeline with very early chemistry. But being open to -- and just -- and open to the understanding of the pathogenesis of the complexity of the diseases we're going after that many will take combinatorial approaches and if there are opportunities that help us build the franchise out that we have, we'll certainly take them. So we're keeping our finger on the pulse of that area, for sure.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

And another question that may be pointed to you, Bruce. A follow-up from Tyler. I'd be interested to hear more about the promise of PKM2 mechanism versus PKR and broadly how the indications are separated.

Bruce Car - Agios Pharmaceuticals, Inc. - Chief Scientific Officer

Thanks very much, Tyler. So the mechanisms are related in terms of them both being tetramers where we would act -- where we would stabilize the active tetrameric form of the molecule with the -- with drug candidates that we have. We have solid material in this space of things that we believe have the potential to be drugs and go all the way. The disease indications for PKM2 relate to tissues that have high levels of expression of PKM2 and examples of those might be the retina of the eye, where it's extremely high in regenerating muscle. It's extremely high in the astrocytes

of the brain. It's in a number of other places, the kidney and so on as well. And we're studying in disease models a very specific to understanding the contribution of the expression of PKM2. It's quite possible that there will be diseases that profit from a combination of both PKR and PKM2 or either alone as well.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

Great. Maybe a follow-up from Michael Schmidt. "What percent of current R&D is not oncology?"

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

I'm waiting for Jonathan to see. So the thing that, I think, both of us are hesitating is the mix has been shifting over time, as we've had some of the oncology programs mature and drift then come down a little bit while we've been ramping up, the spend for thalassemia and sickle cell, and as we put those in the plan for the pivotal programs on a go-forward basis. So I don't know how you want to answer that question, Jonathan, exactly. We were going to see some shift anyway towards genetically defined diseases, but...

Jonathan Biller - Agios Pharmaceuticals, Inc. - CFO and Head of Legal & Corporate Affairs

Yes, that's exactly right. I mean, as we -- we'll be starting up if we hadn't -- even if we hadn't done this transaction, we've been starting up 2 Phase III registration-enabling trials next year for thalassemia and sickle cell disease. We're definitely seeing that shift. I mean the way that we've kind of thought about it to give you a little bit more direction is, if you think about where we are this year. And then we've talked about this kind of hybrid bridge year, next year, as we go into 2022, we will have been -- we'll be a rightsized GDD-focused company, but it will reflect over the course of '21, a company that's in growth mode, right? Driving these 2 Phase III registration-enabling trials, getting ready for a launch in PKD. And so I think like at a higher level without getting into too much detail prematurely, we'd probably be looking at an R&D spend in 2022 for our GDD company that's in the 2/3 of the range of where we're spending across both companies today for 2020, and that's reflecting the growth of the portfolio that Bruce and Chris will be managing and driving forward.

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

Okay. Maybe one more follow-up from Alethia. "So how are you thinking about developing earlier stage assets like AG-946 now that the pipeline has narrowed?"

Christopher J. Bowden - Agios Pharmaceuticals, Inc. - Chief Medical Officer

Want me to take that, Jackie?

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

Sure, I'm happy to have someone else talk.

Christopher J. Bowden - Agios Pharmaceuticals, Inc. - Chief Medical Officer

Alethia, it's Chris here. I think that 946, if you think about where we are in the early stages of development of that molecule as we enter into healthy volunteers. And then (inaudible) on the presentation that Jackie walked you through and sort of what Bruce just presented is that we'll first understand the initial pharmacokinetics, PD, early safety data of that molecule. We have a reference frame with mitapivat that we can think about it (inaudible) properties dependent on that initial data. And then what we do in terms of taking it forward, if there would be next steps, if there would have to clear those early hurdles, we would then be to start considering some of those other indications and applications that Bruce and

Jackie have talked about. One thing that we get lots of questions about, is this a replacement for mitapivat in the 3 diseases that's where mitapivat is far advanced and that is entire thalassemia and sickle cell disease, and we've consistently said it's unlikely. The reason why is that mitapivat has 3-plus years of safety data now in adults on pyruvate kinase deficiency stretching out for 4-plus years and beyond. So we really know a lot about the safety profile of that drug. We're getting ready to bring it into kids. And so if -- we have a lot of confidence in it. Now May 946 have a -- so that's where mitapivat is, as we've said multiple times over in the past and emphasizing today (inaudible) pyruvate kinase activation and where 9 -- what the next steps could be for 946, it gives us a lot of different ways to go, but as always, you've really got to see it clear those initial hurdles of safety, pharmacodynamic activation. And that's having the expertise of 6 years in the clinic with mitapivat with PK activators and with an extensive research and preclinical understanding of the target and the diseases that are involved with it and the expansion possibilities that you heard today, we can really think about what the next steps could be for 946, if it passes its initial hurdles in healthy volunteers and potentially a sickle cell cohort.

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

Great. Holly, are you canvassing the landscape?

Holly Manning - Agios Pharmaceuticals, Inc. - Director of IR

I think we've answered pretty much all of the questions in here. So I will turn it over to you to close this out.

Jacquelyn A. Fouse - Agios Pharmaceuticals, Inc. - CEO & Director

All right. So thank you very much for hopping on the call with us today at short notice. We're really excited about where we're going. I hope you both hear that in our voices, see it in our eyes and hopefully, the slide deck, which for anybody who hasn't had time to fully digest it yet, has a lot of information in it. We designed it to serve as a presentation deck for today, but also as a reference document that people can go back to and digest a little bit. So we're excited. We're very grateful for everything that all of our people have done to put us in a position of strength to be able to do this today to take this step with our strategy and execute on the transaction with Servier that's going to enable it. So thank you very much to all of you. Thanks to the team here, and we wish you all a great upcoming holiday break and a terrific start to 2021, and we look forward to following up with any of you who want to follow-up. So thank you, team. Thank you very much.

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