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## CORPORATE PARTICIPANTS

**Brett P. Monia** *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

## CONFERENCE CALL PARTICIPANTS

**Guyn Kim** *BMO Capital Markets Equity Research - Analyst*

## PRESENTATION

**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

Good afternoon, everyone. My name is Do Kim, one of the biotech analysts here at BMO. Our next presentation and fireside chat is with Ionis Pharmaceuticals. And with us today is CEO, Brett Monia. Ionis is clearly one of the leading biotech companies in the RNA targeting antisense therapeutic space. Brett, I want to thank you for joining us today. And perhaps a start is -- for the investors less familiar with therapeutics and biotech, provide us a brief background on the company and the platform of your antisense drug.

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**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

Sure. Happy to, Do. And thanks for the invitation. It's a pleasure to be here. So for those not familiar with Ionis, we are the pioneer of the field of antisense technology, technology that we set out to create years ago. And along the way, what we essentially did was create and validate not only the antisense field, but we actually created the sector you just referred to Do as -- referred to as RNA therapeutics with now, we believe we're leading the way in even though many other companies have now entered obviously.

Today, we have 3 marketed products; SPINRAZA, which is a true blockbuster for spinal muscular atrophy; TEGSEDI for hereditary TTR amyloidosis in patients suffering from the polyneuropathy manifestations of that disease; and WAYLIVRA for a ultra-rare disease. In Europe. It's approved for an ultra-rare disease called familial chylomicronemia syndrome or FCS. But that's -- those products are real transformational medicines and breakthroughs. But what's really remarkable is the fact that we -- right behind those, we have 6 Phase III studies right now in progress underway, including a drug using our most advanced chemistry called LICA that's targeting all forms of TTR amyloidosis, not just the polyneuropathy that I referred to earlier.

And APOCIII LICA, also in Phase III for all kinds of triglyceride related disorders. And then we also have Phase III Huntington's disease, a large cardiovascular indication due to a risk factor called (inaudible) and an ALS drug called SOD1. So real rich late-stage pipeline, rich mid-stage pipeline, all of which is setting us up for additional Phase III studies next year.

And with the pipeline so -- as rich as the one we have in mid to late stage, we're projecting actually 10 or more new drug applications for potential approvals to reach market, starting in 2022 through 2025, to add to the 3 that are already on the market.

So the technology is really delivering, and we're expecting a vast increase in the number of new products over the next few years.

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## QUESTIONS AND ANSWERS

**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

And to follow-up on that, the currently approved products and some of the near-term pipeline drugs, it sounds like these antisense drugs specialize in rare diseases and just difficult conditions to treat.

How would you see RNA targeting drugs, their role currently versus what could happen in the future and the overall therapeutic state?

**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

The -- yes, we're -- we believe, and I think the progress being made in RNA therapeutics really justifies my conclusion that the RNA therapeutic space will represent a major sector of the pharmaceutical industry's ability to deliver medicines to patients for a very long time, and it's only going to grow. Today, there are several companies now with marketed products in RNA therapeutics. And I believe that we've only just scratched the surface by far.

I actually think that this will be a sector of the pharma industry's ability to -- and biotech industry's ability to deliver products to market that will be really second to none as large as small molecules and certainly larger than antibodies once it really hits its peak because of the ability to do a few different things. One is to be able to go after undrugable, what's called -- referred to as undrugable targets. So targets that we know cause human diseases but are not approachable with small molecules or antibodies or other means -- through other means. And second, because of the efficiency.

Because these drugs are -- represent a platform, we have the ability to move drugs forward very rapidly because of the similarities from one drug to another. And I think that's reflected by the fact that a company the size of Ionis, which is really just -- with our recent acquisition of Akcea, is about 800 employees. We have a pipeline of 40-plus drugs, including the late-stage drugs I've referred to earlier. So I think we've only just scratched the surface in our RNA therapeutics.

And I think that it will be a dominant mechanism approach for drug discovery in the industry for many years to come.

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**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

Great. And you mentioned your acquisition of Akcea. How does that acquisition fundamentally change your business strategy going forward? For us, it seems like a big move on your part.

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**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

It is a big move, Do. It was a big move, and we acquired -- we completed the acquisition of Akcea, our -- and for those that aren't familiar, Akcea is a -- was a commercial organization that we created, and it was to be and was, for about 4 years, our commercial affiliate. They would take drugs that we developed and they were commercializing -- they were intended to commercialize them. They were commercializing TEGSEDI and WAYLIVRA, and they still are, but now they're owned by Ionis.

When I set out as the new CEO of Ionis in the beginning of the year, I set out my vision, which was to build on the -- all the great progress we've made over the years at Ionis, really building on our excellence in research and drug development.

And what I -- what my vision was, was to build on that and strengthen those areas, but also to add to them by building on our commercial capabilities. And to build out the Ionis-owned pipeline and then to start commercializing our own products under our roof, in addition to the great strategic partnerships we have with so many pharma companies.

And the step to acquire Akcea was just a step to accelerate that whole process. Akcea has tremendous commercial capabilities, expertise, a lot of smart people, a lot of experienced people on the commercial side. And so it was a key step to move this process forward more rapidly. In addition, the drugs that we put into Akcea to commercialize eventually -- as well as the ones that are in there now that are on the market that they are commercializing we believe in, and we wanted full control and full access to all the upside of that pipeline.

And that's another reason to acquire Akcea is to really bring more value to Ionis and it's shareholders based on acquiring the pipeline, not just the commercial capability.

So it was a key step for Ionis, and it's a step that's going forward very well right now.

**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

Fantastic. And that's actually a good segue to the Investor Day that you held yesterday, and you had a particular focus on your wholly-owned programs. Maybe you could provide some of the highlights from that Investor Day and run through your accomplishments that you've had for the year and what the goals are for next year?

**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

Yes. Happy to. So we had our Investor Day yesterday, which is normally in person. Of course, it was remote because of the current pandemic situation. We focused on new areas that we hadn't really did a deep dive into earlier this year. We had a webcast earlier this year in our -- did a deep dive into our neuro franchise, which, I think, is one of the best in the industry as well as our cardiometabolic franchise, we did a deep dive on earlier this year.

Yesterday, we wanted to focus, as you said, Do, on some new things. The Ionis-owned pipeline and particularly how that's shaping up in our own cardiometabolic and neurological disease franchises, the drugs that we own and are in full control of. And second, the progress in those pipelines, the drugs that we're prioritizing. And as part of that presentation, we highlighted the really exciting data for the first time from our angiotensinogen program, a wholly-owned program for Ionis, in which we demonstrated, and we provided an update on the Phase II data, which showed pretty remarkable reductions in blood pressure in patients that were refractory to 2 or 3 medicines.

These are drugs are -- these are patients that are on 2 or 3 other drugs as -- antihypertensive drugs and still couldn't control their blood pressure. And we showed quite an impressive level of blood pressure reduction in those patients. And we also highlighted, in the neuro pipeline, several drugs that are Ionis owned, including our prion program, which, we think, is a very exciting program that has a very rapid path to drug -- to drug approval. And that program is going to -- we're expecting to reach clinical testing next year.

In addition, we highlighted what we just touched on a few minutes ago. The building of our commercial strategy. How we're going about it, where we are in implementing our commercial plans and what we're going to prioritize in the cardiometabolic and neuro franchise. And what we -- we said we're going to prioritize, there is the TTR LICA, the TTR amyloidosis program, our APOCIII program for triglyceride disorders and then the neuro -- wholly-owned neuro pipeline as well as considering other options for our hereditary angioedema drug and our acromegaly drug and our beta-thalassemia drug.

Finally, we highlighted -- well, two other things. One was the technology improvements. Advances we're making across all aspects of our technology, including new routes of delivery, where we discussed the great progress we're making in pulmonary delivery of our antisense drugs. We now have 2 drugs in development for pulmonary diseases. And we had proof-of-concept this year for our lead drug, ENaC for -- which is now in a Phase II study in cystic fibrosis. And then also an update on our oral delivery program, which we're making solid progress on to move -- to potentially achieve commercially viable oral delivery in the future.

And then finally, we did -- you said what the future and what is next year shaping up -- look like, we touched on that. We provided a glimpse. I provided a glimpse and a vision towards the future, including next year. Next year, we're expecting quite a lot of clinical data readouts, including the Phase III readout in our SOD1 ALS program, and 5 or 6 data readouts from our Phase II pipeline as well. And this is all setting us up, like I said earlier, for a really, what I think, is an impressive increase, a vast increase in the number of new products to reach market over the next few years. And we expect our next commercial product to be our SOD1 ALS drug, which is, as I said, due to read out next year.

So a lot of news coming out next year and really setting us up for tremendous growth for years to come.

**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

Great. So let's go down that path, what your near-term growth drivers are, SOD1, you think, may be your next product on the market. Could you go over what disease that tackles? You're currently in partnership with Biogen for that development, perhaps discuss your current collaboration with them? And what your expectations are for that thermal trial?

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**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

SOD1 ALS, our drug -- our lead drug for ALS is targeting a genetic form of ALS due to mutations in the SOD1 gene, really is important for so many reasons, is -- this is of course, important for patients suffering from ALS mutations in SOD1. And this is a particularly rapidly progressing form, very aggressive form of ALS due to mutations in that gene. And there's no treatment options really for -- certainly no disease-modifying treatment options for this disease.

It's important for those patients. It's also important, I think, because it really will shine light on the potential of our other ALS drugs because it's a very, very similar mechanism. We're targeting the root causes of ALS. We have 3 other drugs that are in development for ALS, 2 others that are targeting other independent genetic causes of ALS. I mentioned SOD1. We also have a drug that's going to read out next year, a Phase II readout for mutations in a gene called C9ORF that target ALS. We're also planning to start a registrational study for a third genetic form of ALS targeting FUS mutations in a gene called FUS in ALS. That one is a wholly-owned program that Ionis is controlling. The first 2 I mentioned are with Biogen.

And then we have a fourth drug in development for ALS that's tarting what's referred to as broad ALS, nongenetic forms of ALS, if you will. And that drug is also partnered with Biogen, which is now in a Phase II study in sporadic or broad ALS.

So the SOD1 drug is important on its own right for SOD1 patients, but it's also, I think, will really give us insights and confidence that -- for the entire franchise for ALS that we have, which I think is the leading -- easily the leading franchise for tackling all forms of ALS.

Our Biogen collaboration -- I should also say that we're feeling pretty good about side on ALS because the Phase II data was very encouraging. In our Phase II study that led to this initiation -- rapid initiation of Phase III, we actually saw pretty good evidence that patients were doing better on tofersen -- name of the drug is tofersen for SOD1 ALS. So we're feeling pretty good about the outcome in the study, and we can't wait for the data to read out next year.

Our Biogen collaboration is a strategic partnership in neurological diseases in neuromuscular disease. It's a collaboration that has expanded 3, 4, 5x since we -- since our first partnership, which was focused initially on SPINRAZA. And it's a research and development and commercialization partnership, in which we work very closely on R&D. And then they are our commercial partner for the neurology drugs that enter the pipeline with Biogen. And it's quite a pipeline, in which we're working with them on broad indications like Alzheimer's and Parkinson's and also severe rare diseases like ALS. And neuro developmental diseases like Angelman's disease and many, many other serious neurological diseases.

But in addition, we have the ability to grow our own pipeline independent of Biogen, which we're doing. I mentioned prion before. We also have our own -- and I mentioned FUS-ALS. That's one that we're running. And we also have other drugs in our neurological pipeline that are growing. And we expect the Ionis-owned neuro pipeline to grow rapidly and expand rapidly going forward. It's a top priority for us.

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**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

Wonderful. And I'm sure ALS patients and clinicians are excited to finally have a therapy that could potentially modify the disease and slow down progression. That's great.

Before going into some of your owned -- wholly-owned neuro programs, can we spend some time talking about the Huntington's program with Roche. It's a data set that, I think, a lot of investors are anticipating. It is a disease where, similar to ALS, no real good treatments are out there. Where are we in that program? What can we look forward to?

**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

Yes. But this is another very exciting late-stage type program in our late-stage neurological disease pipeline. We're -- the drug is tominersen and it targets the root cause of Huntington. It blocks the production of mutant Huntington protein in the central nervous system. And we have shown preclinically that when we administer this drug that we can actually reverse disease and prevent progression and even reverse disease progression in models of Huntington's disease. And we've shown preclinically, including in nonimmune primates and now in humans, very importantly, that we can substantially lower the levels of mutant Huntington in the central nervous system as measured by Huntington levels in the CSF that we can measure.

And we've shown this that these reductions are very long-term, sustainable and well within the range that are predicted to show benefit in patients based on preclinical data. This study is -- as I said, is now in late-stage Phase III development. It's -- the name of the study is called Generation HD. It's about 800 Huntington disease patients. The study is fully enrolled. Patients are being treated for 25 months, and we're following the progression using our scale called the Huntington Disease Rating Scale.

And this study has 3 treatment arms. It's placebo. Patients are being treated every 2 months and patients are being treated every 4 months. And again, in both scenarios, we're seeing reductions, and we're projected to get reductions in the Phase III study that are well within the range of efficacy based on preclinical data. This Phase III study is due to read out in 2022, and potentially file in 2022 based on -- depending on the data. Huge opportunity and huge unmet need, as you mentioned, Do, in patients with this genetic form of neurodegenerative disease that afflicts generations after generations of families.

Next year, there's also data coming out from an open-label extension study from the Phase II study that we ran, in which patients are being followed for 15 months, noncontrolled. All patients are on tominersen. And an update on that study will be presented by Roche, our partner, in which they'll be looking -- showing more data on Huntington reductions. We'll also be looking at some clinical endpoints to help set the stage for what we expect -- might expect to see in Phase III the following year, safety and tolerability. And they'll also share some data next year on a natural history study that they initiated 15 months, again, which they're following the patients with Huntington's disease, their progression using similar endpoints as in the open-label extension in the Phase III study.

So you get -- we'll be able to get a sense next year of how patients are doing on tominersen in a uncontrolled 15-month treatment arm as well as in a natural history, in which we're looking at how the disease progresses in these patients over 15 months.

So next year will be very interesting for that. And it sets us up really well for the Phase III results in the following year.

**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

Fantastic. And I sense that there's a level of confidence for antisense to work in these neuro programs. We're talking about genetic diseases, where it's been extremely difficult, if not impossible to get an effective therapy in. What's the basis of this confidence? And how can we use that to see whether your wholly-owned neuro programs have a chance of success in the clinic?

**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

Yes. Our -- when you think about neurological diseases, particularly neurodegenerative diseases, when you really think about the progress that's been made in the industry, it's pretty dismal. It's sad. And when you think about how long we've known about Huntington's disease and ALS and diseases like Alzheimer's disease, and how little progress has been made. Like I said, it's been pretty dismal.

We worked on validating, asking the question, could we use RNA therapeutic strategies for neurodegenerative diseases? And we invested 10 years of research, understanding the medicinal chemistry and optimizing and understanding how to deliver and understanding the pharmacokinetics and safety and pharmacodynamic effects and the durability and so on. And that led to SPINRAZA, which is a blockbuster for the treatment for all

forms of spinomuscular atrophy, which is saving the lives and of babies with SMA and making people with older -- with less severe forms of SMA live better lives.

So it's -- that was the first. And then right behind that, we've now shown, in patients with Huntington's disease, this durable reduction of the root cause of the disease, I mean Huntington, as I referred to earlier. So we're hitting the target that causes the disease. And then I referred to SOD1 ALS before. We were in our Phase II data, was very -- giving us a lot of confidence that this drug is going to help patients. And we also showed in that study that we can knock down the SOD1 mutant protein, the cause of that disease.

So these are 3 programs that are showing -- giving us a lot of confidence clinically. Of course, we have a wealth of preclinical data that I don't -- I won't go into right now for dozens of programs. And then next year, we're going to build on that. We're going to have the SOD1 ALS Phase III data readout. We're going to have the C9ORF ALS data readout from Phase II that I mentioned before. We're going to have an update on the Phase II data in Alzheimer's patients that are treated with our antisense targeting tau, our MAPT program. I mean, this is just going to lend more and more confidence to the platform, our ability to tackle all forms of -- essentially all forms in neurodegenerative diseases.

So it gives us great confidence because every -- all of our clinical studies are delivering on what we wanted them to deliver on so far. So -- and as far as the Ionis-owned neuro pipeline, it's much of the same. We're targeting root causes of diseases. And we're working in areas where there really are no treatment options available, whether it's your leukodystrophies like Alexander's disease or another form of ALS, targeting FUS mutations, or prion disease, a terrible disease that can either be genetically caused or sporadic forms of this protein, prion protein that causes rapid degeneration of the central nervous system in depth.

We've shown, preclinically, that we can really impact these diseases in animal models. And we believe that like we're seeing with SOD1, Huntington and SPINRAZA or SMA, that we should be able to do the same in our own -- for our own drugs, for our own pipeline as well as our partnered programs in neurological diseases.

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**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

And while it sounds like you have a lot going on in the neurology franchise, you also have a completely separate and equally broadly reaching cardiovascular franchise. Can we talk about what is the next area of growth? And there you currently have WAYLIVRA approved. And even though TEGSEDI is a neuro targeting disease, but you are eventually going try to capture the cardio portion of that illness. What should we expect next out of that franchise?

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**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

Absolutely, the biggest contributor from our pipeline are really, what I see is, really substantial growth over the next few years is in neurological diseases and cardiovascular diseases. And cardiovascular is a big one, just like neuro. In cardiovascular today, we have 3 Phase III studies in progress. And if we get a chance to, maybe we could talk about pelacarsen the Lp(a) program, which is really the biggest opportunity.

But for the Ionis-owned -- and that's partnered with Novartis. But for the Ionis-owned pipeline, we have 2 big drivers in the cardiovascular space. One is our treatment for TTR amyloidosis, a follow-on medicine to TEGSEDI. As I said earlier, TEGSEDI is just tackling the polyneuropathy form of a hereditary version of TTR amyloidosis. But the follow-on is targeting the big indication -- the biggest indication, which is the cardiomyopathy indication, which is -- there are -- there is a genetic component to it, but the vast majority of the patients with this disease suffer from cardiomyopathy and eventually, it's a lethal disease. It's a very large end market, and that's a drug that's in Phase III that we're running our TTR LICA drug that's in a Phase III cardiovascular outcome trial.

The other drug that we're running Phase III on, it's really another big value driver that you referred to as our drug that is really outstanding drug that manages triglyceride disorders. We're now in Phase III. These are patients with very high triglycerides that cause severe metabolic diseases, particularly high-risk for pancreatitis, which can be lethal or -- and/or cardiovascular disease due to very high triglycerides over long periods of

time. This drug, another LICA, our most advanced chemistry targets APOCIII, a protein that is a master regulator of triglycerides. We've shown substantial reductions in triglyceride in patients with very high triglycerides in several different clinical trials.

And the familial chylomicronemia syndrome patients, the FCS, which is now in Phase III for patients with triglycerides above 1,000. These are patients with milky white blood due to high triglycerides, and their risk is pancreatitis. But in addition -- and that's an ultra-rare disease, 3,000 to 5,000 patients or so around the world, but in big, big need for a drug.

But the bigger upmarket opportunities are several. One is a disease population that we call sHTG, or severe hypertriglyceridemia patients. These are patients that aren't as high as FCS, but they're high, about 500 or so. And they, too, are at very high-risk of pancreatitis and -- which can be lethal. And this is millions of people in the United States alone. And we're confident that this drug will control triglycerides in all triglyceride disorders, including in this patient population. And we're thinking about starting a Phase III study in that patient population potentially next year in addition to FCS.

And then there's the third population, which is are just patients that have a cardiovascular -- they are at risk for cardiovascular death or morbidity due to mildly high triglycerides, in the 200 to 500 range, if you will. And that's also an opportunity for us, which is even bigger than the sHTG market opportunity. And we're considering how to target that population as well.

So big, big opportunities in the Ionis-owned cardiovascular pipeline in late-stage development in TTR LICA and APOCIII LICA.

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**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

And you also previously talked about hypertension. Is that an opportunity for Ionis to commercialize on its own? Or is it one of those bigger commercialization efforts that you're going to look for a partner to do?

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**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

We're planning to -- yes, we think this is a really good-looking drug right now based on the Phase II data we've generated in patients with refractory hypertension as well as in patients who are controlled on antihypertensive agents. But then we show that we can replace those antihypertensive agents with our drug, AGT-LRx, and we were able to keep them under control. This is a drug we're planning to bring forward through Phase II and then eventually Phase III ourselves. We'll consider a partner at some point if it makes sense and as it makes sense.

Obviously, this is tens of millions of people suffering from refractory hypertension around the globe, and having a partner to maximize the value of a product like this to potentially help us through Phase III, but also commercialization, could make sense at some point. So we're planning on moving this forward ourselves for quite a while now, and we'll decide on what's the best partnering strategy to work with Ionis to maximize the value of the product down the road. But right now, we're going this alone.

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**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

Okay. And throughout our conversation, you talked about LICA drug and the LICA technology. I think that a great advancement in your platform. Maybe we could spend some time on what we could expect next coming, in terms of next-generation technology and your efforts in aerosol and oral forms of your therapies?

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**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

Sure. There's new routes of delivery, like you just referred to, aerosol and oral. And then there's also new LICAs, Do, that I think are worth highlighting, that are opening up new organ systems, such as pancreas and skeletal muscle. And we're getting pretty close, and we're thinking that we might

have a new LICA to open up new organ systems for new -- to tackle new diseases, potentially reaching development next year and we'll touch on that if we have time. You asked about aerosol and oral, aerosol delivery for pulmonary disease is very exciting.

This is a platform or an approach in which we get the drug into the lung, deep into the lung, and we can penetrate and get into cells and show target engagement in the presence or absence of like a thick mucus layer, which can be present in COPD, cystic fibrosis and so on. And we showed this year that we can get very good target reduction of our lead program, ENaC, targeting the epithelial sodium channel in normal volunteers, and this drug now is in cystic fibrosis in a Phase II study due to readout next year. It's also in a Phase II study in COPD chronic bronchitis as well.

And we think that this could turn into -- we referred to it before as cardiovascular and neurological diseases, those are 2 main franchises. Pulmonary could -- has a potential to grow into a third franchise. We have a second drug going into development that will be in clinical testing next year for lung diseases, fibrosis. And we are expecting a third late next year, maybe the following year for lung diseases, IPF.

And so we see this growing as a franchise. And one of the advantages, I forgot to mention before, I was going to say, is that we get the drug not only into the lung, but we also have minimal systemic exposure. So that's a key advantage. You want to get the drug to where you want it to go, and you want to limit the exposure to other organ systems. And we have insignificant levels in the peripheral blood system when we deliver to the lung. So this is an emerging franchise.

As for oral delivery, we're continuing to work on oral delivery. We've made great progress over the last few years with our partner, AstraZeneca, as well as ourselves. We had a bit of a step back, and we talked about it yesterday in that we decided with AstraZeneca to stop the oral Phase I PCSK9 program. But I think that people should appreciate the fact that both companies have been sought enough to give us confidence that, we think, the oral -- commercial vial oral delivery, will be successful in the future with our platform. And that's why both companies are continuing to invest in expanding our research collaboration to optimize oral delivery for the future for all of our drugs in our pipeline that we think would benefit from an oral strategy.

The other reason to do it was because the subcu PCSK9 program is just showing such impressive results. And AstraZeneca is really focusing on getting that drug to Phase III development as rapidly as possible as a potential best-in-class PCSK9 inhibitor of any in the field.

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**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

Even though we've run out of time. I want to pose 1 more question since we had a delay in the start. So you -- Ionis has been able to accomplish so much in pipeline development, primarily because you have partnered your drug and avoided expenses and costs related to late-stage development and commercialization.

Now that you are advancing your wholly-owned products through -- all the way through approval and commercializing on your own, how are you going to balance the investment in your own pipeline and pushing revenue growth? How do you look at that going forward?

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**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

So we are in a very enviable position of having such a strong balance sheet, strong financial position. We've been profitable over the last 4 or 5 years in a row. Our guidance this year is to be net profitable, again, and meaningfully profitable, and we're expecting to hit our guidance this year. We have the advantage of revenue streams from multiple sources. We have revenue streams from our partnerships, which provide revenue in forms of upfront milestone payments and royalties. And our royalties have gotten quite attractive over the years with being well into the 20% range with a number of our key programs for large indications with partners like Pfizer, Novartis and others.

In addition, we have our commercial revenue from drugs like SPINRAZA and TEGSEDI and so on. And we're expecting a vast increase in the number of commercial revenue in the near-term in the next several years as the products I mentioned before, reach market, both the partners as well as our own drugs to reach the market.

So continued financial growth, revenue growth is something we expect to do -- see just from both R&D partner revenue as well as commercial revenue. With that said, we believe in investing as a #1 priority at Ionis over the next couple of years to maximize the value that the technology brings to shareholders, patients, to the company because we think that there's a lot of opportunity for investing in building our Ionis-owned pipeline, building in our -- building up our commercial capabilities to maximize the value of the Ionis-owned pipeline, but also to invest in new technologies that expand the scope of antisense technology.

And eventually, in the future, also diversify the types of platforms we have at Ionis that complement antisense, but do things different than antisense to deliver even new types of drugs for the long term. So profitability is something that we've done very well over the last few years. It's not the #1 priority over the next couple of years because, I think, we're going to have massive profitability for -- once all these drugs start hitting the market over the next few years. I think we'll still have a good shot at profitability and revenue growth, for sure, revenue growth, but we are going to be investing in building our commercial and Ionis-owned pipelines as well as technology going forward to really bring what we think is the maximum value to the company.

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**Guyn Kim** - *BMO Capital Markets Equity Research - Analyst*

Wonderful. Brett, thank you so much for joining us today. Congrats on all the progress. And I think Ionis has a bright future. I appreciate your time here.

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**Brett P. Monia** - *Ionis Pharmaceuticals, Inc. - Founder, CEO & Director*

Thanks, Do. It was a pleasure.

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