Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated presents at UBS Biopharma Conference 2023

Thursday, November 9, 2023 12:00 PM

Event Participants

Analysts 1
Colin Bristow

Executives 2
Charles Wagner, David Altshuler

Colin Bristow Analyst

Good afternoon, and welcome to the UBS Biopharma Conference. I'm Colin Bristow, one of the biotech analyst here. It's my pleasure to have Vertex Pharmaceuticals with us here today. On behalf of the company, we have Charlie Wagner, CFO; and David Altshuler, the Chief Scientific Officer. So thank you both for your time today.

Colin Bristow Analyst

Maybe we can just kick off with cystic fibrosis, obviously, a sort of major franchise for you guys, continue to show impressive quarter-on-quarter growth. But from an investor perspective, it feels that this is well understood. It's pretty well modeled. As you look at consensus estimates and you speak to investors, what do you think is underappreciated about this opportunity, if anything.

Charles Wagner Executive

Yes, Colin, thanks for the question. Maybe I'll start and just a recap for folks. We just increased guidance for the year in CF to an approximate estimate of $9.85 billion for the year. Importantly, that gets us to 10% growth, and it's our ninth consecutive year of at least double-digit growth. So continued strong growth there.

Yes, I think it's -- I think the trajectory in CF is fairly well understood. I think the thing that we need to continue to remind people is that there is further growth from here. If you look at what's driving the growth this year, it's annualization of patients who came on medicine last year in markets where we had new reimbursement. It's younger age groups. We have the

approval for TRIKAFTA in 2 to 5 this year.

We're expecting approval in 2 to 5 in the U.K. and Europe later this year.

And importantly, we continue to increase our estimate of the number of patients worldwide with CF. Patients are living longer. The patient population is growing. And so all of those factors, more patients, younger age groups, new reimbursements driven the growth to date and will continue to drive the growth into 2024. And I think the other thing I would point out, obviously, we're awaiting data on the Vanza triple.

That represents an opportunity for patients. It also represents an opportunity, not only for patients to switch to a better medicine, but also for patients who previously discontinued one of our medicines. There are roughly 6,000 or so of those folks who would have the opportunity to come back on a new medicine. And then lastly, I'm sure we'll touch on it.

We're moving forward in the clinic with our mRNA therapy, which would benefit the 5,000 or so patients who don't produce a protein. So what we see from here is continued attractive growth in CF. Even though we've put up great numbers for a long time, there's more growth to go. And I hope that that's fully understood.

Colin Bristow Analyst

Great. A common question we get from investors, especially as they sort of -- you're trying to understand or handicap the growth for CF is just what's the exclusivity period? And as the older products lose exclusivity, how does that impact the more novel agents like TRIKAFTA, et cetera. So help us think through that and some of the time lines.

Charles Wagner Executive

Yes. I mean for -- I guess it's important to note, TRIKAFTA is such a fantastic medicine that in geographies where it's approved for -- down to younger age groups, the vast majority of patients switch as soon as they can. And you can see it in the numbers, obviously, more than 90% of the revenues are coming from TRIKAFTA at this point. And TRIKAFTA IP goes out to 2037. So we're not in a situation.

We're worried about loss of exclusivity like other companies necessarily. The franchise is growing, is durable, is long-lasting. And then with Vanza, we'd have the opportunity to take IP out even further. We haven't commented on that specifically. So I think we're just in a fantastic position overall with the portfolio.

David Altshuler Executive

Maybe the other thing to add to that from a science and medical point of view is that remember that there is no other medicine that's approved than -- other than TRIKAFTA for people who have only one copy of Delta F, which is about half of the population. And then the people who have 2 copies of the Delta F, have about a 4% increase in FEV1 with SYMDEKO but a 14% FEV1 difference, which is night and day with TRIKAFTA. So between half the population, not having another approved medicine and the other half having just a totally transformative difference between TRIKAFTA and the other medicines. If the other medicines, some of them have earlier patent exclusivity, no one's going to take those

medicines instead.

Colin Bristow Analyst

You touched on the Vanza triple already. Can you just, one, remind us on the timing of when we should expect to see the top line? And two, what should we expect to get in the top line?

David Altshuler Executive

Sure. It's a disclosure. It will be early '24, when we'll have that completed and we've obviously analyze the data, and then we'll disclose it. And the top line, as we've said before, we're very confident that Vanza should have higher levels of CFTR function in patients for 2 reasons. One, using our human bronchial epithelial cell assay in the laboratory, which has quantitatively translated through a dozen different molecules in many clinical trials, Vanza has higher levels of CFTR function at clinically relevant concentrations than does TRIKAFTA.

That's the preclinical data.

The clinical data is we did Phase II studies with Vanza. We did separate Phase II studies with TRIKAFTA. We did the correct comparison, which really requires doing PK/PD analysis because there are different patients, different nonidentical PK, you can't just compare the raw numbers. You have to do the right PK/PD. We see that Vanza has higher efficacy than TRIKAFTA when we do it right.

So preclinically and clinically, there's strong evidence for more efficacy.

What -- the way we designed the study is it's not yet known how much more FEV1, that's the measure that people have historically used, which is how much air you can blow through a straw at one second. It's been the regulatory endpoint. It's not clear if we're -- if there's a ceiling effect or not, we just don't know because no one's ever dosed up this high the curve. So the way we designed the study is a noninferiority study because we don't know if there's more FEV1 to have, but then with secondary endpoints of sweat chloride, which is actually the measure of CFTR function, as well as a potential for superiority and other things. So we'll obviously read out the top line results.

But the other point I want to make just to close is that you might ask, well, why is this medicine of the potential for being better for patients and what if there isn't more FEV1, not saying it won't be, we just don't know yet. And the key thing that we know is that more CFTR function leads to better outcomes for patients. And the reason we know that is, one, natural history. If you look at people who carry different mutations who have different levels of CFTR function, higher levels of CFTR function means better outcomes.

Second, if we look at our clinical trial data, we know that while a fraction of people on TRIKAFTA have essentially normal or carrier levels of CFTR function, majority do not, and the clinical trial data says that we can move those people to even higher levels of CFTR function. They had better outcomes. So it's very -- we're very confident that the key thing for patients is more CFTR function to approach carrier levels, and that will lead to better outcomes. The exact profile of what that looks like, we're going to have to learn from the first study in history of Vanza that has the potential to go even higher than TRIKAFTA.

Colin Bristow Analyst

So in terms of your expectations for the results, is your sort of base case noninferiority on FEV1 superiority on sweat chloride. Is that fair? Is that what I'm hearing?

David Altshuler Executive

I think what I'm confident in is, one, we should see higher to CFTR function as read out by sweat chloride. And two, that the profile of the medicine will be quite confident will be better for patients overall. I'm not going to speculate on exactly which measure and exactly which way because it's really just that when we got from ORKAMBI and SYMDEKO like levels to TRIKAFTA like levels, that was a new day in the disease, and we learned what that could do. Now we have the potential to go even higher than that. and we have to learn from the 1,000-person year-long clinical program in Phase III, but that's going to tell us what that profile is, and I believe it will be better for patients, but I'm not going to speculate on exactly what number and what things because we just don't know.

Colin Bristow Analyst

So under the outcome of just on sweat chloride alone sort of superiority, directional improvement, is that enough from a commercial perspective in your mind?

David Altshuler Executive

Sure. We've done commercial research that has asked doctors what they think of this and what everyone -- what that data shows and it's what we believe is that the community understands that the disease is caused by abnormalities in CFTR function caused by inherited mutations that people who are carriers are completely well. They have absolutely no -- nothing. They're healthy. And that patients, therefore and doctors want to get to highest level of carrier CFTR function.

And so I do believe that commercially that seeing that you can normalize CFTR function is going to be compelling for doctors and patients. Obviously, the -- they're going to want to see the clinical data and understand what it means. But I think that there is an understanding, just as like in other settings, you want to normalize the underlying disease. You don't want to be left with the residual disease and some fraction of people even on TRIKAFTA have residual defects in CFTR function that we want to boost up.

Charles Wagner Executive

Colin, I was going to say, the reason I defer to David on that question is because the decision to switch is really between a patient and a physician. We're not driving it in any way. So with TRIKAFTA, we have seen the vast, vast majority of patients switched to TRIKAFTA because it's a superior medicine, offers a greater benefit, greater profile. That's not been driven by the company in any way. Similarly, with Vanza, we're dealing thankfully with an incredibly well-educated patient population, physician population as well.

They will be the ones to make that decision and drive that. And again, we'll see soon.

Colin Bristow Analyst

You literally answered my next question in terms of assuming approval, the move would be to switch the TRIKAFTA population over to Vanza.

Charles Wagner Executive

There will be switching. We won't be driving it, candidly.

Colin Bristow Analyst

Sure. And you said you've not disclosed the IP situation for Vanza at this time.

Charles Wagner Executive

Not yet.

Colin Bristow Analyst

One of the other benefits of the Vanza triple is obviously a margin uplift for you guys. Can you just talk about that a little bit and help us quantify it?

Charles Wagner Executive

Yes. So across our existing portfolio, we have a royalty burden in the high single digits. We would expect with Vanza, given its chemical composition that it would have a royalty burden meaningfully lower in the single digits.

Colin Bristow Analyst

Okay. That's helpful. Moving to VX-522, when will we next see -- when will we see the initial Phase I data? And what should we expect it to be in there?

David Altshuler Executive

So VX-522, as you know, but just for the group is a medicine aimed at the 5,000 or so people with CF who don't make any protein and, therefore, can't respond to our CFTR modulators. And so in that setting, where we worked with Moderna for many years to develop a LNP inhaled, LNP mRNA medicine that could restore CFTR expression to the lungs of people with CF. And that would only be for the 5,000 or so people.

We're in the single ascending dose in patients with that medicine, and then assuming good data, we would move to multiple ascending dose. We don't expect it could be, but we don't expect to see meaningful efficacy after single dose just because it's too short. So it will probably be -- it will be some time we hope next year when we've got the multiple ascending dose data. And the meaningful measurement will be, obviously, efficacy and safety. Efficacy would be FEV1.

Safety, obviously, traditional safety measures. It's an inhaled medicine, not a systemic medicine. So you can't measure sweat chloride. So it's going to be about lung function.

Colin Bristow Analyst

Okay. That's helpful. And just last one on CF. Last week, the U.K.'s NICE published a draft guidance saying that the CF, the Vertex are not cost effective. I was just wondering what you

thought about that report?

Or what maybe some of the shortcomings that drove that conclusion?

Charles Wagner Executive

Yes. Importantly, that's a draft document from NICE not unexpected. We entered into our reimbursement agreement in the U.K. 4 years ago, part of the agreement and part of the process, we expected that to be occurring around this time. That said, obviously disappointed with the draft report, and we see serious issues with the methodology that was used.

We have provided tremendous patient benefit in the U.K. over the last 4 years. We have accumulated with TRIKAFTA globally, tens of thousands of patient years of real-world evidence that show the incredible and transformative impact of the medicine. And that's not fully appreciated in the methodology that NICE uses. So we are in the process.

We've had conversations with them before. But we are committed to ensuring sustainable access for patients in the U.K. and in all the markets that we serve. I'm confident that the strength and the profile of the medicine will carry the day, and we'll continue through the conversation.

Colin Bristow Analyst

Great. Maybe we could switch gears and move to pain. So this is obviously front and center for you and investors. I would say that your turnaround this feels very positive. And could you just articulate to us what's sort of driving that confidence and positive tone?

David Altshuler Executive

Yes, I'll start with the -- the unmet need is very great in pain, as we know, both acute pain where opioids are used or not being used as much in many cases because of the safety and tolerability and addiction potential. So there's a lot of unmet need there. And also, in particular, in sort of moderate to severe, what's called neuropathic pain, either diabetic or what's known as lumbosacral radiculopathy sciatica, things like that. There's just a lot of unmet need.

And it's been clear for about 20 years that there are 2 targets, and I'll focus on one of them. They're partners with each other, what's called the selective sodium channel NaV1.8 and NaV1.7, but our sort of people in genetics, sometimes human genetic refer this as like God's gift to pain research. We say that because the genes are only -- it is sort of trying to design the perfect target for any therapy. We wanted something that's only expressed in the tissue of interest and nowhere else you can't have side effects. That is necessary for the function you're trying to interrupt and has no other functions such that it would be dangerous to inhibit it.

And that's what NaV1.8 is. It's a selective sodium channel only expressed on the nociceptors, which are the peripheral pain-sensing neurons. And based on human genetics and now our pharmacology data from 5 out of 5 positive Phase II studies, inhibiting this channel can block the transmission of pain signals from the periphery to the brain. And critically, it's not

expressed in the brain.

So most pain medicines, if you think about pain medicines that are used today, they're either your sort of aspirin, ibuprofen, Emzed and tylenol, all of which act as sort of anti-inflammatory is blocking the tissue distally or there that affect your cognition, like anti-Lyrica and the gabapentin, they're anticonvulsants, they're not pain medicines. Opioids block the brain's perception of pain. Tricyclics are antidepressants. They don't actually -- they're not pain medicines. They're basically affecting your cognition.

That's why they have so many side effects.

So having medicines that have this unique target that are highly selective that have 5 out of 5 positive Phase II studies and a clean safety profile to date makes us optimistic. Obviously, we haven't yet seen any of the Phase III data yet for acute pain. We haven't yet seen the Phase II data for neuropathic pain. So we, like everyone else, are very excited to do that, but our confidence is based on the unmet need, the human biology and the pharmacology to date.

Colin Bristow Analyst

On the sort of mechanism in the pharmacology, your drug design in chemistry has always been extremely highly regarded and I think it's driven a lot of your success to date. How has that been sort of translatable or leverageable in the context of pain and NaV1.8?

David Altshuler Executive

Yes, it's a great question. And actually, inside of Vertex, it's understood that we've been working on pain as long as we've been working on CF, that it's the same people. So Paul Negulescu and Sabine Hadida, who, together with Fred Van Goor won the Breakthrough Prize this year and the Wiley Prize, which are 2 of the most prestigious prizes in science for their discovery of the CF medicines. Paul and Sabine have led the pain program as well for 20 years. So it's the same people.

They both use our human genetically validated targets. They both use human cells as the assay technique. So in CF, that's the human bronchial epithelial cells in pain. It's actually human dorsal root ganglion neurons, which are -- when people pass away, they donate their tissue sometimes to science, and we use those as the -- so we use cell lines. We don't use artificial cancer cells.

We use human dorsal root ganglion, which are the exact cells in which the drug is meant to act.

Our chemistry approach, we use every -- we were the original structure-based drug design company 35 years ago. We've been doing what people now call AI and drug discovery for 30 years. We use all of the techniques of human cells, cryoEM and AI, but also having spent many years studying these targets. We're not trying to cover the landscape. What a lot of companies seem to do is say, we'll have 100 targets and we'll do a shot on goal and see if any of them work are not experts in any one.

Whereas we've been drilling deep on this target for many years. So I think we have as much expertise in pain as we do in CF. And I think that's why we've discovered medicines that no

one else has been able to discover.

Colin Bristow Analyst

So we've seen some Phase II data for the abdominoplasty and bunionectomy populations. And I think the publication had some -- there's a balanced commentary, right? And so in some of the focal areas of, not concern, but just questions were around time to onset and efficacy relative to standard of care. I think -- could you -- walk us through each of those and how you're thinking about them?

David Altshuler Executive

Yes. I mean we personally think they are extremely encouraging and actually also putting it in the context of those -- those were the only 2 Phase II studies done to date with VX-548, but there was a previous molecule VX-150, which binds to the same site and it's the same mechanism of action, that we had 3 out of 3 proof-of-concept studies. And the reason we didn't move that one forward it was just -- it was a -- it turned out with dose range, it was a very high dose, so it wasn't an ideal medicine. So we didn't pursue it. But when we look at the data, what we see are 5 out of 5 studies positive.

They all have, if you look across them, and it was commented by one of the commentaries not the other -- the safety profile is thus far clean.

So every other pain medicine has side effects. And these to date, mainly in Phase II studies, we'll see more data. With Phase III, it looks very clean. And the efficacy is 5 out of 5, met the primary endpoint, 5 out of 5x clinically meaningful efficacy. And we used in all of the acute pain studies, the 2 that were published in New Journal and the 150 study previously, a reference arm, which was a clinically-used opioid, not as a comparator.

The study was a Phase II study, so it wasn't powered for superiority, but it was there, and you can see equal or greater efficacy of our medicine in those studies. So we saw it as very positive.

And some of the commentary in that New Journal article was actually about Phase II studies for pain. It actually wasn't really about our drug. If you read the article, it was sort of about like how much smaller studies, what can you learn from them, but we're not trying to learn from one study, we're trying to learn from the mechanism, what we know about the nonclinical data and the 5 proof-of-concept studies. And all that makes us feel confident. But again, we haven't seen the Phase III data yet.

So it's always -- this is a business where we -- everything is making us confident, but at the end, we have to see the data and when we see the data, we'll know what it is, and then we'll be able to act.

But the other thing is the Vertex strategy is always to do serial innovation. And just as in CF, we went KALYDECO, ORKAMBI, SYMDEKO, TRIKAFTA, now we have vanzacaftor. We have in pain, just as we've had in AAT, as we had in AMKD and all of our programs, we have follow-on molecules that are even better. So when we look at the opportunity, it's -- 548 is great, but we also have already invested in the next things, some of which are in the clinic. So we feel very

good about the long-term prospects as well as the short-term readout.

Colin Bristow Analyst

And on the point around sort of onset of pain relief relative to study success.

David Altshuler Executive

Yes. It's actually rapid is the bottom line. If you look at the data, actually, it's rapid. So it didn't -- it doesn't seem meaningful to us. And if you look, it's very early on the efficacy.

Colin Bristow Analyst

There was a disparity at least from a sort of PK perspective in terms of Tmax between bunionectomy abdominoplasty. Can you just speak to why that is?

David Altshuler Executive

I can at least tell you what might be the case. I can't -- but bunionectomy is a bony -- it's a surgery on the bone of the foot. And so it's local anesthesia and people eat afterwards. People who have abdominoplasty, which is abdominal surgery tend to have delayed gastric emptying. So if I had to speculate, I would speculate that in a disease where there's no effect on digestion, you might have more rapid absorption, but it's not really about the medicine, it's probably about the patient.

Colin Bristow Analyst

In the context of one of the goals here is to kind of remove opioids from the equation, is a noninferiority outcome in the acute pain setting a win?

David Altshuler Executive

Absolutely. I think that the profile that we believe would be transformative. And frankly, everyone we talk to, we believe, to be transformative would be to replace opioids, which have in addition to their challenges with addiction that are very well documented, have many side effects ranging from confusion, nausea, respiratory depression, constipation, rash, all which limit use of opioids beyond the addiction potential. A clean profile with meaningful -- clinically meaningful pain relief for moderate to severe pain is a transformative medicine.

Colin Bristow Analyst

So we're going to get the DPN data before year-end and then the acute pain data, I think 1Q '24 is your latest current. Is there anything that -- when we get the DPN data, is there anything other than safety? And even though the doses are different, is there anything that you'll be looking at or that we should be looking at in terms of reading through to the efficacy outcomes in acute?

David Altshuler Executive

Basically, no. I mean it's in this following sense, there are different indications. There are different patients and while we have every reason to think they will be positive because we've done a previous neuropathic pain study with VX-150. And obviously, we've done the 3

previous studies in acute pain with 150 and 548, they are different indications.

And so it's -- I don't think there's any real read-through in terms of this study and that study also one is a Phase II study that's smaller and the others are large Phase III studies. And I think the other thing we announced this week is we're starting a study in lumbosacral radiculopathy, which is just to give you a context of neuropathic pain, which is a very large opportunity. A diabetic peripheral neuropathy is about 20% is our estimate of that indication -- of that field and lumbosacral radiculopathy, which people often think of sciatica, that's lumbosacral radiculopathy is the nerves coming out of the spinal cord getting into the periphery.

They have to go through a little hole in the spine called foramen. And if it's the level that is the sciatic nerve and it's called sciatica, but sometimes it's above and below that and the totality is called lumbosacral radiculopathy. That's a disease where the nerve is pinched and about 90% of the people do not need surgery and don't get surgery. They just suffer for a long period of time pain until it eventually sometimes resolves. And so that's a very large opportunity as well, and we're starting a Phase II study of that.

And again, while my -- if I had to guess, I would expect it to be positive in both based on the mechanism of action. There's not really a direct read-through from one to the other because they are different patients with different mechanisms of action.

So I think each one is a big opportunity in that zone. Obviously, are open and would -- is that it will work in all of them, and we can help lots and lots of patients with pain. But each one is a meaningful opportunity and each one is sort of a different opportunity based on the fact that the patients are different.

Colin Bristow Analyst

Marketing the drug in pain would be a very different setup than to what you guys are used to and what you're doing in CF, obviously. Can you speak to the strategy there and the infrastructure build?

Charles Wagner Executive

Yes. I guess it's -- we get this question a lot, and I would tell you the commercial model is not as different as people think. CF, of course, is highly concentrated, and we have commented from time to time that we have fewer than 20 salespeople in the U.S. to cover the market for CF. It's very well, as I mentioned earlier, a well-educated patient population and physician population.

So it is highly concentrated. But importantly, every disease area that we've chosen to focus on, whether it is sickle cell disease, beta thalassemia, pain, AMKD, et cetera, fits our specialty commercial model. So we see an opportunity to segment the market in a way where we can work with a specialty commercial model. We don't need thousands and thousands of salespeople. It's a relative smaller sales effort.

In the case of pain, we've commented, if you look at, maybe we'll take acute pain, for example. There are 80 million people a year who are treated for moderate to severe acute pain,

somewhere between 1 billion, 1.5 billion treatment days. But importantly, 2/3 of those days are -- the prescriptions are either written or influenced in an institution, so either at a hospital or a surgery center, perhaps a ton of discharge might be filled in a retail setting. But the concentration of the prescription is in that setting.

And then just some quick math, there are maybe 2,000 or so hospitals that roll up into 200 IDNs that represent 80% of the market as well. So you're talking about a sales force of maybe a couple of hundred people to cover something like that in the U.S., not thousands and thousands, and thousands. And importantly , we would be engaging, not only at the hospital level, but at the IDN level. And then additionally, as a company, we're engaging at the state and federal level as well. And there are increased -- there have been restrictions on opioid prescriptions for some time.

Increasingly, there are no incentives for prescription of nonopioids. And we've talked about the benefit of the NOPAIN Act, which was passed back in December, which creates an add-on payment to provide the opportunity for economics to not get in the way of prescribing a nonopioid.

Now there aren't any effective nonopioids available. We would hope to have the first but we think with this engagement at the federal level, state level, IDN level, and a continued campaign of education around the profile of a medicine like this that we can serve it with our specialty model very well.

It's also perhaps why we're not going everywhere with pain. So we've talked about -- the example I gave you there was acute pain. And then people tend to think of acute and chronic. But within chronic, we've subsegmented into neuropathic pain because we think that can be served with a specialty model as well. So DPN, LSR, other forms of chronic pain, so maybe musculoskeletal pain are often served in more of a GP setting.

We don't think we can cover that with a specialty model. So that's not part of our focus initially.

Over time, we do think, based on some of the comments that David has made with previous trials, that the medicine could be effective for some of those chronic pain states, but it doesn't fit our specialty model. So it's possible that in the future, we would look at other ways to access that, perhaps do partnership or licensing. But the opportunity in acute and neuropathic that is right in front of us is large enough and fits our model, that's where we're focused.

David Altshuler Executive

And the only thing I'd add to that is moderate to severe pain is a high-value indication. So in addition to being a specialty indication because once somebody has moderate to severe pain, they're either in a hospital setting like having surgery, in which case it's a specialist surgeon or an anesthesiologist or they're seeing an orthopedist or a neurosurgeon for their spine or they're seeing a pain specialists. But also, they have the greatest need. And I think one lesson in pain medicines over the years is like going where the need is greatest, and therefore, the value is greatest. I don't just mean commercial, I mean medically is the place to go.

If you go to people with very mild pain, it's just a different benefit risk scenario, it has definite value. So I've always thought myself that helping the people with the really intractable pain was the greatest benefit to society. It happens also to be a commercial specialty model and have high value. So I think it's like the right place to be.

Colin Bristow Analyst

One question we had since your quarterly updates and the additional information you're starting a trial in LSR was do you have the DPN data in-house? Have you seen it? Is that what's giving you the confidence to start this?

David Altshuler Executive

No.

Colin Bristow Analyst

Okay. I just needed...

David Altshuler Executive

Sometimes people run a little bit of commentary, though. So the answer is no, we don't have the DPN data and we don't know what it is, obviously, what the results are. The data, look at data study is, but we don't know what the results are. The timing of this, I get why people have a question about it. I think it's sort of 2 components.

One is that we -- starting LSR now because LSR has evolved in the regulators and the communities mind over last decade where it used to be thought of as a musculoskeletal condition because it involves the spine. But we've always thought of it as a neuropathic condition. So we needed to interact with regulators to make sure that we had a shared understanding of what we were doing. Having had some of those discussions, we feel now confident going forward with LSR. It has nothing to do with the DPN trial.

Another question would be that, well, why not wait for the DPN trial? And then you'll know, again, one is a metabolic nerve condition based on diabetes. The other one is a mechanical nerve condition based on the spine. There's not direct read-through. So even -- and each one is a large opportunity commercially.

So whether the -- if you do the decision tree and you go, well, if DPN's positive, would you do LSR? Yes. If DPN was negative, would you do LSR? Yes. As soon as we'll get started.

Colin Bristow Analyst

Okay. That makes sense. Another actually Phase II data questions just came to my mind. The abdominoplasty Phase II comparator on look like it underperformed versus kind of historical data sets we've seen. That didn't appear to be the case in bunionectomy.

Just any comments there.

David Altshuler Executive

I personally think it's noise. It's sampling variation. These are Phase II studies. I know you know

this, but just like these are Phase II studies, dose-ranging each arm is pretty small. And that's because we're -- and they're just not large enough for a study for the -- to really get highly precise estimates.

And so I think that the way I look at them is we're looking to see is the drug active. We're trying to get the profile. We're trying to get the safety and everything, but you can't really get a highly precise estimate to myself. I tend not to try and read too much into things that I think are sampling variation. But when I look at all of the studies, it gives me high confidence that every study has been positive, met the primary point, similar overall results, similar safety profiles.

I'm very confident in that.

Colin Bristow Analyst

What can you say about the powering and the hierarchy of testing of the end points in the Phase III?

David Altshuler Executive

What I can tell you about the powering is it's very well powered. And what I mean by that is the Phase III studies. And what I mean by that is that if you look at our Phase II studies, as I said, which are in the order, they're all different than the order of 100, 200 people and have multiple arms. They have all met their primary endpoint and been very clear separation of the drug from placebo. Because the Phase III program has to meet safety criteria, we have 1,000 people in each of abdominoplasty and 1,000 people in bunionectomy, and a 250-person safety and efficacy study in a broad range of endpoints because that's what we agreed with the regulators would potentially support a broad acute pain label.

So from the point of view of like meeting the primary endpoint, the study is exceedingly well powered.

Colin Bristow Analyst

Okay. The open trials, we've seen -- there's an assay called VX-708, which just completed Phase I. Could you just share a little bit more on this? What's the mechanism future?

David Altshuler Executive

Yes. So we have actually 708. There are actually are others, we don't report out now, that's assets that early-stage development just because the stage of the company. But it's a NaV1.8 inhibitor. We have other NaV1.8 inhibitors, and they -- as we always do, we're looking to serially innovate and find molecules that have even better properties or additional characteristics that might be desirable and 708 is such a molecule.

And we continue to discover such molecules in our labs. And I tend to think of pain -- where we are with pain today is a bit like where we were with CF in 2010 or so in the sense that we didn't yet then have an approved medicine, but we had multiple assets that would prove out to be valuable between KALYDECO or can be SYMDEKO and also built a foundation that led eventually to TRIKAFTA and where we are today.

And when I look at our pain program, I see VX-548 in acute nearing the end of its Phase III, 548 in neuropathic pain with both the DPN study that will read out this quarter and also another study, another big indication. And then other molecules behind that have the potential to augment or extend what we can do. And that gives me -- I tend to think long term. I've been around the company now one way or another for 12 years. So like it's like -- it gives me great confidence we're going to get there.

I have very good confidence, extra confidence in 548, but it's also like we have the whole -- the foundation for really transforming lives of people with pain and that's exciting.

It's really been -- it's our approach in every disease area. We focus on serial innovation. We don't go one asset at a time and then regroup. We are typically pursuing multiple assets based on our knowledge of the biology so that we have the greatest chance not only of succeeding, but also moving fast.

And actually also, the other thing we expect is that if we succeed, and we're confident that that's a very likely outcome, other people who run more me-too companies where they wait for someone else to innovate, and they try and jump on the bandwagon, I never actually understood why other companies will innovate and then wait to see the data and then let everyone else be at the same place they are.

So the actual investment required to make sure you're 5 years ahead of everybody else, that's why we are where we are with CF. So like we just keep rolling along if everything were to fail and some various -- where you could always stop. But you have to plan for success. And so we are already planning for success and saying, well, if others are copying what we're doing now, we've got to be years ahead of them and we are.

Colin Bristow Analyst

Maybe let's switch to another program, the CRISPR-based DMD program. We follow the DMD space closely. We've been very interested in the technology acquired for [Axonics]. It's been 4 years since that acquisition. And I'm just -- perhaps what are some of the unanticipated challenges you've had getting that to the clinic?

David Altshuler Executive

Yes. I mean I think I'd say that DMD remains unfortunately a disease with tremendous unmet need. And it was disappointing to everyone, I think, last week's data readout where microdystrophin didn't show what is primary end point. And -- but that -- our hypothesis 4 years ago was that we didn't invest in microdystrophins because dystrophin is the largest protein in the genome. It's a shock absorber that connects the outside of the muscle to the inside of the muscle cell, and we just never were confident that a quarter of the size, there was never any human data or animal data that really indicated microdystrophins would work.

So it's not terribly surprising, but disappointing for patients that it doesn't appear like it to be very effective.

So our approach has always been and remains to use an approach gene editing to restoring near full-length dystrophin. Because full-length dystrophin is known to benefit patients

because there's something called Becker muscular dystrophy, where people inheriting near full-length dystrophin of the sort that you could recreate with gene editing, and they do very well and they have symptoms, but they're much, much, much better. So that's what our strategy has been.

And from a -- there's sort of 2 components to any genetic therapy, there's the payload, can you achieve the sort of gene modification you seek and there's delivery. And I think that from the point of view of the payload, made really great progress and feel good about the gene editing as an approach and ever more committed to this idea based on recent data of near full-length dystrophin.

From the point of view of delivery, clearly, high-dose AAV one thing that has evolved in the recent years is just observing everybody who's gone in the clinic with high-dose AAV. And based on our preclinical data, we think more work is needed before we'd be prepared to go forward with that. So a lot of the focus will be on that and delivery is the key concept.

Colin Bristow Analyst

Any new time lines that you can speak to? And is it still very much on when versus an if in terms of this therapy making it to the finish?

David Altshuler Executive

Yes. I mean, it's too early to say what the time line is because, obviously, we just got these recent data and we're still understanding them and figuring out the next steps are, our commitment to trying to bring this forward remains full on both because of the unmet need in the current state of the field and also the potential of the therapy we have. So we're very committed to that, but I can't say exactly what the time line is just too soon after getting the recent results.

Colin Bristow Analyst

Switching gears again to the diabetes program. VX-264 in clinical studies are underway when do we start to see some data on that? And I imagine with that, well, you'll open up the [indiscernible] and will understand a little bit more of the design, the materials that you've kind of alluded to.

Charles Wagner Executive

We've not given any timing on data for 264 at this point.

Colin Bristow Analyst

Okay. Is it -- at least conceptually, is it fair to say that you released one patient's worth of data AAT. I think in these sort of settings, small numbers of patients can be very meaningful, is that at least something you're open to?

Charles Wagner Executive

It's true that -- like in cell and gene therapy, the trials tend to have smaller patient numbers. We don't have any intention of disclosing patient-by-patient data for 264. When we have the

appropriate cohort size and the appropriate time that's when we'll release the data.

Colin Bristow Analyst

Okay. Switching to exa-cel, just trying in the last couple of minutes, move through a couple of things. Well, congrats on the recent AdCom. Can you walk us just frame the opportunity here in terms of patient numbers, market size? And how should we think about the cadence of our launch in this population?

Charles Wagner Executive

Yes. Listen, we're really excited, obviously, with the outcome of the AdCom and for sickle cell disease, specifically looking forward to the December 8 PDUFA date. We've commented previously that across North America and Europe, there are roughly 160,000 people with sickle cell disease and beta thalassemia. We think that roughly 20% of them or 32,000 would be appropriate candidates for a therapy like exa-cel right out of the gates. And so that alone represents a very significant multibillion-dollar opportunity.

We did take some time on the earnings call this week to just talk about the patient journey a bit. Well, there's a lot of excitement among patients, physicians, we are very excited. The sort of -- there is a journey for patients as they meet with their hematologists decide that they are interested in the therapy, they go through a battery of tests to make sure that they're appropriate. They would get referred to an authorized treatment center that has worked with us to be a point of entry for patients in this journey. And then they go -- for those that advance, they go through cell collection, gene editing, manufacturing, infusion, et cetera.

And importantly, people ask me typically about revenue, revenue occurs at infusion.

So you've got these patients who are going through a multi-stage multi-month process. And so we just wanted to set that expectation. But in terms of our readiness, and I think patient readiness is very high. So we are going to be ready to go on December 8, assuming a successful approval. We will have authorized treatment centers signed up, all of our commercial organization in place is in place, all of our manufacturing capabilities are in place and ready.

And so we'll be eager to see patients queuing up essentially post approval.

We also are very confident that there will be access and reimbursement in place as well. So there are no rate limiters other than it takes patients a little bit of a while to go through the journey.

In 2024 will be a foundational year. We are focused on making sure that everything goes really well for patients and physicians. I think with this community, there is an element. Some folks are perhaps going to want to see some success stories. They're interested in the success stories from the clinical trials, but even locally in some of the treatment centers, there's a local patient community.

So we're very excited about helping folks through the journey and just wanted to lay that expectation out.

Colin Bristow Analyst

Maybe one last question for you, Charlie. You've got $12 billion cash on the balance sheet, incredible cash flow generation. Just how are you thinking about priorities now and share buybacks, potential dividend? And then just given where the biotech market backdrop is, do you have -- do you see greater opportunity and/or an increased appetite to do business development?

Charles Wagner Executive

Yes. We've been very consistent and I think very disciplined, and I also think very successful with our capital allocation strategy to date. We've said that our top priority is investment in innovation, both internally and externally. With some of the cell and gene therapy programs, there is a larger CapEx component. So we are earmarking some capital dollars for that.

We have been very active in BD over the last several years. And I think it's important to note I know people tend to like to characterize some of the BD as earlier stage. That said, if you look at our clinical pipeline, 40% of the programs in the clinic have benefited from BD that we've done in recent years. So this is not BD that pays off at some point in the future, this is BD that's in the clinic now.

We've had actually a very active year. I think we're approaching 8 or 9 transactions this year on the BD side. So that's going to continue to be our primary focus is investment in innovation. We have carved out some capacity for share buybacks. We have a larger authorization in place where we -- a $3 billion authorization in place, and we've been active executing against that throughout the year.

We continue to be active buyers. So that focus, that dual focus of innovation with a little bit of room for share buybacks is appropriate for us. We have no intention of initiating a dividend at this point. The strategy has worked well, and we're going to stick with it.

Colin Bristow Analyst

Fantastic. Well, thank you for your time. Congrats on all the progress. We look forward to pain, and thank you, everyone.

Charles Wagner Executive

Thank you.

David Altshuler Executive

Thank you.