Vertex Pharmaceuticals Incorporated

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David Risinger

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Charles Wagner, David Altshuler

David Risinger Analyst

All right. So well, good afternoon, everyone. My name is Dave Risinger. I cover Diversified Biopharmaceuticals for Leerink Partners, and it's very much my pleasure to welcome two members of the Vertex leadership team. Immediately to my left is Chief Scientific Officer, David Altshuler, and to his left is CFO, Charlie Wagner.

So I wanted to thank them for coming in from Boston to be with us here today. And obviously, the company has had tremendous momentum and delivered some very compelling data. So once again, thank you for taking the time. I know that you have a lot more work ahead as well.

David Risinger Analyst

Why don't we start with pain? It'd be great to hear what you're hearing from the field, what perspectives physicians are sharing with you on VX-548?

Charles Wagner Executive

Yes. Listen, David, thanks for hosting us today. We appreciate the opportunity. And maybe before I dive into that, just to couple of -- so you mentioned the great data. We have had quite an exciting 100 days or so since early December.

We've announced multiple regulatory approvals for CASGEVY. We released data in our Phase II DPN trial, data on our Phase III acute pain trial, data in our Phase III vanza trial in CF reported in the fourth quarter and gave guidance for the year. So it's been certainly a very busy and exciting time for us over the last few months. And with that though, we're excited to kick off 2024, continued execution in CF, successful CASGEVY launch, moving programs to the clinic,

including the pain program, which you described. So on pain, we released very positive Phase III results in acute pain recently.

We are incredibly excited about the opportunity on VX-548, which is our medicine, has the potential to be the first class of new pain medicine in decades. As you know, today, physicians and patients essentially have a choice between NSAIDs and opioids for moderate-to-severe acute pain. NSAIDs have limited effectiveness, opioids have greater effectiveness, but a significant burden of side effects, including the potential for addiction. VX-548, we think, stands out remarkably in that setting as a medicine that is both effective and safe. And certainly, that's shown in the Phase III results, and David can comment on that.

In terms of reaction so far, it's been overwhelmingly positive. We expected that. We have -- with VX-548, we have a steering committee consisting of a dozen or so doctors who are experts in pain. They've been enthusiastic about the program all along, and we're really thrilled with the data that we released. We've done market research.

We've talked to 600-or-so physicians, including orthopedic surgeons, plastic surgeons, anesthesiologists, pain experts, et cetera. Among those 600 physicians, the overwhelming majority are interested or very interested in prescribing a medicine like VX-548 because they really don't have any great alternatives today. Beyond the physicians, we've begun compliant pre-approval information exchanges with decision-makers on formularies at the institutional level in hospitals and IDNs with PBMs, with payers. And of course, we have ongoing conversations with state and federal legislators as well. And across the board, the reaction has been very positive.

Again, as I mentioned, there has not been an alternative. It's interesting. There are -- all hospital systems and all states have some sort of rules or restrictions around opioid prescriptions. 18 states have actual requirements for a physician to advise patients and consult with them about non-opioid alternatives. 13 states have pending similar legislation, and yet there's really been nothing for them to talk about.

And so with the potential for the advent of VX-548, we see a tremendous opportunity to both transform the way that pain is treated but also provide a societal benefit, particularly in the U.S. where the opioid crisis continues to be a significant burden on society.

David Risinger Analyst

Excellent. That's very helpful perspective in context. Thank you. So maybe turning to David. Could you just comment on one of the pushbacks that we got on the bunionectomy results, was somewhat slower onset than the abdominoplasty trial, and just put that into context in terms of the potential treatment paradigm once it's approved.

David Altshuler Executive

Yes. No. Thank you. We're very pleased with the profile of VX-548, safety, efficacy and including time to onset. But let me explain why?

When people come into a hospital setting with an injury, acute injury or in the postoperative setting, they're going to be given an IV medicine because IV medicines have like 5-minute

onset, all oral medicines take some time because you have to absorb it and get into the bloodstream. But within that context, the data for VX-548 is actually very encouraging for an oral medicine. One measure was the time to 1-point reduction in pain in this 10-point scale, that was 30 and 60 minutes for abdominoplasty and bunionectomy. Another that's clinically important is the time to a clinically meaningful reduction, which is a 2-point reduction, 30%. That was 2 and 4 hours.

And if you look at the history of data of oral medicines for pain, that's actually very typical and appropriate. So I think the question often is around how you deal with someone who comes in and has pain control in a few minutes, that's always going to be an IV medicine.

David Risinger Analyst

Makes sense. And maybe you could talk a little bit more about how you see the opportunities, and I'm not sure which one of you wants to address the question. But just help us understand the treatment of pain, whether -- or breaking down the market between elective surgeries, prescriptions that may be given a discharge versus in the hospital, et cetera.

Charles Wagner Executive

Yes. So we'll stick with acute pain for this part of the conversation. Our work tells us that there are 80 million people in the U.S., who seek treatment or prescription for moderate-to-severe acute pain each year. Average course of treatment is roughly around 14 days, 14, 15 days or so. So that translates into over 1 billion calendar days of treatment and over 1.25 billion treatment days.

That is a significant market opportunity. And if you look at how it breaks down, with roughly 50% of the prescriptions are related to patients who are experiencing that pain as a result of a surgical procedure. And specifically, of the 1 billion-plus treatment days, 15% of them are in the hospital setting, 35% of them are either at discharge or filled at retail post discharge and then 50% is nonsurgical, which would include pain states like a fracture or a sports injury or bad sprain, that sort of thing, some of which is seen in the hospital, some of which is seen in a general practitioner's office. So with that opportunity, you can -- it's important to remember though that with VX-548, we're going for a broad label for moderate-to-severe acute pain. So we're not looking to just serve postsurgical pain or some other pain state, looking for a broad label.

That's why the trial was designed the way it was designed. We had an arm in abdominoplasty, an arm in bunionectomy and then an open trial with a bunch of different pain states to demonstrate effectiveness there in the results in that arm, were also very, very positive. So when you look at the opportunity, we are focused on the full 1 billion-plus treatment days. And I think the point we've been trying to make with people is, going forward, while VX-548, we think, is an incredibly compelling profile and a great alternative to opioids that hasn't really existed. There will still be situations where prescription NSAID is appropriate.

There will still be situations where prescription opioid is appropriate. But we think there are a number of situations where an alternative like VX-548 will be such a compelling combination of effectiveness and safety that we will take a significant chunk of the market, and when you talk about over 1 billion treatment days, you don't have to imagine significant market

penetration at branded pricing to end up with a franchise that is a multibillion-dollar opportunity. And so that's how we look at it. We don't necessarily have to serve every corner of the market to have a big business.

David Risinger Analyst

Excellent. And then back to you, David. With respect to the publication of results that's forthcoming, obviously, you're going to have additional details. Anything that you would point us to focus on or questions that you're getting that will be answered when those results are published?

David Altshuler Executive

Not so much in so far as we presented in the press release in our quarterly call, sort of the primary endpoint, the meaningful secondary endpoints. We also published in the New England Journal earlier last year, the Phase II study in acute pain of VX-548, and so there's a lot more data about that and the Phase III basically tracked with the Phase II. So there's nothing in the data from the Phase III study that's going to change the overall interpretation of the results. They're all very promising.

David Risinger Analyst

Okay. Excellent. And then, Charlie, can we just go back to the commercial opportunity, just how you're prepping for that, how you would frame that, how the organization is kicking it into gear for what is such a broader market opportunity than you have with your existing approved medicines?

Charles Wagner Executive

Yes. Thank you. Yes. Yes, listen, we've obviously had tremendous commercial success with our CF medicines. Important to note that we've been working on pain for a long time on the research side of things more than 20 years.

We've had a lot of time to think about how to approach this market, how to prepare for it, and how to build on the commercial success that we've had in CF? What I would say is that with the pain program, we've had our core resources hired in-house and operating for some time now. And with the release of the Phase III data, we've ramped up our sort of final pre-commercial investments in the field. So whether it's in the sales organization in key account managers that will cover IDNs, medical liaisons who will focus on more of a high science cell. We are out talking to physicians and institutions, as I described, in a compliant way.

We've started to have conversations that would set us up to go through P&T committees to get on formulary and be part of the established protocol in a hospital system. I think importantly, that process in each institution is well documented and therefore, well understood. We know it's a process. It's probably a months-long process, not a weeks-long process and not a year's long process, but a months-long process. We are working now to understand exactly what data is going to be required to make those conversations most effective, and we'll be driving that forward once we get to the point, hopefully, with approval next year.

In addition, given what I described earlier about where the market is, it's also going to be important for us to have relationships outside the hospital. And so that means PBMs, payers, formulary decision-makers outside the hospital. Those conversations are underway as well. We're talking to the largest PBMs who represent 75% of the retail market for pharmacies, those are going well. And then lastly, whether it's payers or at the state or federal government level as well, you certainly have seen a tailwind from policy announcements.

We've commented previously about the NOPAIN Act, which was put into effect in December of 2022 -- will take effect -- was passed in December 2022, will take effect in 2025, where Medicare has provided for add-on payments for non-opioid pain relievers, so to economically level the playing field between opioids and non-opioids in the outpatient setting. There was recently legislation -- bipartisan legislation introduced to the House and the Senate for an act called Alternatives To PAIN, which is, again, a similar attempt to level playing field, it would prevent in Medicare Part D, would prevent a requirement for step-through from opioids to non-opioids, it would prevent a requirement of preauthorization for non-opioids. And it would, again, level the playing field in terms of co-pays for opioids and non-opioids. So I think we are seeing tremendous momentum again, given all of the problems associated with the opioid epidemic and all of the shortcomings associated with the profile of opioids. There's an incredible interest in a non-opioid pain reliever like VX-548, and whether it's in the hospital setting with physicians, with administrators or with the PBMs or with the government, we see tremendous traction at this point.

David Risinger Analyst

Got it. That's helpful. And can you just comment on the notion? I think some investors that are more bearish on VX-548, assume that payers will advantage the generic opioids, but it seems to me that it may be difficult to limit access to a non-opioid if at a minimum, starting with the Chief Legal Counsel of many of these entities, but would love to get your perspective.

Charles Wagner Executive

Yes. I mean listen, I think -- again, for medicine like VX-548, which represents such a compelling combination of efficacy and safety, it's hard to imagine any institution looking to disadvantage a medicine with that profile. Our conversations with payers and PBMs have been largely focused on Chief Business Officers and Chief Medical Officers at this point. So we haven't spoken to any Chief Legal Officers. But again, for the reasons cited, I think there's a really strong pull for an alternative here, and those conversations have been going great so far.

David Risinger Analyst

Great. And obviously, your serial innovation has been extraordinarily successful in CF. David, could you talk a little bit about the vision in pain?

David Altshuler Executive

Absolutely. So as you said, our strategy is to try and open new areas with a first-in-class medicine, but then continue to move forward rapidly with better and better medicines until we can expand and enhance the benefits we can bring to patients and stay at the front of the

pack. And so in pain, there are 3 elements that we're focused on. The first, beyond VX-548 as our initial and very exciting medicine, first is to have an IV and oral medicine because as I mentioned a few minutes ago, for the immediate onset of pain in someone who comes in to say, an emergency room or for the post-surgical transition from the operating room to the floor, IV medicines are important. And VX-548 simply doesn't have the physical properties to be an IV formulation, but VX-993, which has completed its Phase I study for oral also is -- we have an IV formulation coming.

So that's the first thing to try and have both IV and oral for the acute pain setting. The second is the possibility of combining a NaV1.8 inhibitor, like VX-548 or 993 with a NaV1.7 inhibitor, that combination could have even greater benefits because NaV1.7 works together closely with NaV1.8 in the pain-sensing neuron. Both are only expressed in the pain-sensing neuron, both are genetically validated. So the second goal would be to probably enhance benefit by either having NaV1.7 alone or a combination. The third is to see if it's possible to do even better than VX-548.

We don't know if it's possible or not because the profile is excellent. But if anyone is going to see that if there could be anything more to be had, we're going to be the people to do that.

David Risinger Analyst

Excellent. And so just to follow on there. So for 993, you ran one Phase I trial, but you're also conducting another oral, I mean, and then you're going to start an IV trial later this year. Could you just remind us about that second Phase I trial for the oral. And then for NaV1.7, will the initial development, assuming you can move it into Phase I at some point in the future, would that be as a monotherapy in terms of initial testing?

David Altshuler Executive

So first, with regard to 993, as you said, the oral has completed Phase I and we're going to be moving forward into Phase II studies in both acute pain and neuropathic pain to evaluate its profile. We are also -- with an IV formulation, you have to do a different first-in-human studies, it's a different approach, a different modality of delivery, but nonetheless, we'll be doing that as well as we plan to do later this year. With regard to NaV1.7, it's a little early to say because we're still preclinical. We haven't entered the clinic, but I think it's fair to say that NaV1.7 alone as a mechanism is worth evaluating, certainly many companies, really almost every company that worked in this area, worked on the NaV1.7 inhibitor for years and could never find a medicine that both had the ability to inhibit NaV1.7, but also the specificity to not inhibit any other protein, including selective sodium channels, we've been able to do that now in the laboratory. So one would be to evaluate its effect on its own.

So we'd have a portfolio potentially of NaV1.7 and NaV1.8, and then also be worthwhile to look at them in combination because the way it works, NaV1.7 initiates and NaV1.8 propagates the action potential, both are restricted only to the pain-sensing C-fibers of peripheral nerves. So there's every reason to think that possibly they could have a synergistic effect as well as effects of their own. So I hope this helps people see how between oral and IV between the different possible mechanisms. We see VX-548 as a great entry to the field, but we also see it opening a door to something that could be a much broader and more impactful

set of potential benefits in the years to come.

David Risinger Analyst

Excellent. Well, I could spend the full half hour on pain, but we should probably move on. So with respect to vanza, congrats on the results. I'm hoping maybe, Charlie, you could just kick off with a framework for how we should think about it as a commercial opportunity and then we'll go from there.

Charles Wagner Executive

Yes. Actually, I'm going to reverse it and ask David to talk a little bit about the profile because I think it sets up the commercial discussion very well.

David Risinger Analyst

Okay. Sure.

David Altshuler Executive

So TRIKAFTA is an amazing medicine, as we know, tremendous efficacy now taken by over 90% of -- approved for over 90% of people in the age groups taken by the majority of people with CF diagnosed in the world today and has not only short-term benefits, but has long-term data. But we set out to see if we could do better because we know that the ultimate goal we've had for many years in CF is to bring as many patients as possible to CF, ideally all to carrier levels of CFTR function because we know carriers have absolutely no phenotype or disease as early in life as possible to avoid any organ damage. With TRIKAFTA, we are down to age 2 but we set out, say, could we find a medicine that would drive even better levels, lower level -- higher levels of CFTR function, which can be measured with lower sweat chloride. And so that's what vanzacaftor delivered. We see a higher -- a greater ability to normalize CFTR function to give you two metrics.

One is a sweat chloride less than 60 is below the diagnostic threshold. So when someone comes in with a possible CF, you measure sweat chloride, if it's over 60, you have CF. If it's between 30 and 60, you might have, but usually less severe, and you have to look at clinical data. If it's below 30, which is the carrier level, there's -- it's not CF. So for less than 60, people in the vanza trial, which was ahead with TRIKAFTA, were twice as likely to be under 60 with vanza as opposed to the odds were twice as high, I should say, between vanza and TRIKAFTA.

And then below carrier levels 3x as likely to be below the 30 threshold, which should be associated presumably with no underlying disease process. And maybe a particularly striking number was we did this study not only with 12 and above, which is typically the case. We were able to move rapidly so that we also had a 6 to 11 cohort. And the 6 to 11 cohort, 95% of the children in this study had a sweat chloride level below the diagnostic threshold of 60. So if you imagine being a parent of someone with a child, you're trying to decide what medicine to put them on, if there's a medicine, you can put them on before they develop the kind of organ damage, not to mention suffering that's typical of CF, and you can get 95% chance of being below the diagnostic threshold, that's going to be very appealing to people.

And needless to say, but important to say, the safety profile was very similar, essentially

indistinguishable from TRIKAFTA, which has a remarkable long-term safety data and also it's once-a-day instead of twice-a-day. So it's a very appealing profile.

Charles Wagner Executive

Yes. And so given what David described, you can imagine we're working as fast as we can to go through the regulatory process and commercialize vanza. We'll be filing middle of this year for approval. We're using a priority review voucher. We would like to go as fast as we can with this medicine.

And we will be fully ready, assuming approval will be fully ready for launch, at the appropriate time. I would say, we think about patients in a couple of categories. Number one, there are roughly 6,000 patients who have discontinued one of our medicines for one reason or another. We have an incredibly high level of persistence among our patients. But nonetheless, some stop from time to time.

There are about 6,000 of those patients. We've seen historically that when we introduce a new medicine, those patients who have discontinued or eager to try the new medicines to see if it can work for them. So that's a great opportunity for patients to come back on medicine. Additionally, we do think that there will be significant switching from our existing medicines, though too early to describe exactly the rate of switching. As David described, vanza has incredibly compelling profile, so does TRIKAFTA.

And so we expect some people will be eager to switch right away. Others may follow in time. So for that reason, we haven't characterized the rate of switching. And then maybe the last point I would make, aside from all of the wonderful patient benefits that David described, vanza carries a lower royalty than the rest of our CF portfolio. So there's some economic benefit to the company over time as well.

David Risinger Analyst

That's very helpful. So why don't we pivot to CASGEVY. It would be helpful, I think that Street expectations are low for the initial launch. But it'd be helpful for you to talk a little bit about the patient journey and what needs to happen before even a single dollar of revenue can be booked.

Charles Wagner Executive

Yes. So we've talked about this, CASGEVY. We are incredibly excited about this. We have a potentially curative therapy here for a patient population who has really had very little in the way of alternatives. And so excitement among patients, among physicians at Vertex is honestly very high.

And we see it as a tremendously large opportunity. We've commented previously that across North America and Europe, we are roughly 35,000 patients among a much larger population of people with CF and thalassemia, who -- the 35,000 though, who would be initially appropriate for this type of therapy. That represents a large multibillion-dollar opportunity over time that we are committed to capture. In terms of the launch this year, we have sort of asked people to think about the patient journey. So for a patient and their physician, they'll go

through a consultation period to figure out if the patient is right for a therapy like CASGEVY.

They have to have a series of tests done if they decide to move forward. There's a cell collection process, which happens in a couple of steps. It's an outpatient process, not all that significant. Then we go to the gene editing and the manufacturing of the actual product itself and then the patient and the physician have to schedule a time for the procedure to take place, involves myeloablative conditioning and then the reinfusion of the edited cells, the patient may be in hospital for up to a month or so before they start to heal and gain the benefits of the therapy. So there are multiple steps to the patient journey and multiple months associated with each step.

So for that reason, that will sort of pace the trajectory of the launch. I think importantly though, we are unconstrained in other ways. Our field organization is fully ready to go. Our medical organization is ready to go. Our patient support organization is ready to go.

We've got ample manufacturing capacity. We are onboarding our authorized treatment centers rapidly. We said we're targeting 50 in the U.S. and 25 in Europe. We've got currently onboarded 12 in the U.S., 3 in Europe, 1 in Saudi Arabia, and we can talk about that opportunity as well.

And payers are enthusiastic as well. So we've announced that we've got an agreement with Synergie, which is a collection of Blue Cross Blue Shield organization, representing 100 million lives. We're very close with a number of other commercial payers in the U.S. Additionally state Medicaid organizations representing 60% of the patient population, have already identified their reimbursement pathways, another 25% are close to having that done. And in the meantime, even where we're not fully contracted, both commercial and state payers have committed to single-case agreements for patients who are motivated and wanted to get going on the process, there's a pathway for that as well.

So reimbursement is not an obstacle either. So we're excited. What we now want to see is patients talking with their physicians, getting ready to go through the process. We are initiating our first patients this quarter. I am not going to comment on it further today, but we will provide an update at the end of the first quarter.

David Risinger Analyst

Excellent. There was some lightning there, I think. Sorry. So why don't we wrap up since we only have 1.5 minutes or so just with other topics. So I guess you can turn one hour into 1.5 minutes.

But on the pipeline, what would you highlight as -- I guess, what cards are turning over the next year or so. You've got a lot going on, cards that will be turning over multiple years, but what would you focus on that we haven't talked about?

David Altshuler Executive

Well, as you said, there's a lot going on. I'll just sort of run the list with cystic fibrosis. Obviously, there's the filing of vanzacaftor and also VX-522, which is our LNP mRNA program with Moderna, that's in its multiple ascending dose. So we're looking forward to seeing that

data trying to help the 5,000-or-so people who can't benefit from our CFTR modulators. Obviously, we talked about CASGEVY in the launch.

With pain, we have initiated a lumbosacral radiculopathy study with VX-548 to try and expand the peripheral neuropathic pain. We have a positive study in Diabetic Peripheral Neuropathy, which is about 20% of PNP, LSR is about 40%. Also, we will also be moving forward, as I described, 993 IV and its studies. And then type 1 diabetes, we'll be reporting additional data on VX-880, and also we'll be sharing that at some point in the coming year in terms of medical meetings, which is the immunosuppression and naked cell program. We also have the VX-264, which is the device plus cells program, which has completed Part A of its first trial and we'll be moving into Part B.

We have AMKD, VX-147 inaxaplin, which had a positive proof-of-concept and it's in pivotal development Phase II/III. The Phase II part has completed, and so we're looking -- we're moving into Phase III. AAT, alpha-1 antitrypsin, we have two molecules that are in the clinic. We just started with myotonic dystrophy type 1, VX-670. We have our first autosomal dominant polycystic disease molecule, which is a protein corrector, just like in CFTR to restore function of PC1, the underlying cause of ADPKD.

Did I leave something out -- there's a lot going on. So...

David Risinger Analyst

And that was extremely efficient. So thank you for that rundown...

David Altshuler Executive

Thank you. It's exciting times at Vertex.

David Risinger Analyst

Phenomenal. Really appreciate you being here. Thank you.

Charles Wagner Executive

Thank you.

David Altshuler Executive

Thank you.