Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated - Special Call - Vertex Pharmaceuticals Incorporated

Thursday, December 19, 2024 8:00 AM

Event Participants

Executives 2
Susie Lisa, Reshma Kewalramani

Analysts 10
Jessica Fye, Salveen Richter, Geoffrey Meacham, Michael Yee, Evan Seigerman, William Pickering, Philip Nadeau, Liisa Bayko, Eliana Merle, Mohit Bansal

Operator Operator

Good morning, and welcome to the Vertex Pharmaceuticals suzetrigine Phase II results in LSR conference call. [Operator Instructions] Please note this event is being recorded.

I would now like to turn the conference over to Ms. Susie Lisa, Senior Vice President, Investor Relations. Please go ahead.

Susie Lisa Executive

Thanks, Drew, and good morning all. I'm Susie Lisa, as the Senior Vice President of Investor Relations. Thank you for joining us on this conference call to discuss results from Vertex's Phase II study of suzetrigine in painful lumbosacral radiculopathy or LSR. Making prepared remarks on today's call, we have Dr. Reshma Kewalramani, Vertex's CEO and President.

Joining her for the question-and-answer portion of the call is Charlie Wagner, Chief Financial Officer.

We recommend that you access the webcast slides as you listen to this call. The call is being recorded, and a replay will be available on our website. We will make forward-looking statements on this call that are subject to the risks and uncertainties discussed in detail in today's press release and in our filings with the Securities and Exchange Commission. These statements, including, without limitation, those regarding Vertex's ongoing work with suzetrigine in pivotal development in diabetic peripheral neuropathy and future studies in lumbosacral radiculopathy including the anticipated timing of these studies. Our

expectations for our suzetrigine programs in acute and peripheral neuropathic pain including next steps and other programs in our pipeline are based on management's current assumptions.

Actual outcomes and events could differ materially. I'll now turn the call over to Reshma.

Reshma Kewalramani Executive

Thanks, Susie. Good morning, all, and thank you for joining us on short notice. Vertex's differentiated R&D strategy continues to progress in new disease areas, and we are pleased to announce results this morning from our Phase II proof-of-concept study with the selective NaV1.8 inhibitor, suzetrigine, in patients with painful lumbosacral radiculopathy or LSR. Let's jump right into it with Slide 3. The study met its primary endpoint with suzetrigine achieving a clinically meaningful and statistically significant within group reduction from baseline of 2.02 points in the weekly average of daily leg pain intensity measured on the NPRS scale at week 12 of treatment.

The consistency of suzetrigine's within group treatment effect is remarkable, with a clinically meaningful reduction in pain across all studies done to date.

However, the study also saw similar reductions in the NPRS in the placebo reference arm. The placebo effect in this study was a 1.98 point reduction from baseline to week 12. In short, the treatment response curve of suzetrigine did not separate from placebo as I'll detail shortly. Importantly, suzetrigine's safety profile continues to be excellent, similar to the findings in our Phase III study, the adverse event rate in the suzetrigine arm was lower than the adverse event rate in the placebo group. Let me share two additional key points on this slide.

Our interpretation of the study. And our hypothesis emerging from this trial, informed by post hoc analysis we conducted is that a high placebo response in this study led to a lack of separation of the suzetrigine and placebo response curves. Importantly, we believe we can innovate in pain clinical trial design to better control the placebo effect and in so doing, succeed in pivotal development with suzetrigine. As such, our next steps are to: one, take all the learnings from this Phase II trial and innovate on study design to better control the placebo effect; two, prepare for regulatory interactions; and three, secure FDA's agreement on an optimized Phase III clinical trial design and requirements for expanding the PNP or peripheral neuropathic pain indication beyond diabetic peripheral neuropathy. Pending regulatory agreement, we plan to advance suzetrigine into pivotal development.

To frame the challenge and the opportunity more fully, recall that peripheral neuropathic pain is a collection of painful conditions unified by the same underlying pathophysiology of nerve impairment. There are approximately 10 million patients treated for PNP each year in the U.S., representing a multibillion-dollar market today despite the fact that essentially all prescriptions are generic. Nearly 20% of these patients have DPN, where we are currently enrolling a Phase III program and about 40% of these patients have LSR. These more than 4 million LSR patients have a significant unmet medical need. The currently available treatment options are associated with high rates of discontinuation, inconsistent dosing, polypharmacy and off-label use.

Unlike in DPN, where studies have been conducted for decades, study design, drug

treatment effect, placebo treatment effects are well understood and multiple drugs have secured regulatory approval. In LSR, no drug has been specifically approved for this indication. There are very few Phase II randomized controlled studies and no Phase III trials evaluating a systemic treatment. This leaves many gaps in understanding, including what constitutes a meaningful between-group reduction in LSR. On the backdrop of these challenges with LSR, we see opportunity.

To be clear, to be successful in LSR, we need to innovate in both discovering NaV1.8 and NaV1.7 inhibitors, as we have been doing, and in clinical trial design to control the placebo treatment as we see from this study. We look forward to doing so and bringing the promise of suzetrigine and our portfolio of NaV1.7 and NaV1.8 inhibitors alone or in combination for this difficult-to-treat condition. Given the lack of studies and standards as LSR, we set out to learn more and run a Phase II study in this condition with 3 goals in mind: one, gauge the magnitude of the treatment effect of suzetrigine in LSR; two, understand the magnitude of the placebo effect in LSR; and three, add to our knowledge of the 12-week safety profile of suzetrigine. Our aim was to gather this information via the Phase II study, learn and then use those learnings to inform our next steps for suzetrigine in LSR. I'll come back to this point.

But before we go there, let's go to Slide 6, which shows the Phase II study design. The evaluated dose of suzetrigine was 69 milligrams once a day and included a placebo reference arm. Patients were randomized to receive either suzetrigine or placebo following a 7-day run-in period to establish their baseline pain score on the NPRS. The primary endpoint was the within group change from baseline in the weekly average pain intensity on NPRS at week 12. We also assess other efficacy endpoints as well as the safety and tolerability of suzetrigine.

Patients, on background stable over-the-counter doses of ibuprofen and naproxen, were allowed to continue taking these doses and acetaminophen was allowed as needed throughout the study. Lastly, the placebo arm was included as a reference group, no direct comparison between suzetrigine and placebos plan, and the study was not designed nor powered for between group comparisons. Slide 7 details the baseline characteristics and demographics which were generally balanced across parameters between the 2 groups. Just over 40% of patients in each arm were on background end stage and continue taking it throughout the trial. The weekly average of the NPRS was around 6.

The results are on Slide 8. For the primary endpoint of within group change from baseline in the weekly average of the pain intensity on the NPRS at week 12, suzetrigine showed a reduction of 2.02 points. This is both statistically significant and clinically meaningful. The placebo reference arm showed a similar within group reduction in the NPRS with a mean change from baseline of minus 1.98 at 12 weeks. Slide 9 summarizes safety and tolerability, which adds to the growing body of evidence supporting suzetrigine's favorable safety profile.

Suzetrigine was generally well tolerated with 12 weeks of treatment. The rate of suzetrigine-related AEs was 22.9%. For context, the rate of placebo-related AEs was 32.4%. The majority of AEs were mild to moderate. There were no serious AEs related to suzetrigine, and there were no AEs that led to treatment discontinuation in the suzetrigine arm.

On Slide 10, we plot the time course of pain relief in the suzetrigine and placebo arms on 1 graph. Both the suzetrigine arm and the placebo arm showed similar reductions in the NPRS

over time. The magnitude of the suzetrigine response from baseline to 12 weeks was statistically significant. It was clinically meaningful. It was consistent with clinical studies of Vertex NaV1.8 inhibitors in other neuropathic pain clinical studies, and it was also consistent with the magnitude of pain reduction with medicines approved for neuropathic pain.

Yet, despite these findings, the suzetrigine and placebo arms did not separate, which was unexpected. To better understand these results, we further interrogated the data. The placebo response in this study was high. Moreover, we found high site-to-site variability in the placebo response with some sites having high and some sites having low placebo treatment effects. Putting this all together, our hypothesis is that the high placebo treatment effect observed in this study, driven by some sites led to a lack of separation of the suzetrigine and placebo curves in the primary analysis.

Moving to Slide 11. To evaluate this hypothesis, we performed post hoc analysis. Let me describe what we did, and then I'll describe the results shown on the slide. As mentioned, when we looked at the NPRS data by site, we observed that there were sites with higher placebo response curves defined as pain reduction of more than 2 points and lower placebo response curves defined as pain reduction, less than 2 points.

We segregated the sites into these 2 groups. Of note, approximately 40% of sites were lower placebo response sites. We then analyze the primary and other endpoints at these lower placebo sites. What did we find when we did these analyses? In the lower placebo response sites, as shown on this slide, we found that the suzetrigine treatment effect was similar to the suzetrigine treatment effect in the primary or overall analysis.

And there was a separation of the suzetrigine arm and the placebo arm. This separation of the NPRS score in the suzetrigine and placebo arms in this analysis is in line with expectations. In other words, here, given the suzetrigine within group performance, of approximately a 2-point reduction, the suzetrigine NPRS pain reduction curve did indeed separate from the placebo NPRS curve. I want to emphasize that this is a post-hoc analysis. And as such, comes with all of the caveats of such analyses and needs to be considered hypothesis generating, not conclusive.

I put weight in this analysis because, one, we had sufficient number of sites to evaluate the suz and placebo effect in the low placebo sites as 40% of the sites were such lower placebo sites. Two, we performed additional analyses that support the robustness of this effect. Three, the suzetrigine treatment effect is consistent in the lower placebo site analysis and the overall or primary analysis. And the suzetrigine response in this study is consistent with the treatment effect seen with other Vertex NaV1.8 neuropathic pain clinical trials. Four, it is also consistent with the treatment effect of other approved medicines in neuropathic pain; and five, high placebo effect and site-to-site variability are known challenges in this space.

Slide 12. In summary, the primary results from this Phase II study in LSR demonstrates suzetrigine as a consistent and clinically meaningful 2 point within group treatment reduction in pain and is well tolerated. The adverse event rate is 22.9% in the suzetrigine arm and 32.4% in the placebo arm. Taken together, including the post-hoc analysis, we see the potential of suzetrigine to offer effective pain relief, strong safety and an attractive overall profile for patients suffering from LSR. This is our belief.

We obviously have yet to demonstrate this potential. To do so, to demonstrate this potential, we have to innovate in clinical trial design to better control the placebo effect. Gain agreements with FDA on trial design and requirements to expand the suzetrigine indication beyond DPN, and show that suzetrigine is superior to placebo in a large, well-designed and controlled Phase III trial. This is exactly what we aim to do. Moving to Slide 13.

Vertex is all in on pain. This slide shows the breadth and depth of our programs. We've discussed our plans in LSR at length. Let me close with some highlights in the pain portfolio outside of LSR. We are excitedly awaiting potential approval for suzetrigine in moderate to severe acute pain with the PDUFA date of January 30, 2025.

Acute pain impacts 80 million Americans and is a multibillion dollar market opportunity despite being almost entirely generic. We are advancing additional molecules through clinical development, including VX-993 in 2 Phase II studies, one in acute pain, one in DPN as well as a Phase I study with the IV formulation. And we continue to make progress in preclinical development with our NaV1.7 pain signal inhibitor program that may be used alone or in combination with NaV1.8 inhibitors. With that, we'll be happy to take your questions. I'll turn it over to you, Susie.

Susie Lisa Executive

You ready, Drew?

Operator Operator

[Operator Instructions] The first question comes from Jessica Fye with JPMorgan.

Jessica Fye Analyst

My question is really about what's the right way to think about how you design and power a Phase III trial and what kind of effect size you would want to size and power your trial or to the extent that we can't really use the Phase II to tease that out per se? And then kind of related to that, if there is the ability to identify sites that might have a lower placebo response, I imagine you're going to need to go to a lot more sites in Phase III than in Phase II, i.e., not just be able to kind of identify these Phase II sites where the placebo response is lower. You talked about kind of innovative ways to manage that. Can you outline what some of those strategies are?

Reshma Kewalramani Executive

Jess, this is Reshma. Really excellent questions. I'm going to give you a broad framework to think about this because what we're in the process of doing is completing our interrogation of the data set to understand every last bit of information that we can. And then, of course, we have to go to the agency and confirm that the innovative study design that we want to pursue is acceptable to them for the indication we seek. But let me give you some broad strokes of what we're doing.

So bottom line is sometimes when you do a Phase II study, it teaches you exactly what to do in Phase III. And that's oftentimes the case. Sometimes what you do in Phase II and the results you get teaches you that you need to do something different. You need to innovate further in Phase III. That's what we've learned from this trial.

And so this trial has been exceptionally helpful because remember, the universe of studies in this LSR condition are small. And even in the small universe, there are unfortunate complexities like studies are of short duration. They are not necessarily done in the patient population that we seek to work on, that is to say, pure radiculopathy amongst other complexities. So first, let me tackle your question around sites. It's pretty clear to me that we need to do some of the, let's call it, usual work that we do when you work on any kind of subjective measure like pain, like a limited number of sites, really good training of these sites and sites really training their patients for how to respond to the questionnaires around their pain in a consistent way over time.

So we will not, in all likelihood, be going to more sites, but rather going to a circumscribed number of sites. That might mean it takes a little bit longer to enroll, and that's an acceptable trade-off. With regard to study design, let me give you some examples. One thing that is done in studies with subjective endpoints is a placebo run-in, and what that does is, it excludes patients who have a pronounced placebo effect when you run everyone and you run the -- whoever you screen, you run both groups in on placebo. You then exclude patients with a profound placebo response.

Another thing that's done is enrichment. That's to say, you run patients in on the study drug, and you only include patients who have a response, i.e., if you're not going to ever feel pain relief, you're not included in that design. Some people combine placebo run-in with enrichment. You can do withdrawals as another technique. Withdrawal of the study drug, withdrawal of placebo to test whether the pain that is a placebo response is equal when you remove the study drug.

Those are a couple of examples of what can be done. There are others. And as I said in my prepared remarks, if you want to have a leadership position in pain and you want to have medicines across the pain spectrum, which is what we want to do in acute pain, oral, IV as well as in neuropathic pain, we're going to have to innovate in bringing these medicines forward from discovery research, but we're also going to have to innovate in managing the placebo response, and I believe that we can do it. Now of course, we have to show that, and we're looking forward to doing that in Phase III. I hope that helps.

Operator Operator

The next question comes from Salveen Richter with Goldman Sachs.

Salveen Richter Analyst

You touched on this a little bit, but could you just speak to what was different about the sites with the low placebo effect? And while clearly, there is a placebo effect, can you also expand on your confidence here that you enrolled LSR patients just given the heterogeneity with that population?

Reshma Kewalramani Executive

Yes. Yes. Salveen, I feel high confidence from the data that we have interrogated that we did, in fact, enroll patients with lumbosacral radiculopathy. You can see in the baseline characteristics, everyone had a dermatomal pain distribution, which is what we would expect

to see. That, I think, is correct.

With regard to sites and what's different about these sites, these are all analyses that will require us to think more deeply about. So I don't want you to think that this is certainly what we're going to do. But I'll give you one example. The sites that had lower placebo response rates had higher baseline and NSAID use. That is obviously important information that we're going to take as we design this Phase III study.

Operator Operator

The next question comes from David Risinger with Leerink Partners. We'll go to the next question from Geoff Meacham with Citi.

Geoffrey Meacham Analyst

Great. I wanted to ask you a few things. The first is in this Phase II, what strategies did you guys use to try to mitigate the placebo response going into it? And the second thing is beyond some of the innovations in Phase III, is there a way to take advantage of the novel mechanism or something in a Phase III that could sort of convey to the FDA, look, this is an opioid alternative, for example, maybe looking at sort of unmet need and sort of the opioid segment of that population? I'm just trying to think of maybe even more creative ways to add to the study beyond just pain scores and looking beyond the placebo washing kind of type of thing.

Reshma Kewalramani Executive

Yes. You bet about the details, Geoff. I'm happy to share. 100% on what you say about the fact that this is a non-opioid and the magnitude of the treatment effect, and look, what I'm about to say to you is cross-study comparisons and you have to take this with a grain of salt. But when you look at opioid that are used in -- it's not exactly LSR, but an opioid, I think it's a NUCYNTA was studied in a clinical trial of chronic low back pain with radiculopathy, so let's call it similar.

The reduction in pain the -- within group reduction in pain in that opioid was a 2 on this NPRS score. In that study, the placebo response was better controlled. So 100% that there is a lot of innovation to be had and lots of ways in which by clinical trial design, by end points, by statistical methods, we have to consider, work through and gain agreement with the agency for how we can best conduct the Phase III study. You asked about what did we do? We -- let's call it, conventional approaches.

We use all the conventional approaches to manage the placebo effect here, small number of sites, training of the sites, sites trading the patients really being very attentive to the inclusion criteria, all those traditional things were done here.

Operator Operator

The next question comes from Michael Yee with Jefferies.

Michael Yee Analyst

Great. Maybe just a two-part question. On the subgroup analysis of the 40% of patients that

you showed on Slide 11, do you think that is a solid representation of what you think the clinical magnitude of efficacy is for this drug ultimately if you have to run the study, it looks like about 0.75 benefit. So maybe just talk about the overall effect of the drug that you think this drug does have if you had run a correct study? And then secondly, just on the AE profile.

Can you just remind us if you saw anything on creatinine clearance or renal? I know that was a question previously, and I just wanted to hear about that if there was anything here on AE profiles that you would want to point out.

Reshma Kewalramani Executive

Yes. Mike, let me take the creatinine question first. Nothing on creatinine, nothing on creatine clearance converted to GFR, use whichever formula you want, there was nothing there. And as a reminder, this is also a 12-week study. On Slide 11, I think that's the slide that is the post hoc analysis of the treatment effect in the suzetrigine arm plotted on the same plot as the within group placebo effect.

Yes, I think that this is representative of the true treatment effect of suzetrigine. And I think this is what we can expect if we are able to control the placebo effect in Phase III. Let me tell you why. The suzetrigine treatment effect, the within-group treatment effect, is in this analysis, it's minus 1.86. It's pretty darn close to what we saw in the overall study, which was a minus 2.02.

Let's just call it approximately 2 both in the post hoc analysis and in the overall analysis. Let's just call it a 2. That is what we see in Vertex NaV1.8 inhibitor studies, the small fiber neuropathy study with VX-150 was about a 2. The DPN studies, as you know, was about a 2.2. And if you look at all neuropathic pain, just because there's more studies in there, when you have trials that are positive when the drugs are approved, the magnitude of the treatment effect is about a 2.

So I feel like this is indeed the proper representation of suzetrigine, and you can get the suzetrigine within group response here or in the overall study. The key, of course, is the difference in the placebo response rate. Here, it's 0.86. In the overall study, it was, let's call it, a 2, it was 1.98 reduction, but let's just call it a 2.

And I do believe that you're not going to get to a placebo response of 0. No study has ever gotten to that. But if you look at the totality of the evidence, you can get close to a 1, 1.3 in that range. And that's the range that we would expect, innovate and plan to get down to in our Phase III trial. And I just want to be clear, we haven't done yet.

We have to show that, and that's what we are intending to do.

Operator Operator

The next question comes from Evan Seigerman with BMO Capital.

Evan Seigerman Analyst

Thank you for all the details. Can you expand on whether there was any observed sleep benefit from the suzetrigine or placebo treatment? And if so, maybe quantify the magnitude

of the benefit. I know that was a key secondary endpoint.

Reshma Kewalramani Executive

Yes. Evan, on the primary analysis, where there wasn't separation of the curve, there wasn't separation of any of the secondary endpoints, including sleep benefits. In the post hoc analysis, where there was separation of the curve where the suzetrigine treatment effect was basically the same about a 2, but we had better placebo effect, let's call it, more in line with the broader neuropathic pain condition. The DCIS, that's the sleep scale also showed commensurate improvement. I don't have the numbers on me, but it was clearly separated in the post hoc analysis.

It was clearly not separated in the primary analysis.

Operator Operator

Next question comes from William Pickering with Bernstein.

William Pickering Analyst

For the post hoc analysis, I was wondering if you could comment on the 2 arms. Were they well-balanced in terms of baseline pain severity? And just any kind of broader comments on the robustness of that post-hoc analysis.

Reshma Kewalramani Executive

Yes. Yes, you bet. Yes, we looked at the balance between these 2 groups in the post hoc analysis, One thing that we benefit from is about 40% of the sites were the lower placebo treatment effect sites, so we had enough sites to look at. And generally speaking, they were balanced, these 2 groups. As I said, there were a couple of things that were different.

For example, one thing that was different is the use of NSAIDs. There was more NSAID use in the lower placebo group. But generally speaking, they were balanced.

Operator Operator

The next question comes from Phil Nadeau with TD Cowen.

Philip Nadeau Analyst

Two from us. So I guess, first on the post hoc analysis. Mathematically, it seems like the only way you can get the results on Slide 11, given what happened in Slide 10. Is it in the other 60% of sites, placebo beat suzetrigine by approximately 1 point. So can you describe the data from the other 60% of the sites?

Was that difference because placebo had a minus 3 improvement in pain score? Or did suzetrigine perform worse in those other sites than it did in the 40% of sites? That's question one. And then question two, why is the next step of Phase III here? It seems like you're going to test innovations, different hypotheses on how to control the placebo effect.

Isn't there a faster and perhaps cheaper way to do that through a Phase II trial rather than moving into a long and expensive pivotal?

Reshma Kewalramani Executive

Yes. So Phil, you have a very interesting and good question around the statistics. And obviously, when you have an overall response where the 2 groups don't separate and you -- then you do a post hoc analysis where one group separates from the other, the overall effect still has to be true. But no, it's not -- the effect in the other group, the higher placebo group is basically a small difference, it's like, I don't know, 0.2 or something like that favoring placebo, but it's not a 1-point difference. And what it basically tells you is that this is not a finding by chance, and of course, we did additional statistical analyses to understand any bias we may have introduced by doing these analyses, and to understand whether this was a finding by chance.

And we're satisfied that this is a good analysis, still it's post hoc and its hypothesis generating, not conclusive. Regarding your question about Phase 2, this is an excellent question. I think the reason the field is played by not having made progress in this condition is because we haven't done large well-controlled studies and really examined with innovative clinical designs, what we can do to manage the placebo effect. Whether you call it Phase II or you call it Phase III, we need to do a study versus placebo that's large and well-controlled that demonstrates statistically significant differences between the 2 groups. When you do that, you are doing a Phase III study.

I'm looking forward to doing it because I'd like to have that study then be represented in a label and broaden the label in peripheral neuropathic game beyond DPN.

Operator Operator

The next question comes from Liisa Bayko with Evercore ISI.

Liisa Bayko Analyst

I hear everything you're saying. I wanted to understand sort of more about the regulatory strategy in the event that you do go down this path. And for suzetrigine doesn't show statistical separation from placebo and LSR, kind of what's the broader strategy for expanding the label into neuropathic pain? I know you need more than one study, and I know you have the other study going on. So just curious how you're thinking about that.

And I know also the guidelines are kind of on hold to some extent or have been withdrawn. So curious about any FDA interactions you've had on that?

Reshma Kewalramani Executive

Yes, you bet, Liisa. So our -- let me go back a few steps. In neuropathic pain, you know we already have our program up and running for DPN. So this is all about how we expand beyond DPN. You also know that there are many conditions in peripheral neuropathic pain in that umbrella, DPN, LSR, herpetic neuralgia, small fiber neuropathy, et cetera, et cetera.

Our preferred path to expand the label is to go through DPN and LSR and have those 2 because in combination, that represents more than 50% of the PNP indication, have those 2 conditions and those studies then lead to a broad PNP label. There are, of course, other ways to get there. Another way to get there would be, for example, 2 DPN studies and then studies

in individual neuropathic pain conditions. In the old guidelines, the agency had particular expectations about numbers of studies and how many indications and they would go one by one. But I think the agency has also said that they are looking to evolve from that and perhaps to a few indications, and that could lead to a broader indication.

So I think that my preferred path has not changed. I would still prefer to go via DPN and LSR to PNP, but there are other ways.

Liisa Bayko Analyst

Okay. And then just a final question from me. Can you comment at all on discontinuations and how that was handled in the study and then any use of rescue meds?

Reshma Kewalramani Executive

Yes, yes. The study had a high maintenance of their subjects that were enrolled. It was more than 90% in both arms. For patients who were -- for patients with rescue therapy, over-the-counter acetaminophen was allowed in both arms, and there was high use as is in all of these studies in both arms of over-the-counter Tylenol and acetaminophen. It's like 80% or so in both arms used PRN, that's to say, as needed acetaminophen.

No differences on that.

Susie Lisa Executive

Drew, we'll take two more questions, please.

Operator Operator

Yes. The next question comes from Ellie Merle with UBS.

Eliana Merle Analyst

Could you just elaborate a little bit more on these other PNP indications of potential strategies? So specifically, what other PNP indications do you think suzetrigine might be best suited for and your latest thinking on development plans there? And I guess, do you have any plans to start anything here in the near or medium term? And if so, what would that look like?

Reshma Kewalramani Executive

Yes. My sentiment around PNP hasn't changed. This is underlying biology. Pain signaling, all pain signaling goes through NaV1.7, which sets off the action potential, initiates the action potential and NaV1.8 which propagates the action potential. From everything we know and just foundational basic biology that has been studied over the last many decades, that's the case for all pain, not just neuropathic pain.

Therefore, my impression, my perspective on the best way to get to the full peripheral neuropathic pain indication is by way of DPN and LSR, as I said, because when you put those 2 together, you're at more than 50% of the patients who have these PNP conditions. As I mentioned, there are certainly other ways to do it. You could do individual studies in each of these conditions. And we ourselves have done studies, for example, in small fiber neuropathy

with the predecessor molecule VX-150, that one was also a positive study. The within group treatment effect of VX-150 was about a 2, the placebo treatment effect in that study was about 1.

So there are definitely other ways to do it, but my preferred path is still to go via DPN and PNP. Those are the -- DPN and LSR to get to PNP. And those are -- that's part of the regulatory conversations we need to have to gain their agreement on that.

Susie Lisa Executive

Last question, Drew.

Operator Operator

Yes. The last question will come from Mohit Bansal with Wells Fargo.

Mohit Bansal Analyst

Just wanted to understand the clinical significance of 1-point reduction, how meaningful that is? And it seems like -- I mean, post hoc analyses on site selection and number of sites which had placebo -- low placebo response kind of gets a lot of risk. So just wanted to understand, isn't it a very risky path to take on with the Phase III trial given the variability in LSR indication?

Reshma Kewalramani Executive

Yes. Thanks for the question, Mohit. The question you asked around what is reasonable to expect for a between group difference is truly an excellent question and the field does not have an answer. The way the field defines clinical meaningfulness is a within group change from baseline. And while there's no specific measure of clinical meaningfulness in LSR, broadly speaking, in the pain area, that is 2 points, within group 2 points.

That's exactly what suzetrigine achieved.

And as I said, it's just hard to do the analysis in LSR because there aren't many studies. But if you broadly speaking, look at peripheral neuropathic pain, the average of all studies is around 2. So I feel very good about the suzetrigine within group treatment effect. So what do you do with the between group? What you do is you power it for statistical significance because there isn't an agreed-upon criteria for that.

And again, if you look at -- no one's ever taken a study to Phase III in LSR. So there's nothing to look at there. There's no approved medicine specifically for LSR, so nothing to look there. So if you look, broadly speaking, at peripheral neuropathic pain, which is kind of dominated by DPN and chronic low back pain with radiculopathy, though that's kind of the study set that you'll see, all of the positive studies have a treatment effect of above 2. Sometimes it's a 1.8, sometimes it's a 2.2, but it's about a 2.

And the placebo response is something south of 1.3. There is one exception to the rule that I laid out these numbers. It's one antidepressant study, where the treatment effect was closer to a 3, but the placebo effect was closer to a 2. And so the difference between them is back down and the achievement of statistical significance was based on one. So there isn't an agreed upon clinically meaningful bar from between groups.

It's based on statistical significance. I hope that helps.

Operator Operator

The conference has now concluded. Thank you for attending today's presentation. A replay of today's event will be available shortly after the call concludes until January 2, 2025, at 11:59 p.m. Eastern Time by dialing (1) 877 344-7529 or (1) 412 317-0088 using replay code 4965951. Thank you.

You may disconnect your lines at this time.