Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated - Special Call - Vertex Pharmaceuticals Incorporated

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Event Participants

Executives 3
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Analysts 9
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Operator Operator

Good day, and welcome to the Vertex Pharmaceuticals VX-548 Phase III Pivotal Program Results in Acute Pain Conference Call. [Operator Instructions] Please note this event is being recorded.

I would now like to turn the conference over to Ms. Susie Lisa. Please go ahead, ma'am.

Susie Lisa Executive

Thank you, Chuck. Good morning all. My name is Susie Lisa, and as the Senior Vice President of Investor Relations, it is my pleasure to welcome you to this conference call to discuss results from Vertex's Phase III pivotal development program of VX-548 in acute pain. 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 are Stuart Arbuckle, Chief Operating Officer; and 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 plans to submit a new drug application or NDA to the Food and Drug Administration

and seek approval for VX-548 for the treatment of acute pain, plans to advance VX-548 into pivotal development in peripheral neuropathic pain and to enroll our Phase II study of VX-548 in lumbosacral radiculopathy, including the anticipated timing of these events, our expectations for our VX-548 programs and other medicines in acute and peripheral neuropathic pain, including next steps, and other programs in our pipeline, are all based on management's current assumptions. Actual outcomes and events could differ materially.

I will now turn the call over to Reshma.

Reshma Kewalramani Executive

Thanks, Susie. Good morning, all, and thank you for joining us on short notice. Today, we're very excited to announce positive results from the VX-548 Phase III pivotal program for the treatment of moderate to severe acute pain. Today's results with VX-548, a novel NaV1.8 pain signal inhibitor, are another important step in Vertex's commitment to transforming the treatment of pain, a significant unmet patient need, and market opportunity.

Here's a snapshot of our journey so far. Less than 2 years ago, we shared the positive results of 2 Phase II studies of VX-548 in acute pain. Last month, we shared the positive results from our 12-week Phase II study with VX-548 in painful diabetic peripheral neuropathy, a type of peripheral neuropathic pain or PNP. And we also began a Phase II study in painful lumbosacral radiculopathy, another type of PNP and the largest within the peripheral neuropathic pain segment in support of our goal of seeking a broad PNP indication. And today, we're announcing positive results from the 3 Phase III trials, a program we designed in support of a broad moderate-to-severe acute pain label.

VX-548 is the cornerstone of our portfolio approach to transform the treatment of acute pain. Our novel nonopioid selective NaV1.8 and NaV1.7 pain signal inhibitors work as illustrated on the right-hand side of the slide. We had high confidence coming into this data readout that the Phase III program would be successful, both in terms of efficacy and safety for 3 primary reasons: one, our pain signal inhibitors target the underlying causal human biology of pain transmission; two, our positive Phase II studies in acute pain were in the same pain conditions using the same endpoint and the dose that demonstrated positive results; and three, the mechanism that is to say signal inhibition in the periphery and its selectivity led us to expect it would be well tolerated without the side effect profile or addictive potential of currently available therapies. With today's results, we have now completed 6 out of 6 positive studies with VX-548, which is remarkably consistent for the field of pain studies. And with these positive Phase III results, we have come full circle with NaV1.8 inhibition.

In Vertex terms, cracking the biology, pouring on the chemistry, delivering compelling pivotal trial results and driving serial innovation to develop a comprehensive portfolio, just as we did in CF. Slide 4 provides the high-level takeaways from this study. Both RCTs met the primary endpoint with statistically significant improvement in pain compared to placebo on the primary endpoint of SPID48, with a p-value of less than 0.0001 in abdominoplasty and 0.0002 in bunionectomy. Both RCT showed a clinically meaningful reduction in pain compared to baseline with more than 3 points of pain reduction from baseline at 48 hours in the VX-548 arm in both studies.

The single-arm safety and effectiveness, or SASE study in patients with pain from surgical and nonsurgical conditions was also positive, and supports longer-term safety and effectiveness in a broad range of acute pain conditions and settings. And finally, across all 3 VX-548 studies, VX-548 was safe and well tolerated.

Our focus now turns to compiling the NDA for VX-548 and submitting to the FDA for the treatment of moderate-to-severe acute pain, and we are on track to do so by mid-2024.

Now on to the details of the Phase III studies. Slide 6 outlines the pivotal program, which was designed with FDA input with the goal of achieving this broad moderate-to-severe pain indication and thus included 3 trials: one, a randomized controlled trial following bunionectomy surgery, a type of hard tissue acute pain; two, a randomized controlled trial following abdominoplasty surgery, a type of soft tissue acute pain; and three, a single-arm safety and effectiveness, or this SASE study, that enrolled patients with pain from surgical and nonsurgical conditions.

The 2 RCTs each enrolled over 1,000 patients with key entry criteria of baseline pain scores of at least moderate pain, which means a score of 4 or greater on the NPRS. The actual mean baseline score was 7.4 in abdominoplasty and 6.8 in the bunionectomy study. Patients were randomized 2:1:2 to receive VX-548 or placebo or hydrocodone bitartrate, and acetaminophen, 5 milligrams, 325 milligrams, which is abbreviated HB/APAP and is the generic version of Norco, and opioid similar to Vicodin. We used Norco at a dose of 5 milligrams hydrocodone, 325 milligrams acetaminophen every 6 hours because it is the most commonly prescribed opioid at the dose and interval within the prescribed range. Treatment lasted for 48 hours in hospital.

In the SASE trial, patients could be treated for up to 14 days in the outpatient setting.

Slide 7 details the primary and key secondary endpoints for the 3 studies. Our press release this morning and my remarks will focus on these endpoints. The primary endpoint for the 2 randomized controlled trials was the time-weighted sum of the pain intensity difference from 0 to 48 hours, or SPID48, compared to placebo. To calculate SPID48, pain is measured on the Numerical Pain Rating Scale, or NPRS, from 0, meaning no pain to 10, worst pain possible at baseline and at specified times over the treatment period.

The difference is compared to baseline and is calculated at each time point and then integrated over the 48-hour treatment period. Higher SPID48 means better efficacy. SPID is the FDA regulatory enabling primary endpoint for acute pain studies. However, practicing physicians tell us that they also focus on the reduction in pain as measured by the NPRS change from baseline. The NPRS change from baseline is also how clinical meaningfulness is assessed in the field.

I'll therefore review both the SPID48 outcome and the NPRS score over time.

The randomized controlled trials also included 2 key secondary endpoints. First, a comparison of SPID48 of VX-548 to hydrocodone acetaminophen; and second, a time to 2-point or greater reduction in the NPRS score from baseline compared to placebo. Time to 2-point reduction was selected because 2 points is considered clinically meaningful. Note that the minimal clinically important difference, or MCID, in some acute pain studies in the

postoperative setting is considered to be a 1-point change from baseline on the NPRS.

Other efficacy endpoints were also assessed and further details of these will be shared at upcoming medical congresses and in journal publications. The SASE study evaluated treatment with VX-548 for up to 14 days across a broad range of other surgical and nonsurgical acute pain conditions. The primary endpoint for the SASE study was safety and tolerability. The secondary endpoint was the patient perception of effectiveness in treating pain on a measure called the Patient Global Assessment, or PGA, at the end of the treatment.

The PGA is a questionnaire that captures patients' perceptions of the study drug effectiveness in treating pain on a 5-category scale: poor, fair, good, very good or excellent.

I'll now review the key findings from each study, beginning with the abdominoplasty results. Slide 9 shows the results for the primary endpoint in the abdominoplasty RCT. Treatment with VX-548 following abdominoplasty resulted in statistically significant improvement on the primary endpoint of SPID48, as recorded on NPRS compared to placebo. The LS mean difference in SPID48 between VX-548 and placebo was 48.4, with a p-value of less than 0.0001.

Slide 10 details the key secondary end point, the first key secondary endpoint, which tested the hypothesis that VX-548 was superior to hydrocodone acetaminophen on SPID48 following abdominoplasty. VX-548 did not meet the key secondary endpoint of superiority to the opioid in this trial, with an LS mean difference between VX-548 and the opioid of plus 6.6 points. Slide 11 shows the results for abdominoplasty on the second key secondary end point, the time to meaningful pain relief defined as a 2-point or greater reduction in NPRS compared to baseline. VX-548 had a rapid onset of meaningful pain relief in the abdominoplasty study, with a median time to meaningful pain relief of about 2 hours compared to about 8 hours for placebo with a nominal p-value of less than 0.0001.

The graph to the left side of Slide 12 illustrates that the reduction in pain with VX-548 was rapid, sustained over the treatment period and clinically meaningful in the abdominoplasty study, as measured by the mean reduction in NPRS. Two points to be made on this slide. As previously described, in acute postoperative pain studies, clinical meaningfulness is defined as at least a 2-point change in NPRS from baseline or at least a 30% reduction in NPRS from baseline. This NPRS score change from baseline is also the assessment that physicians tell us they prioritize.

The chart on the right of this slide provides both these measures. First, VX-548 drove a mean 3.4-point reduction in NPRS from baseline. And second, this VX-548 result equates to a 47% reduction in NPRS from baseline, and thus, both measures are clinically meaningful.

Slide 13 summarizes the safety and tolerability of VX-548 in the abdominoplasty study. VX-548 was safe and well tolerated in the study. The majority of adverse events were mild or moderate and there were no serious adverse events related to VX-548. AEs, including the common AEs, those defined as having an incidence of greater than or equal to 5%, were consistent with the postsurgical setting. Patients treated with VX-548 had a lower overall incidence of AEs than those patients who received placebo, a notable result.

Next, the key findings from the bunionectomy trial. Slide 15 shows the results from the

primary endpoint in the bunionectomy RCT. Similar to the abdominoplasty results, treatment with VX-548 for acute pain following bunionectomy resulted in a statistically significant improvement on the primary endpoint of SPID48 compared to placebo. In the bunionectomy study, the LS mean difference in SPID48 between VX-548 and placebo was 29.3, with a p-value of 0.0002.

Slide 16 details the first key secondary endpoint, which tested the hypothesis that VX-548 was superior to hydrocodone acetaminophen on SPID48 for acute pain following bunionectomy. VX-548 did not meet the key secondary endpoint of superiority to hydrocodone acetaminophen in this trial with an LS mean difference between VX-548 and the opioid of minus 20.2.

Slide 17 shows the results for bunionectomy for the second key secondary endpoint, which, as with abdominoplasty, is the time to meaningful pain relief defined as a 2-point or greater reduction in NPRS from baseline compared to placebo. VX-548 had a more rapid onset of meaningful pain relief than placebo in the bunionectomy study as well, with a median time to meaningful pain relief of 4 hours for VX-548 compared to about 8 hours for placebo, with a nominal p-value of 0.0016.

The graph on the left side of Slide 18 illustrates that reduction in pain with VX-548 was rapid, sustained over the treatment period and clinically meaningful in the bunionectomy study as measured by the mean reduction in NPRS.

Two points also to be made on this slide. First, as I discussed with the abdominoplasty results, clinical meaningfulness and physician practice focuses on the NPRS score change from baseline with a 2-point or greater change in NPRS from baseline or a 30% or greater reduction in NPRS from baseline considered clinically meaningful.

The chart to the right details the VX-548 results, with a mean 3.4-point reduction versus baseline, and VX-548 drove a 51% reduction from baseline in NPRS. Again, both results are clinically meaningful.

Slide 19 summarizes safety and tolerability for VX-548 in the bunionectomy study. 548 was safe and well tolerated in this study as well. As in the abdominoplasty study, the majority of AEs were mild or moderate. And in this study, there were no SAEs. AEs, including common AEs, again, those defined as having an incidence of greater than or equal to 5%, were consistent with the postsurgical setting.

Patients treated with VX-548 had a lower overall incidence of AEs than those patients who received placebo. And as I said previously, this is a notable result for both studies.

Moving now to the single-arm safety and effectiveness trial. On Slide 21, the SASE study evaluated VX-548 for up to 14 days across a broad range of other surgical and nonsurgical acute pain conditions, including orthopedic, plastic and general surgeries and nonsurgical pain conditions for example, a sprain, a contusion or fracture as detailed on the right side of Slide 21. This study demonstrated favorable safety and tolerability, which was the primary endpoint as well as effectiveness on the secondary end point measured by the Patient Global Assessment Questionnaire at the end of the treatment period. 83.2% of patients rated the effectiveness of VX-548 in treating pain as good, very good or excellent at the end of

treatment.

To pull these data sets together and now to give you the full picture. Slide 23 shows side-by-side that both RCTs met the primary endpoint of pain relief compared to placebo, with a SPID48 LS mean difference from placebo of 48.4 in abdominoplasty and 29.3 in bunionectomy.

Slide 24 puts this primary endpoint into the clinical context, showing the rapid, sustained and clinically meaningful reduction in pain for both studies, as shown on the graphs to the left with the mean change from baseline in NPRS. The charts on the right provide the details showing that VX-548 drove a mean 3.4-point clinically meaningful reduction from baseline NPRS in both abdominoplasty and bunionectomy representing an approximately 50% and clinically meaningful reduction from baseline in both studies.

With that summary of the efficacy results across the pivotal program, let me provide a framework for considering these results in the context of opioids, which are often used as first-line therapy in moderate to severe acute pain conditions.

Slide 25 depicts all studies described in the literature, that have studied opioids to reduce pain in both the post abdominoplasty and post bunionectomy surgery settings and evaluated SPID as the efficacy endpoint. This slide includes all VX-548 acute pain studies, both Phase II and Phase III.

This is a busy slide, so let me draw your attention to a few points. First, the VX-548 results are quite consistent across Phase II and Phase III and across bunionectomy and abdominoplasty with a SPID48 score of about 30 to 50. You can see this at the top of the slide to the very far right. Second, the efficacy of VX-548 is also consistently strong. As you scan the far-right column of the table, which provides the SPID48 scores from all of the studies, you'll see that the SPID48 scores for opioids vary from about 4 to about 110 and the medicine that achieved the highest SPID48 of 107.6 at the bottom of the slide is IV morphine.

Of note, IV morphine also achieved SPID48 scores of 56.2 and 57.5 in 2 other studies. Another point that may provide context is in the middle of the page, where you can see the results of IV tramadol in abdominoplasty and bunionectomy, where it achieves a 25 in 1 instance and a number a little bit more than 50 in another instance.

Lastly, it is gratifying to have the consistent strong efficacy of VX-548 in combination with the kind of safety and tolerability results that VX-548 has delivered, including lack of addiction potential by way of its mechanism of action. This is what makes VX-548's overall efficacy and safety profile so very compelling.

With that broader context, Slide 26 summarizes the safety profile of VX-548 in the pivotal program. Across all 3 studies, the majority of AEs with VX-548 were mild or moderate in severity. Across all 3 studies, reflecting more than 2,400 patients, there were 0 SAEs related to VX-548. And in general, the AEs in the 2 RCTs were consistent with the postsurgical setting.

Finally, in the 2 RCTs, the incidence of AEs in the VX-548 arms was lower than in placebo. The Phase III results demonstrate VX-548 offers the compelling combination of both a strong

efficacy and a strong safety profile that can be used for moderate to severe pain across a range of pain conditions, both surgical and nonsurgical and across a range of settings, both inpatient, surgical centers as well as in the ER or outpatient setting.

In the treatment landscape today, in general, the options for acute pain center around: one, limited efficacy medicines with good tolerability; or two, opioid medicines with therapeutic efficacy, but known risks, including addiction potential. Neither is a very satisfying choice for patients, physicians or society and 1 need to look no further than the opioid crisis in America to recognize the gravity of this situation.

It is for this reason the high unmet need that we're so very excited with these results. VX-548 could be the first new class of acute pain medicines in over 20 years, and 1 with truly transformative potential that could be used as first-line therapy. It holds the potential to fill the therapeutic gaps depicted on Slide 27 and gives us enthusiasm for the significant opportunity for this non-opioid, peripherally acting, pain signal inhibitor with therapeutic efficacy, compelling safety and tolerability and by way of its mechanism of action, no concern for addictive potential. We look forward to the prospect of bringing VX-548 to the approximately 80 million patients who are prescribed a medicine for their moderate-to-severe acute pain every year in the U.S.

Slide -- the next slide details the breadth and depth of our pain portfolio, which reflects our goal to transform the treatment of pain and our commitment to serial innovation. You've seen us do this in CF, and we aim to do the same in pain and every other disease in our sandbox.

To conclude today's results -- sorry, to conclude, today's results, put a fine point on the body of evidence that our selective NaV1.8 inhibitors represent the first potential new class of acute pain medicines in over 2 decades. Today's results demonstrate the safety and efficacy of VX-548 in acute pain across multiple surgical and nonsurgical pain types and multiple settings. VX-548 has secured both fast track and breakthrough designation, and we are moving quickly to submit our NDA, targeting a broad label for the treatment of moderate to severe acute pain. We are on track to make the submission by mid-2024.

We came into the Phase III VX-548 pivotal data readout with high confidence and have been working towards rapid submission of our NDA and also preparing for potential commercialization. Our prelaunch activities are underway, and we continue to build out our specialty capabilities for acute pain so that we can meet our goal of bringing this potentially transformative non-opioid medicine to millions of patients who are waiting.

With that, we'll be happy to take your questions.

Operator Operator

[Operator Instructions] And the first question will come from Geoff Meacham with Bank of America.

Geoffrey Meacham Analyst

Congrats on a great data set. Just have a couple of questions. The first, I know hydrocodone is a tough comparable over 48 hours for both studies for superiority, and I get the positioning

on no addictive potential, but how do you think payers will view efficacy relative to cost benefit for 548? And then the second question is just on onset of action. It looks like 548 starts to separate, but after 8 hours, pain is probably worse than that initial period.

So I want to get your perspective on that as well.

Reshma Kewalramani Executive

Yes, absolutely. Geoff, thanks so much for the kind words. It is really a great data set, and we are very excited. Let me take the question on onset, and then I'll turn it over to Stuart to talk about the payers. As you look at the pain studies, I'd look at both studies together.

You know how notoriously difficult it is to do studies in pain. And I think it's very valuable to look at the overall data set to look at the bunionectomy as well as the abdominoplasty. In both of those studies with the placebo, it's about 8 hours to the 2-point change, which is the clinically meaningful change.

And with the 548 medicine, it's much less than that. So 8 hours for placebo. In abdominoplasty, it's 2 hours for 548 and in bunionectomy it's 4 hours. But remember, that's to the 2-point number. We did secondary endpoints, and I didn't share all of the endpoints here today.

But looking at the change, the time to 1-point improvement, which is a minimal improvement, it's like 30 minutes in abdominoplasty and something like 60 minutes in bunionectomy. And of course, you'll see all of those results in the full data set.

Stuart, over to you for a comment on how you see this profile with payers.

Stuart Arbuckle Executive

Yes, thanks for the question, Geoff. I think payers are going to be terrifically excited about the VX-548 profile, and this is why they know that they are just about -- the opioids are just about the only effective medicine that's approved for moderate-to-severe acute pain. But they're also very well aware of the significant adverse events up to and including addiction potential. And that's why just about every payer in the government and commercial sector, just about every hospital, just about every state has restrictions in place that govern who can prescribe opioids, for which patient types, what length of prescription they can be given. And all of that is as a result of the well-known link between the use of opioids in the acute setting and their use chronically and subsequently dependence and addiction risk.

So we know that the payers don't like opioids, but reluctantly, that's the only thing that really is available right now to treat moderate to severe acute pain. And now there's going to be another treatment option, 1, which is an entirely new class of therapy that has both compelling efficacy, but as Reshma has outlined, a really good-looking safety and tolerability profile.

And I think what we're going to see is more of the sort of see change that we've seen over the last couple of years, which is away from legislation and guidelines that are looked to restrict the use of opioids, but more things that are going to remove financial incentives and other barriers and encourage the use of nonopioids. And we've talked previously about the NOPAIN

Act, this add-on payment for the outpatient setting in the ambulatory surgical center setting to provide an add-on payment for non-opioid pain management. I think we're going to see more legislation like that, that's going to be looking to try and encourage the use of opioids consideration -- sorry, reduce the barriers to the use of nonopioids, consideration of nonopioids in advance of opioids, things like reducing co-pays or equalizing co-pays between a branded medicine and generics.

So as I say, I think payers are going to warmly welcome the advent of a truly non-opioid pain med that has this compelling combination of efficacy and safety and tolerability.

Operator Operator

The next question will come from Evan Seigerman with BMO Capital Markets.

Evan Seigerman Analyst

Just taking a step back, kind of following up to kind of what Stuart was just talking about. Maybe talk a little more about the policy environment that will support the commercialization of this product, assuming approval next year. Can you also speak to the physician feedback you may have gotten from this initial read of the data?

Reshma Kewalramani Executive

Yes. Evan, let me maybe give you a quick view on at least some physicians. Obviously, the data are brand spanking new. We had a chance to talk with the Steering Committee of the trial, and they were overjoyed. I'll turn it over to Stuart to talk about the policy environment.

I'll just make a top line comment, which is, we are in a moment in time where the ill effects of opioids and the addictive potential of opioids, even in short-term use is well known. There's no education needed on that front. And as Stuart talks about, we are now moving from a place where it's all about policy restricting opioids to policy encouraging non-opioids, except before today, we didn't have a medicine that could do what 548 does. Stuart, a few more comments on the policy environment.

Stuart Arbuckle Executive

Yes. Evan, I'll just amplify what I said in answer to Geoff's question. I referenced NOPAIN, the act that was put into legislation at the end of 2022. We know there is a NOPAIN 2.0, which is looking to do something very similar for the inpatient hospital setting, which is clearly a very important setting of care for the treatment of moderate-to-severe acute pain. We know there's other legislation pending, which is looking to do in places like Medicare, something similar that's looking, as I said, to equalize things like co-pays for a branded non-opioid to the same or no more than a generic non-opioid to make sure that there are no financial barriers to patients being able to access a truly effective non-opioid medicine.

There are already guidelines, including CDC and other that recommend the use of nonopioids in -- ahead of opioids. But as Reshma said, really until the advent of this new class of therapy, there hasn't really been a truly effective pain relief of a moderate-to-severe acute pain that is a non-opioid that patients and physicians consider -- that could consider. So I do think -- there has been a sort of a 180-degree shift, if I can put it, in the legislative environment from

looking to restrict opioids.

I think there's now going to be a legislative environment that is looking to provide a tailwind to the use of a truly effective non-opioid medicine like 548.

Operator Operator

Next question will come from David Risinger with Leerink Partners.

David Risinger Analyst

So could you please talk about the median time to pain relief in the studies, and also discuss whether you believe that your additional NaV1.8 inhibitors that are in Phase I testing may offer faster time to pain relief.

Reshma Kewalramani Executive

[Dan], it's Reshma. Let me just make sure I make this point again. We shared 1 of the assessments that we made in terms of time to pain relief in today's press release and in the slides that I shared. And that is the time to meaningful pain relief, which is 2-point improvement. And that is -- that was versus placebo.

That's the predefined secondary endpoint. And that's the number that is 91 minutes or -- I'm sorry, 480 minutes, so about 4 hours with the placebo. It's 475 with the opioid and it's like 119 with VX-548. But the comparison is 548 versus placebo.

The second time to improvement of pain measure that we have is the time to 1-point improvement. That's the minimally important difference. We didn't share those results because it wasn't a key secondary endpoint. But as I said, in the abdominoplasty study, it's around about 30 minutes for 548. And in the bunionectomy study, it's round about 60 minutes for VX-548.

In terms of what are we -- so it's really excellent in that regard. In terms of what are we looking for, for 993, which is the next NaV1.8 inhibitor on deck. It's making its way -- that one is actually already finished Phase I, and that's the one we're looking to move to Phase II this year. And then there's many more after that, and there's also NaV1.7. It's basically the same thing that we did in CF.

If it is possible to get even better than 548, we are determined to be the ones who do so. So what are we looking for? We're looking for more of what we just delivered with 548.

Operator Operator

The next question will come from Salveen Richter with Goldman Sachs.

Salveen Richter Analyst

Congratulations on the data. With regard to reduction in pain with the mean NPRS scores over the treatment period, as we look to bioequivalence versus opioids, how are you thinking about profile over time, noting the convergence at 48 hours? And then secondly, in the context of the profile that's now emerged for VX-548, just speak to your approach to

commercialization and if that, in any way, has been impacted here?

Reshma Kewalramani Executive

Yes. Thanks, Salveen. Really appreciate the kind words on 548 and the profile versus opioids. Physicians tell us that one measure that they prioritize and look at is that NPRS over time. And specifically, what they're looking at is what pain do you start with and what pain do you end with?

That's one of the slides we showed. And is that pain score more than 2 points? And is the reduction more than 30%?

And in the case of VX-548 it is 3.4 points and is about 50%. It's 3.4 points of reduction across both studies, and it's about 50% reduction across both studies. And it is interesting that you point out, and it's true that when you get to the 48-hour time period, it's virtually the same for the opioid and VX-548. And I think that's a very important finding because what it tells you is where -- whatever you start at, you end at the same place, except you can end at this place, which is -- it's a clinical -- beyond the clinical meaningfulness of 2 points and 30% with a non-opioid with the kind of safety and tolerability that we showed and because of its mechanism of action without the risk of addiction.

Stuart, over to you for some comments around commercialization.

Stuart Arbuckle Executive

Salveen, I would say the profile that we've released today really just adds to my excitement about being able to take the first new class of pain med for acute pain to market for over 20 years now. And that profile, which is that blend of compelling efficacy with a really great looking safety and tolerability profile, we know really fills an enormous need in the marketplace.

As we've said a number of times, there's 80 million, 8-0 million patients a year in the United States receive a prescription for moderate-to-severe acute pain and their choices are really limited. They either have products which have relatively limited efficacy, but a known tolerability profile, and on the other end of the spectrum, they have opioids, which they know can provide really effective therapeutic efficacy, but have a significant adverse event profile, including, but not limited to addiction potential. And so there is this enormous unmet need in the market, which has frankly led to suboptimal management of acute pain. And that's the opportunity that VX-548 is going to be able to satisfy. So we're tremendously excited about it.

We're committed to our specialty sales and marketing model. As I've mentioned a number of times, we'll be looking at recruiting round about 150 sales representatives to focus on about 2,000 institutions, hospitals, surgery centers, things like that, that account for the majority of patients who are being treated with moderate-to-severe acute pain. And I can't wait to bring those people on board in advance of an FDA approval down the line here. It's a really exciting day for us and for patients.

Operator Operator

The next question will come from Liisa Bayko with Evercore ISI.

Liisa Bayko Analyst

I'm curious if you could provide any additional insights from the third study, the sort of all-comer study? Were there some types of surgeries where you maybe got a stronger response? You had an 83% good or better, for the remaining 17% were those clustered in any particular areas? It seems like there's a little bit of a difference. And I don't know if this is just like study variability between response in bunionectomy and abdominoplasty, which are different models, so I was just curious about that.

And then the follow-up is where you might present this data in terms of upcoming medical conferences?

Reshma Kewalramani Executive

Yes. Yes. Sure thing, Liisa. With regard to the single-arm safety and effectiveness study, we explicitly didn't include abdominoplasty or bunionectomy. We were looking to broaden the patients with different kinds of pain, but we had all sorts of surgical patients, be it orthopedic, plastic, ENT, and we had a whole host of nonsurgical pain.

And the results were equally good across all of the different pain types, surgical -- within the surgical category and across surgical and nonsurgical. And Liisa, as you think about bunionectomy and abdominoplasty, I think that the point you make about the fact that the numbers are different, it's actually kind of interesting how similar the VX-548 overall efficacy between abdo and bun in Phase III and between Phase II and Phase III are. We're somewhere between SPID48 scores of 30 and 50 across a number of trials. That's really remarkable consistency.

And if you look at Table 25, it was a slide that we pulled together from the literature, you'll see that drugs -- even well-known drugs, like the 2 I called out, performed differently over different studies, whether it's the same condition or not. With regard to -- so for me, the consistency and the strength of the efficacy looks really good. And where we'll be presented? I don't know yet. I'm sure it's going to be at congresses this year, but these results really are just fresh.

And I'm sure the team is busy thinking about where they can show the data, but I do expect it will be this year.

Operator Operator

The next question will come from Jessica Fye with JPMorgan.

Unknown Analyst Analyst

This is Nick on for Jess. Congrats on the data again. Two from us. Is there any chance that 548 could be combined with OTC pain medicines like Tylenol? And then also, looking ahead, how are you thinking about commercialization ex U.S.

here?

Reshma Kewalramani Executive

Yes. Let me take number one, and I'll let Stuart take number 2 about commercialization, geographically speaking. So it's a very interesting question you raised. The comparator opioid that we used in the study in both Phase II and Phase III is Norco. And as I said in my prepared remarks, when you break it down to figure out what is Norco, Norco is hydrocodone, the opioid plus acetaminophen.

So it's actually 2 medicines. It's not singularly an opioid. And it is known that the hydrocodone effect is better when you combine it with acetaminophen. And that dual combination we took versus our singular VX-548. So yes, can VX-548 be combined with acetaminophen or ibuprofen?

Absolutely. Is that what we did in our study? No, because we did a pure VX-548 to demonstrate the strength of the efficacy and also the safety profile of VX-548. But absolutely, it can be combined. And I expect that it will be.

Just to round out combinations and permutations, I wanted to also let you know that the DDI profile, the drug-drug interaction profile of VX-548 is very favorable, and it can be taken with all of the usual medications that you would expect people to be on, antihypertensives, medicines for lipid lowering, et cetera, et cetera.

Stuart, over to you for commercialization in terms of geography.

Stuart Arbuckle Executive

Yes, Nick. So given the unmet need in acute pain and in particular, the sadly opioid epidemic here in the United States, our focus with 548 in the development of acute pain has been to develop it and commercialize it firstly here in the United States.

I will remind you, though, that across the pain program, we are also looking at neuropathic pain, and we recently reported the Phase II data on VX-548 in neuropathic pain. Neuropathic pain also has very significant unmet need here in the U.S. but also has very significant unmet need in the rest of the world. The treatment options there are also relatively limited, characterized by variable efficacy and also significant adverse event profiles.

And as that profile -- as that program progresses, we are looking at the opportunity for pain, not just here in the United States, but outside of the United States as well.

Operator Operator

The next question will come from Debjit Chattopadhyay with Guggenheim Securities.

Debjit Chattopadhyay Analyst

Congrats on cracking open the NaV1.8 target. Couple of questions here from my side. Could you sort of elaborate on the use of rescue meds antiemetics and time to recovery in the recovery room, the totality of which might drive adoption post-surgical -- in the postsurgical setting. And then where do you really see adoption? Is this more of a post discharge from the hospital where patient gets another 4 to 5 days of scripts and it's not under the DRG?

Reshma Kewalramani Executive

Debjit, was the first part of your question, did you also say antiemetics?

Debjit Chattopadhyay Analyst

Yes or...

Reshma Kewalramani Executive

Yes, yes, sure, sure. So with regard to rescue medicine, as you know, in the acute pain setting, rescue medicines are ubiquitous, and that was the same in this study across the board in all 3 arms, more than oh, gosh, 75%, 80% of people used rescue medicine, which was ibuprofen, Tylenol that kind of medicine, but it was -- it's ubiquitous and it's used -- it was used in all 3 arms. The specific data we'll share along with all of the other endpoints.

I want to address your very good question about antiemetics. If you look in the safety table, you will see that the incidence of nausea is quite different in the VX-548 group versus the opioid group, and nausea was specifically 1 of our secondary endpoints. So you'll see this when it comes out in full form as well. And it's vastly different with much less nausea in VX-548. So the use for antiemetics is obviously going to be lesser because that's just simply not a prominent feature with our medicine, which is 1 of the things that I'm very happy about.

You had a question about adoption. Do we see it in hospital? Do we see it outside of a hospital setting? Stuart?

Stuart Arbuckle Executive

Yes. Thanks. So just to clarify, what we're seeking with VX-548 is a broad label for the treatment of moderate-to-severe acute pain. That could be post-surgery, but that is not the extent of the label that we are seeking. We're looking for a broad moderate, severe acute pain label so that the medicine would be able to be used in pain across a variety of different conditions.

And indeed, a variety of different settings just as you were outlining, and that's the reason why we designed the Phase III program as we did.

In terms of where am I anticipating utilization, I'm expecting given the profile we've shared today that we're going to get broad adoption of 548. I do think we're going to get usage in the institutional setting for patients who have had a procedure or have been -- remain in the institution. But I also think we are going to get utilization at discharge, as you said, for ongoing pain management when people leave the institution.

One of the things that you threw out there was the DRG, and this goes back to the comment I was making about financial incentives or disincentives for certain medicines. The reason why NOPAIN Act is so important is it addresses in the outpatient setting and the ambulatory surgical center setting this issue of a financial disincentive to use a branded medicine when generics are available within the DRG. And what NOPAIN Act does, just to remind people, is it creates an add-on payment for the non-opioid pain management. As I said, we know that there is [indiscernible] to do to look at NOPAIN 2.0. NOPAIN 2.0 would look to do the same thing for the inpatient setting, so that there would be an add-on pain medicine for non-opioid pain management over and above the DRG.

So that's why I think it's so important to focus on some of these policy initiatives, which I think are going to provide tailwinds to the use of a truly effective non-opioid pain medicine.

Operator Operator

The next question will come from Brian Abrahams with RBC Capital Markets.

Brian Abrahams Analyst

Just given the safety profile that you're seeing here, can you talk about the potential for exploration of even higher doses of 548 in future acute pain work? And maybe also on the dosing, how do these results shape your plan for dose levels you might test in future chronic neuropathic pain studies as well?

Reshma Kewalramani Executive

Yes. We think we've reached the appropriate dose for VX-548 in acute pain. And you can see it with the really terrific results from this morning along with the safety profile that we showed. As we discussed when we were talking about the DPN results in December, there is accumulation of VX-548, and we've known that. And so I expect that the dose for DPN to be the doses that we studied in Phase II.

As I said, the exact dose that we're going to be advancing to Phase III depends on the conversations we're going to have at our end of Phase II meeting with the regulators. But you'll remember, in DPN, we studied 23, 46 and 69 milligrams. And here, in acute pain, we have a 100 milligrams for the first dose and 50 milligrams for the subsequent doses.

Operator Operator

Next question will come from Michael Yee with Jefferies.

Unknown Analyst Analyst

This is [indiscernible] on the line for Michael Yee. Congrats on the results. I guess I'm interested in your interpretation that VX-548 actually looks similar to Vicodin in both studies and in fact, was statistically inferior to Vicodin in the bunionectomy study. And secondly, I think it seems like there's also advantage in less dosing frequency. So maybe can comment on that, how important is that in your commercialization?

Reshma Kewalramani Executive

I think your question was around the therapeutic efficacy of VX-548 and then a question on dosing. Okay.

Unknown Analyst Analyst

Yes.

Reshma Kewalramani Executive

So on the therapeutic efficacy, I want to be doubly clear that the comparisons made in the study are VX-548 versus placebo for the primary endpoint. That primary endpoint was met

statistically. And on the key secondary endpoint of 548 versus the opioid, it was not met. I want to be very clear about that.

The discussion we were having that is related, but separate from the SPID48 score, which was this primary endpoint versus placebo and secondary endpoint versus opioid is a, as I said, similar but different construct. That is about the NPRS score over time, not the SPID48. The NPRS score feeds the SPID48, but if you look at the NPRS over time, what you see is you start at approximately the same number, round about, let's just call it a 7, in abdominoplasty and bunionectomy. And in the 548 arm, when you look at the improvement in the pain score, it's 3.4 points in both abdominoplasty and bunionectomy.

And then you can do that same analysis for placebo, and you can do the same analysis for the opioid. And then you see when you look at where you start, which is about the same place, baseline NPRS score, and you look where you end the NPRS score at week 48, that number is approximately the same for the opioid group and the 548 group, and it's different than the placebo group.

And when you look at that and translate that NPRS score into percent, so the relative improvement, it's about 50% for the VX-548 group across both studies. And then that cable can show you what it is for the other arms.

Stuart, there was a question about how you see the dosing of 548 be -- how you see it in terms of commercialization?

Stuart Arbuckle Executive

Yes. So the dosing frequency being twice a day, which is what VX-548 is, is clearly great and is an advantage. I would say it is a tertiary benefit after compelling efficacy and a really good safety and tolerability profile. Remember, this is acute pain. These are people who are in acute pain.

They want relief from their pain without the risk of significant adverse events and the potential for addiction. So I would say it's important.

But in terms of a hierarchy, I would say efficacy and safety and tolerability are higher up the list of things that physicians and patients are looking for.

Operator Operator

The next question will come from Terence Flynn with Morgan Stanley.

Terence Flynn Analyst

Congrats on the data. I was just wondering if you can share any data that might have been collected from both trials on time to discharge for both 548 and Vicodin?

Reshma Kewalramani Executive

Yes, that's such a great question, Terence. The study was a 48-hour study. So it's 48 hours in all of the arms. But that is certainly something that I'm sure we and the community will be exploring because the safety profile of VX-548, we would lead you to believe that patients

would do better and that they would be able to leave the hospital, especially because of the nausea component and some of the other known concerns with opioids. But in this study, it was 48 hours as a treatment period.

Susie Lisa Executive

With that, Chuck, can you read out the replay information? We'll conclude the call. Thanks very much, everyone.

Operator Operator

Yes, ma'am. Thank you for attending today's presentation. A replay of today's event will be available shortly after the call concludes by dialing 1 (877) 344-7529, or 1 (412) 317-0088 and using the replay access code 10185969. Thank you, and have a great day, everyone.