Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated - Special Call - Vertex Pharmaceuticals Incorporated

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Susie Lisa Executive

Good evening, everyone. My name is Susie Lisa, and I'm the Senior Vice President of Investor Relations for Vertex Pharmaceuticals. Thank you so very much for those of you here in the room for joining us in Philadelphia at the American Society of Anesthesiologists for our Vertex suzetrigine update. Thank you as well to all of you on the webcast. Tonight, Vertex is extremely pleased to have 2 physicians here for you to share their views on the Phase III data, the pain landscape and the potential for suzetrigine.

Our first speaker will be Dr. Todd Bertoch. He is a Diplomat of the American Board of Anesthesiology, and he is CEO of CenExel JBR Clinical Research based in Utah -- it's a clinical research organization based in Utah, excuse me. Dr. Bertoch is a principal investigator for the suzetrigine Phase III randomized studies in acute pain.

We're also joined by Dr. Ashraf Habib, Professor of Anesthesiology, Professor of Obstetrics and Gynecology and Chief of Division of Women's Anesthesiology at Duke University Hospital. We'll also provide some highlights on our commercial strategy in acute pain. For that, I'm excited to introduce to you tonight Duncan McKechnie, who is our Senior Vice President, Head of North America Commercial. Duncan leads all of our commercial efforts in North America across all of our CF products, including TRIKAFTA as well as for CASGEVY as well as for the pain franchise.

Duncan has been with Vertex for over a decade, having joined after 13 years of leadership roles at Novartis and began his career at GlaxoSmithKline. For the Q&A session, we ask that you focus your questions primarily while we have the physicians here for doctors Bertoch and Habib, but they'll also be joined by Duncan as well as our CFO, Charlie Wagner; and Paul Negulescu, who's SVP and leader of our pain program and a member of Vertex's research leadership team. For those on the webcast, we recommend that you access the webcast slides as you listen to the call and 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 Friday's press release and in our filings with the Securities and Exchange Commission. And with that, I'll now turn the call over to Dr.

Todd Bertoch.

Todd Bertoch Attendee

As mentioned, my name is Todd Bertoch. I'm an anesthesiologist and I'm the principal investigator for the clinical trials that I'll be discussing here tonight. I'm also a consultant for Vertex Pharmaceuticals. So there are at least 9 distinct voltage-gated sodium channels in humans. The NaV1.8 channel expressed on peripheral nociceptors and DRGs has a critical role in transmitting pain signals.

Suzetrigine, which we'll be discussing tonight is a potent oral non-opioid small molecule that selectively inhibits peripheral NaV1.8 nociceptors. Because NaV1.8 channels are not expressed in the brain, suzetrigine, unlike opioids, doesn't have the potential for -- addictive potential. So suzetrigine has the potential to be the first treatment for moderate to severe acute pain from a new pharmacologic class in over 2 decades. Today, I'm excited to report on the II phase clinical -- Phase III acute pain clinical trial studying suzetrigine in over 2,000 subjects, making them the largest ever Phase III trials in their respective indications. Those indications abdominoplasty and bunionectomy are well-established models accepted by the FDA as representative of acute pain states in general.

So subjects underwent either full abdominoplasty under general anesthesia or bunionectomy under continuous popliteal nerve block with sedation. Upon experiencing moderate-to-severe postoperative pain subject to a randomized to receive either suzetrigine with 100 milligram loading dose followed by 50 milligrams every 12 hours or hydrocodone/acetaminophen 5/325 every 6 hours or placebo. The moderate strength opioid combination drug, hydrocodone/acetaminophen was chosen because it is the most commonly prescribed opioid after these procedures. Subjects were then allowed to receive ibuprofen 400 milligrams every 6 hours as needed for breakthrough pain. The primary and key secondary endpoints for this were the same in both clinical trials.

The primary endpoint was SPID over 48 hours for suzetrigine compared to placebo. SPID is a measure of the total pain reduction after treatment using a 0 to 10 numeric pain rating scale, and it's the most commonly used and FDA-preferred endpoint in acute pain clinical trials. The first key secondary endpoint was SPID48 for suzetrigine versus hydrocodone/acetaminophen. And the next key secondary endpoint was the time to meaningful pain relief. This was defined by a 2-point or greater reduction in pain from the baseline pain compared to placebo.

These data were then analyzed to assess suzetrigine's efficacy, both as a monotherapy and an additional ad hoc analysis was done of ibuprofen rescue medication to estimate the potential impact of suzetrigine as a component of a multimodal analgesia regimen. The demographics and baseline characteristics were balanced across treatment groups within each trial. You'll note here on the slide that the average baseline pain in the abdominoplasty trial was higher than in the bunionectomy trial, and we'll discuss the implications of that on an upcoming slide. Both studies met the primary efficacy endpoint by demonstrating statistically significant pain reduction compared to placebo with very highly significant p values. The top half of this table that you're looking at represents the efficacy of suzetrigine as a monotherapy.

The bottom half of the table is an estimate of it's potential impact as part of a multimodal analgesia regimen with ibuprofen. It's important to note that because ibuprofen was given sporadically and only at high pain levels during this clinical trial, these data significantly understate how effective suzetrigine might be in a true multimodal analgesia regimen when concomitant ibuprofen is administered on a regular schedule. So these are the graphic representations of the change in pain intensity from baseline pain over 48 hours for the abdominoplasty trial. On these graphs, lower y values reflect greater pain relief. So the blue line is suzetrigine, the black line is placebo.

The mean pain intensity difference as a monotherapy compared to placebo was minus 3.4 points or a 47% reduction from baseline. Just for reference, the commonly accepted definition of clinically meaningful pain relief is a minus 2-point reduction. The graph on the right shows a similar result when suzetrigine's efficacy is estimated as a component of multimodal analgesia with ibuprofen. For bunionectomy, suzetrigine also showed clinically significant pain reduction at 48 hours with a mean pain intensity difference of minus 3.4 points or a 51% reduction from baseline, and with similar implications for multimodal analgesia as shown on the graph to the right. Suzetrigine did not meet the key secondary endpoint of superiority to hydrocodone/acetaminophen.

However, in an upcoming slide, we'll talk about some of the differences in safety profiles, which I think might be even more clinically meaningful. In both studies, suzetrigine achieved clinically meaningful pain relief much sooner than placebo. It's important to note that these onset times you see here do not reflect the time to the first perception of pain relief, but rather when that relief met the protocol definition of being clinically significant or clinically meaningful. So what appears to be in this slide, you'll see it looks like there's a significant difference in onset time between the abdominoplasty and the bunionectomy trials, and I'll address that on the next slide. You might recall that earlier, I pointed out that the average baseline pain in abdominoplasty patients was quite a bit higher than in bunionectomy patients.

But if we analyze the onset time in the subgroup of bunionectomy patients whose baseline pain score was closer to the average baseline pain score in the abdominoplasty patients, we find that the onset time for suzetrigine are consistent across both indications. The bottom half of this graph suggests that onset times are more favorable when suzetrigine is assessed as a potential component of multimodal analgesia and that makes sense. So turning our attention to the safety data. You'll see here that suzetrigine was generally safe and well

tolerated. In fact, there was actually a lower incidence of adverse events with suzetrigine and both hydrocodone/acetaminophen and placebo.

I've been the principal investigator for over 150 clinical trials in my career. This is the first time I've seen a study drug have fewer adverse events than placebo. I find that remarkable, particularly in a clinical trial with such a large sample size. So concluding the discussion on the RCT study, suzetrigine, a novel orally-administered nonaddictive inhibitor of peripheral NaV1.8 nociceptors was evaluated in historically large Phase III clinical trials for acute pain. Suzetrigine treatment resulted in a statistically significant and clinically meaningful reduction in moderate to severe acute pain over 48 hours, and was shown to be effective both as monotherapy and as potentially as a component of multimodal analgesia with ibuprofen.

Suzetrigine was generally safe and well tolerated with a lower incidence of adverse events than both hydrocodone/acetaminophen and placebo. And so based on these data, I believe the suzetrigine has the potential to represent the first new pharmacologic class of treatment for moderate to severe acute pain in over 2 decades. On behalf of the authors of the RCT study, I'd like to offer sincere thanks to all the trial participants and their families and the site investigators that are listed here on this slide. Also just going to take a few minutes and discuss the open-label companion study of suzetrigine in other surgical and nonsurgical conditions. This study looked at safety and patient satisfaction over a 14-day outpatient treatment period in a much broader range of acute pain conditions.

Patients received the same regimen, 100-milligram loading dose of suzetrigine followed by 50 milligrams orally every 12 hours for 14 days or until resolution of pain whichever occurred first. Ibuprofen and acetaminophen, were available as needed for pain and importantly, opioids were not part of this perioperative treatment. Indications that were looked at in this trial included postoperative pain after orthopedic, plastic, ENT, general and neurologic surgery. In addition, there were a wide range of nonsurgical painful conditions essentially from head to toe. Of the 256 subjects enrolled, only 4 subjects withdrew from the study due to a lack of efficacy of the treatment regimen.

So to me, the key takeaway from this is that the overwhelming majority of patients went through the entire 14 days of treatment postoperatively without a single dose of opioids. There were 2 serious adverse events, both determined by investigators to be unrelated to suzetrigine and the most common regular adverse event noted during the month long duration of the trial was headache. As you can see here, there was a very high percentage of patients who rated the effectiveness of suzetrigine for treating pain as good, very good or excellent. This is just a tabular rendition of the same data with over 83% of patients rating effectiveness as good, very good or excellent. And so to conclude, based on these SASC data and the RCT data, suzetrigine, a novel orally administered nonaddictive inhibitor of peripheral NaV1.8 nociceptors has the potential to represent the first new pharmacologic class of treatment for moderate to severe pain in over 2 decades.

And with that, I'll turn the time over to Dr. Habib.

Ashraf Habib Attendee

Thank you, Dr. Bertoch. Good evening, everyone. Thank you for being here. My name is Ashraf

Habib.

I'm a Professor of Anesthesiology and Professor of Obstetrics and Gynecology at Duke University and also the Chief of the division of Women's Anesthesia, which is the division of Obstetric Anesthesia. I'll tell you a little bit about my practice. While I'm an obstetric anesthesiologist, I also practice in the general surgical population in patients undergoing gynecologic surgery, urologic surgery and a broad range of other surgical models. And I have a clinical and research interest in acute pain. Over the years, I have conducted many studies looking at interventions to optimize the management of acute pain after the surgery, looking at interventions from nubbing medications, local anesthetic techniques or systemic drug administration and have performed a number of meta analysis on the topic as well.

I've also, in my institution led the development of enhanced recovery protocols, which rely on the use of multimodal analgesic regimens, primarily in the gynecologic patient population and in the cesarean delivery patient population, also being part of a national expert group with the Society of Obstetric Anesthesia and perinatology devising the multimodal recommendations for pain management after cesarean delivery. So how do we manage acute pain today? So I mentioned the word multimodal analgesia enhanced recovery a couple of times. So what does this mean? We -- our aim for managing acute pain is to improve the management, improve the pain relief that the patients get while minimizing the side effects that they get from their pain medications.

And one of the most commonly used pain medications, as we know, are opioids. And opioids are associated with a number of adverse events ranging from nausea, vomiting, sedation, constipation, respiratory depression, which could be life-threatening. And many data have come over the last few years showing that actually, there's a risk of persistent opioid use. For many patients, the trigger for starting to be addicted to opioids or suffering from opioid use disorder starts actually from the prescription opioids that they get after their surgery. So because of all of that, we try to use interventions that either abolish or minimize as much as possible the use of opioids, what we call opioid-sparing techniques.

And if we look at the way we manage pain, the pain pathway is complex and involves a number of different receptors. So there are different targets within the central nervous system where we can manage pain and address pain management. So the basic principle of multimodal analgesia if you use drugs that work on different areas or different receptors within this pathway with the goal of, number 1, improving pain relief because you're addressing it from different angles; and number two, you use a lower dose from each drug in order to achieve this goal. So there are a number of cocktails that are used for pain management. So as anesthesiologists, I start this in the preoperative period.

We give some medications to patients before they go to surgery. And typically, we give them nonsteroidals, acetaminophen and Tylenol before surgery. And then we use a number of medications during the procedure to help to optimize pain management. And then postoperatively, we put them on, again, a multimodal regimen, which typically nowadays consists of nonsteroidals and acetaminophen and try to keep the opioids for rescue. If there is a surgical model or a type of surgery where we can use numbing medications, local anesthetic techniques, nerve blocks, we do that as well during the procedure and

postoperatively is the same concept.

We use nonsteroidals, we use acetaminophen, and we keep opioids for rescue. So basically, we try to minimize the use of opioids as much as possible. One issue that the anesthesia community has encountered, yes, we try to use drugs from different classes, but there are some drugs that have side effects. I'll give you an example. A few years ago, when enhanced recovery protocols became popular, gabapentin, you might have heard of gabapentin, is a medication that mainly an antiepileptic, but it has analgesic effect.

And we used it a lot in the context of enhanced recovery protocols only to realize a few years later, we knew that it had a sedative effect. And it actually increased the risk of respiratory depression slowing of breathing and could be potentially life-threatening when used in conjunction with opioids. So there are many medications that could be used, but have side effects. So we have to be careful with the with the concept of maximizing pain relief, but in the same time, paying particular attention to the side effect profile. That's why I think the suzetrigine presents really an exciting development in this area.

For many years that I think I mentioned a couple of times, what we currently have are the nonsteroidals and the acetaminophen, which we have a reasonable safety profile. We try to give them to every patient. And then this could be adequate for some patients, but from some other patients, from some other types of surgery, those are really not adequate to provide pain relief. So what is our next stop? Our next stop currently is opioids.

And for all the reasons for all the side effects that happens with opioids, we try to minimize that. But we don't have anything in the middle. So we're stuck if we don't get good pain relief with nonsteroidals and acetaminophen. We don't have something to fill the gap in the middle. We just go directly to opioids with the potential of side effects that we discussed.

So that's why I think suzetrigine is an exciting potential addition to our field for what we currently have. How would I use it? What I think is the potential role of suzetrigine in the acute pain management? As I thought about it, I thought probably I will think about it in three ways. The first one, we try to spare opioids or reduce the amount of opioids that we use as much as possible.

So I would see it as an addition to the use of nonsteroidals and acetaminophen. So if I had it available, I will add it to these two agents in order to -- and give it on a regular basis in order to avoid or reduce the use of opioids as much as possible. The second scenario would be, let's say, it is not possible for whatever reason, not for availability, for cost, whatever reason it is, it's not practical to use it on a regular basis for my patients. I will have it as a second step, if the patients get their nonsteroidals and their acetaminophen and they don't get adequate pain relief, then I will have suzetrigine given next before, hopefully, to avoid giving to opioids subsequently. The third way I think of its use is its implementation in some patients who cannot take nonsteroidals.

Nonsteroidals are great agents. They have shown to have maybe 20% to 30% opioid sparing effect. But unfortunately, they are associated with side effects. There are some patients who cannot take them. Patients who have renal dysfunction, for instance.

Patients who might have a bleeding risk. There are some types of surgery where the

surgeons are not keen on giving their patients nonsteroidals after the surgery because they are concerned about the bleeding risk of those patients. Some patients who have surgery on their bowel. Some surgeons are concerned about their anastomosis that they do. So there are a number of patients.

Some older patients might be sensitive to the effect on the kidneys from giving nonsteroidals. So all of these patients, yes, nonsteroidals are great, but I might not be able to use them. So I find that suzetrigine might be a great agent to fill the gap for those particular patients to give them this in conjunction with acetaminophen because I have not been able to give nonsteroidals to those patients. So these are the 3 ways. I think that the potential role for suzetrigine in acute pain management.

I think it's an exciting development in our field, and I will turn now to Duncan McKechnie. Thank you.

Duncan McKechnie Executive

All right. Good evening, everybody. Thank you, Dr. Bertoch and Dr. Habib.

So it's my pleasure to share with you some of our thinking on the commercial preparations for suzetrigine. So I'll start off with some numbers. I'll orientate you to the right-hand side of the slide. There's round about 80 million people in the U.S. each year suffer from acute pain.

And of those 80 million patients, round about 40 million, or obviously, half of them are given opioids for moderate-to-severe pain. And as you can see on the left-hand side of the pain and as you just heard from Doctors Habib and Bertoch, although we know opioids are effective in mitigating pain, albeit by altering the perception of the pain rather than treating the pain, we know that they also come with significant tolerability and side effect profiles as just recently mentioned, including things like nausea, vomiting, constipation and respiratory depression as well, of course, as the rather well-known issues regarding dependency and addiction. So the schema at the bottom of the slide really describes where we're thinking the suzetrigine offers a new modality in the treatment of moderate-to-severe acute pain, pending FDA approval. You can see you've got Tylenol and ibuprofen on the one hand, and you've got opioids on the other hand, and we believe that for those 80 million patients, there's a great opportunity for suzetrigine in between those two existing modalities. To understand that a little bit better, we recently conducted a survey called the State of Pain survey, where we interviewed round about 550 HCPs in the U.S.

and just over 1,000 patients. This was entirely focused on acute pain only. And I'll just touch on some of the results here. You can see on the left-hand side, just under 90% of physicians reporting that their concerns around side effects of current medications lead them to feel that they are inadequately treating acute pain, and indeed just under 80% of them expressed concerns around the potential for addiction from opioids even with the use of opioids for moderate-to-severe acute pain. And on the right-hand side, you can see that patients also expressed a desire for new alternatives to treat their pain, particularly ones that were non-opioid in nature.

So in summary, we believe that suzetrigine, which we're describing as a pain signal inhibitor, offers the opportunity to be a treatment modality in between acetamenophin and Tylenol on

the one hand and opioids on the other hand. And I'm sure you've seen these stats from us before, but there's around about 1 billion calendar days worth of treatment in the acute pain market here in the U.S., two-thirds of those patients are treated in institutional settings and about half of the prescriptions originate in those institutional settings, so by institution think hospital or ambulatory surgical center. And there's round about 2,000 high-volume hospitals that really drive the majority of the market and those 2,000 hospitals, round about 60% of them ladder up to one or other of the 150-or-so IDNs that exist in the U.S. So we believe that the acute pain market is a specialty market for us to access. So in terms of our launch readiness, as you would expect, we are well underway at this point in time.

The target action date from the FDA for suzetrigine is January 30 next year. So just a few months away at this point. We have hired appropriate field-based teams. So we have a strategic account lead team focused on the IDNs. We also have the territory account managers focused on the hospitals.

They are all fully employed, trained, engaging with customers in a compliant way. We've also started our contracting conversations both with the GPOs for hospitals as well as the PBMs and the GPOs that align to each of the PBMs. We have a broad range of initiatives we're building in order to support patient access immediately post approval. And recognizing, of course, that this is a treatment for acute pain, so people can't wait for 2 or 3 weeks or even 2 or 3 days for treatment, we're working with the various retailers to ensure retail distribution. So essentially, we're trying to ensure there is both physical and financial access to suzetrigine immediately at approval.

And as you know, we continue to engage with the state policymakers as well as the federal policymakers on legislation such as the NOPAIN Act as well as the alternatives to PAIN Act. And in those regards, I think you probably already know that PAIN stands for prevent addiction in the nation. So in summary, we are excited about the opportunity that suzetrigine offers as the first new modality in moderate-to-severe acute pain in 20 years. But even though we're excited about suzetrigine, it's our first NaV1.8 coming to the market. We have a lot of other products in the pipeline as well, and Susie's just going to talk through those very briefly.

Susie Lisa Executive

Thanks, Duncan. One final slide. Consistent with our commitment to serial innovation, there's a broad portfolio of development. At the top here, with respect to suzetrigine or VX-548, you can see the Phase III study that's completed in acute pain, about which you got all the details today from Dr. Bertoch.

And then we have begun enrollment already in the field of peripheral neuropathic pain, for which about 10 million Americans every year receive a prescription medicine. We've begun enrollment in our Phase III study in diabetic peripheral neuropathy. And then we have completed enrollment in our Phase II study of VX-548 in lumbosacral radiculopathy or LSR or sciatica. And we remain on track to provide the Phase II results by the end of this year. Then we're also excited to already be into our next-generation 1.8 inhibitor.

So that's VX-993 and you can see the suite of studies there as well. It's currently in a Phase I

study in an IV formulation in acute pain as well as in two different Phase II studies in acute pain. It's being studied in bunionectomy. And then in the field of peripheral neuropathic pain, it's also being studied initially in diabetic peripheral neuropathy. We have additional NaV1.8 inhibitors that will enter the clinic soon.

And then we're also continuing to work on Nav1.7 inhibitors that could be used stand-alone or in combination with our NaV 1.8 inhibitors. So I think that's a good place to wrap up, and then we're happy to take your questions. We have about, let me see here, 30 minutes. We'd ask that we'll spend 25 or so while we have the physicians in the room again focused on acute pain and the data you've seen today, but we will leave questions for the entire program for the final 5 minutes.

Susie Lisa Executive

So begin there. And maybe as we get organized here in the room, Dr. Bertoch, we did have 1 question that came in via e-mail to start. If you could talk a little bit more about the onset of action with suzetrigine and any concerns or thoughts there? If you could go into that a little bit more?

Todd Bertoch Attendee

Yes. Historically, for acute pain and for analgesics, the determination of time to onset has been done using what's called the double stopwatch technique. It's quite precise when it's used correctly, but there are a lot of operational challenges, especially as you get into a big study. And so in light of those operational challenges for this study, we tried a novel approach to assess the time until a patient achieved a 2-point or greater reduction in pain on the NPRS scale. And we defined as the time to the first perception of pain relief, a 1 point change in pain on that NPRS scale.

So while this did help with the operational challenges associated with the stopwatch technique, in my opinion, I think it significantly overstates the time to onset. There are points that we could talk about more in detail if you want about why that is. But in my personal opinion, I've done many, many of these acute pain clinical trials using the double stopwatch technique and this method. I think that those times are significantly overstated.

Susie Lisa Executive

Maybe Jess, we'll start there. If you could state your name and question for the webcast, please.

Jessica Fye Analyst

Great. It's Jess Fye, JPMorgan. I think there was some discussion around this during the presentation earlier today. But just coming back to the mean pain intensity, different score graphs in bunionectomy and sort of time to onset, can you talk a bit more about any impact of ropivacaine in the initial effect of suzetrigine? Is there some interaction there?

And was that expected? And then also, I just wanted to confirm, I'm not sure if I've seen this number, what was the proportion of patients across each arm in these trials that had rescue therapy? I think you had heard that it was maybe around 80% and really balanced, but just

wanted to confirm that.

Todd Bertoch Attendee

Yes, I'll answer your second question first. It was around 80% that rescued and that was pretty similar across all the arms of the study. Back to your question there, there were some differences in -- now there are two points here. So I want to make sure I answer the question that you're asking. Are you talking about the differences between bunionectomy and abdominoplasty in the SPID numbers?

Or are you talking about differences in what appeared to be efficacy in the bunionectomy study versus the hydrocodone/acetaminophen versus the suzetrigine?

Jessica Fye Analyst

More the later because those are kind of related.

Todd Bertoch Attendee

Well, they kind of are and they kind of aren't. So the differences that you see between the abdominoplasty study and the bunionectomy study with regards to suzetrigine versus hydrocodone/acetaminophen, okay? What we postulate is for the bunionectomy clinical trial, there was a popliteal nerve block, a continuous popliteal nerve block with a long-acting local anesthetic, ropivacaine. So that ropivacine was administered the entire first day after surgery through that night, it was discontinued the morning of surgery. At some point after surgery, the patient achieved a qualifying pain level which allowed randomization and the beginning of dosing.

What we postulate is that there's still some circulating ropivacaine, local anesthetic in the system, that is having some impact on -- because ropivacaine, local anesthetics, are very nonselective inhibitors of sodium channels in general. So what we believe is that there's some still residual circulating ropivacaine impacting some percentage of the NaV1.8 channel. So after suzetrigine is dosed, the efficacy appears to be diminished because you can't inactivate a channel that's already inactivated by ropivacaine, if that makes sense. So we think about the hydrocodone/acetaminophen arm. Those -- neither of those drugs, hydrocodone nor acetaminophen, are impacted by that, ropivacaine, right, because there's a very different mechanism of action for their pain relief.

And so while the ropivacaine is making suzetrigine look less effective, it's actually additive to the apparent effectiveness of the opioid comparator drug. And as evidence of that, if you look back at the abdominoplasty data where a long-acting local anesthetic was not used, you don't see that impact at all. That doesn't happen there.

Susie Lisa Executive

Okay. We'll go here then to Joon.

Joon Lee Analyst

Joon Lee from Truist Securities. Just following up on that question, were regional blocks not done for abdominoplasty because the efficacy there is very different than bunionectomy? So

why is that the case? And part two of that question is if you do -- if you were to use even a longer-acting bupivacaine, like liposomal formulated, how could that have impacted the study outcome?

Todd Bertoch Attendee

Okay. Great questions. So for the abdominoplasty study, to answer your first question, there was a field block with a short-acting local anesthetic used basically to get the patient into the PACU relatively pain-free to allow them to be more awake and alert when it was time to dose, okay? So no long-acting local anesthetic in the abdominoplasty study, and no TAP blocks or any abdominal wall blocks were done in that study. The second question is, what is the impact of a longer-acting local anesthetic in the face of suzetrigine?

In my opinion, these are just additive, right? So when we're doing the clinical trials, we want to eliminate any concomitant analgesics that might be impacting our ability to assess the efficacy of suzetrigine as a monotherapy by itself, so we want -- that's kind of a bother for us. But in clinical treatment, we want to maximize that. And so that would be additive with whatever local anesthetic that you have on board.

Susie Lisa Executive

Go ahead, Tazeen.

Tazeen Ahmad Analyst

Tazeen Ahmad, Bank of America. Question is for both Dr. Habib and Dr. Bertoch. So based on everything that you've said, do you still plan on using, if you're allowed to use, suzetrigine, a local anesthetic as part of how patients are treated pre- and during surgery?

And can you also give us your opinion on whether or not suzetrigine will be obvious to P&T committees that they should be using it because in the past, there have been other attempts from other companies to use non-opioids, EXPAREL comes to mind. Why is this going to be different? And do you have any influence over your P&T committees on that?

Ashraf Habib Attendee

So your first question about the use of suzetrigine in addition to the other multimodal pain therapy that we are currently using. Can you repeat it again?

Tazeen Ahmad Analyst

Yes. Do you plan on still using local anesthetics, pre- and during surgery?

Ashraf Habib Attendee

Look anesthetics like nerve blocks?

Tazeen Ahmad Analyst

Yes.

Ashraf Habib Attendee

Yes. I mean I think it's a good question. So if there's a surgical model where it is amenable to the use of local and anesthetics, I would still plan to use it. It's -- these are tackling the pain pathway from different perspectives. So basically, any additive impact of a local anesthetic plus a systemic administration of drugs would be welcome.

I would plan to use it this way. Your other question relates to...

Susie Lisa Executive

P&T committee.

Ashraf Habib Attendee

P&T committees, yes. So P&T committees basically look at a number of things in order to approve a drug. Number one, does it fill a gap in what we currently have? Does it reduce the risk to the patients? And what is obviously the financial impact of using this particular drug?

So for a non-opioid alternative, there are a number of arguments in favor of introducing an opioid with a favorable side effect profile. So I think for suzetrigine, with the data that we currently have, the data are very encouraging in terms of, number one, showing efficacy, both as a monotherapy as in the ad hoc analysis in combination therapy; and number two, a very good safety profile. For EXPAREL, for instance, we have it approved in our institution. It's institution-dependent based on the P&T committees, but I think for a non-opioid-proven efficacy and good side effect profile, I think it would be approved by P&T committee at least in my institution.

Todd Bertoch Attendee

And I'll jump on there. I agree, I would continue to use local anesthetics, nerve blocks, let's just hit this as hard as we can. As far as P&T committees formulary administrations, I think some other analgesics that have struggled with this in the past have not been orally administered like this. Their safety profile hasn't been the same. It's a really different medication.

So these are going to be prescribed postoperatively as outpatients. There are about 3 reasons why surgeons are really -- or physicians are really pressured we really need something else. We're a little bit in between a rock and a hard place when it comes to this. We are -- for social optics really discouraged from using opioids. There are now legal ramifications for us using opioids.

It's -- there are side effects from opioids that we'd rather not have to deal with, obviously, in our patients. And so there's a lot of pressure on physicians to have something else. And I think that pressure is going to be translated to P&T committees. And I really feel optimistic that something like this is going to get adoption from those committees.

Ashraf Habib Attendee

I'll add another comment, I recalled as Dr. Bertoch was talking. I can think of one instance in the last few years where we struggled in our P&T Committee with an agent, but this was because of the -- it didn't prove to reduce side effect profile. It was an opioid, but it was supposed to work on a different pathway, a different way. And it didn't prove that it reduced

the side effects from opioid.

The quality of the data was not good. So basically, I think one of the important things that P&T Committee looks at is the quality of the data that's being produced, how robust the clinical trials have been done. And the encouraging things about the suzetrigine trials, number one, the data -- the studies were very rigorous, and the data was consistent across all the studies that have been done so far. And this is very important, and you don't see it consistently in acute pain trials.

Susie Lisa Executive

Chris, let's go to Will, and then Jenna.

William Pickering Analyst

Will Pickering from Bernstein. Thank you for the presentation. My question is, what are the patient characteristics and overall clinical presentation that will be most informative in deciding whether to use suzetrigine or opioids?

Todd Bertoch Attendee

Do you want to take that one?

Ashraf Habib Attendee

Yes, sure. So what patient characteristics for -- or surgical models to use suzetrigine. So in my practice, the principle what we try to achieve across the board for all surgical -- all types of surgery is opioid sparing for all the reasons that we have highlighted earlier on. So for me, for instance, I use nonsteroidals and Tylenol for all of my patients across all the surgical models that I use, whether those patients have had a local anesthetic block as type of their procedure or not. So I try to maximize the opioid sparing as much as possible.

So if I -- when I have suzetrigine, I would add it on top of the nonsteroidals and the Tylenol across the board for all of my patients because I want to maximize this across all my patients. Some patients will do well with just those non-opioid option and this is great. And some patients might still use opioids, and this is what we're trying to avoid.

Todd Bertoch Attendee

Yes, I would add, I think where we struggle right now is with the patients that -- there are some mild pain states where acetaminophen and/or NSAID are adequate, right? There's no reason to add suzetrigine to that. But where we really need help is when we have a pain state that doesn't respond to acetaminophen and an NSAID, and my next step -- right now my next step is an opioid, there's nothing else out there. And so being able to fill that gap is hugely important, and there are a lot of people out there right in that little sweet spot. And I don't want to have to give them an opioid.

Susie Lisa Executive

Good, Gena?

Huidong Wang Analyst

Gena Wang from Barclays. Maybe follow up this question, you want to have a step nonsteroidals and then the opioids, right? So in between, maybe give us a sense of what percentage -- I think we saw the number 80 million, what percentage of those patient population you will start with nonsteroidals and then you will have to require to use opioids? So maybe that's the number one question. And the second, I think that for companies, the economic part is very important, the pricing part.

I think in the past, I think the range mentioned was between $10 to $20 per day. Is that still the case? Or what is the latest feedback from the payers?

Ashraf Habib Attendee

So your first question is, what percentage of patients were giving nonsteroidals would go on to need opioids, correct? So I'll give you a couple of concrete data actually from my practice. In our cesarean delivery patients, we have optimized our use of nonsteroidals and acetaminophen. We changed the time of administration. We changed how often we use it than when we started.

And we managed to reduce the need for opioids, especially in the early postoperative period from about 80% to about 60%. So still, despite optimizing this in this particular patient population, 60% of my patients currently still need opioids in the first few days after their C-section and sometimes they're discharged home with it as well.

Todd Bertoch Attendee

And Gena, we haven't commented on price specifically, and we won't tonight, but we are having a number of, I think, really important conversations with payers and other decision makers and maybe Duncan can provide just a little bit of color around some of those conversations.

Duncan McKechnie Executive

Sure. Yes, we started engaging with payers on suzetrigine in November last year, so November 2023, and also began our engagements with the IDNs, so the formulary decision makers at IDNs in October last year as well. So we've been talking to these folks for quite a while. We've also, of course, engaged with the GPOs that we have to negotiate with hospital purchasing. So those conversations are going very well indeed.

We recognize that, of course, we're looking for broad access, no prior authorization because clearly, that would be a barrier to quick access for the patients to get the product when they really need it. So we're engaging in rebate conversations with payers as you'd expect. Those conversations are going well. And as Charlie said, we'll be announcing the price when we have approval.

Susie Lisa Executive

One or two more questions on acute. Go ahead.

Jenna Li Analyst

Jenna Li here from Jefferies on behalf of Mike Yee. Two quick ones from us. In addition to pricing, could you also talk about other parameters, like bookings and stuff that we should be thinking about and perhaps maybe some comps to look at in figuring out what the first year could look like? And another one would be a future chronic pain launch, how would that be perhaps different from the acute pain launch coming up? And could you describe the difference of dynamics of the two markets?

Charles Wagner Executive

I appreciate the question, though. Let's move on to a different question. Let's try to get the most out of the time that we have with the doctors here, and we can take questions offline about comps and other launch dynamics.

Susie Lisa Executive

Go ahead.

Sadia Rahman Analyst

Sadia Rahman from Mohit Bansal's team at Wells Fargo. So both trials were done predominantly women. Curious of the data in the male subgroup, is it similar? Or if that analysis hasn't been done yet, would you expect differences in men? And then can you comment on the potential for combining 1.8 with 1.7?

Is there a potential for increased potency while increasing the therapeutic window for the combo?

Todd Bertoch Attendee

Yes, I'll answer the first question, and I'll defer the second one. As far as male/female ratio, while that's critically important in clinical research to make sure we're looking at both sexes and the impact on both sexes, what we do know from the literature is that past historically, for analgesics, there has not ever been shown to be a big difference between men and women as far as response to analgesics. So we don't anticipate that to be a problem. Obviously, because of the nature of these clinical trials in these models that actually approved and almost demanded by the FDA for us to study these -- use in these clinical trials, there is an imbalance, but I think particularly for analgesics, personally, I don't think you're going to see a big difference based on history.

Susie Lisa Executive

Paul, do you want to take the second question?

Paul Negulescu Executive

Sure. So on the question of combination, there's a rationale for combining 1.7 and 1.8 together because those two channels are expressed in many of the same pain-sensing neurons. So I think when we get as far along as having the 1.7, we'll certainly consider looking at combinations.

Susie Lisa Executive

Here in the middle, Kelly, and then we'll go to the back.

Chun Yu Analyst

Chris Yu, here on behalf of Terence Flynn, Morgan Stanley. Questions for the doctors. So suzetrigine is also being studied in LSR. Just want to see what do you think, is it going to be successful in LSR? And if you want to see clinically meaningful results, what is the delta that you want to see between suze and placebo?

Todd Bertoch Attendee

Well, I'll say -- I will just say this. We're here to discuss these studies. I'm specifically here to discuss the results from this study. I will say I've been doing this a very long time. It's quite uncommon for analgesics that work in somatic pain with very few exceptions to not work in other pain types.

So I would not be surprised if it worked, but I can't comment to any specific data.

Susie Lisa Executive

There, Kristen?

Malcolm Hoffman Analyst

Malcolm Hoffman here for Evan Seigerman from BMO Capital Markets. I have a question for Dr. Habib. You mentioned a third scenario of patients who may not be able to use NSAIDs either because of liver dysfunction or bleeding risk. Is there any way you can sort of quantify what percentage of patients fit into this category?

And how important is it for these patients to have another option other than opioids specifically?

Ashraf Habib Attendee

Yes. Quantifying the patients really varies. There are two ways to look at it. One would be the surgeries where actually the surgeon is not keen to give nonsteroidals. So in this patient population, it would be 100% of the patients.

Some examples would be plastic surgeries, commonly, the surgeons are not keen with flaps, some breast surgery, they are not keen on nonsteroidals, so in this, patient population would be 100% of the patients. In other subset of patients where it's not the surgery specific, but it is patient-specific where you cannot give them nonsteroidals. I will say probably -- again, it varies if it's a surgery predominantly in an elderly patient population. So it will be a higher proportion of those patients cannot get nonsteroidals. It would be more in the region of 70%, if it's predominantly elderly patient population.

If it's a predominantly younger patient population, this would be much, much less than that. It will be probably, I would say, maybe 15% to 20%. And then your other question was...

Charles Wagner Executive

That was it.

Susie Lisa Executive

That was it, yes. Debjit?

Debjit Chattopadhyay Analyst

Debjit from Guggenheim. I'm just curious as to what happens to these patients post-discharge. So do these patients go home with another 5 to 7 days of prescription pain medicines? And in that setting, would you prioritize suzetrigine over NSAIDs or acetaminophens or opioids?

Todd Bertoch Attendee

Yes. I talked about a little bit about the open-label study at the end of my presentation, where basically we were looking at outpatient dosing at suzetrigine over 14 days postoperatively. Roughly half of patients in that study, their pain resolved somewhere during that 14-day period, and another half still had some pain after that 14-day period. Those people then -- suzetrigine was discontinued, obviously, because it was the end of the study -- the end of the dosing period for the study. And then they were discharged on standard of care medication.

So as far as predicting how I might treat that person moving forward, it really is on a patient-to-patient basis. And physicians are going to have to decide how they want to use that medication if and when it's approved by FDA.

Susie Lisa Executive

Angela?

Angela Qian Analyst

Angela Qian from Canaccord for Whitney Ijem. Follow-up to Deb's question. So upon discharge, if they are given a script for suzetrigine, you mentioned patients aren't going to wait 2 to 3 days, but realistically, they're not even going to want to wait 2 to 3 hours at the pharmacy in the event that it could not be covered immediately or if it's too expensive. So for Dr. Habib, Dr.

Bertoch, are you thinking about like a potentially increased workload with pharmacies calling and asking for a new script or something else? How are you thinking about reducing that potential friction when time comes?

Todd Bertoch Attendee

Yes, if I understand your question correctly, and Dr. Habib could probably speak to this better than I can, but my impression is that I would treat this like another physicians in general will treat us like other analgesics that they prescribe. They'll call in a prescription. It's almost always done electronically now. So it's almost immediate.

You're calling that prescription. There should not be a large -- big delay. As far as payers and

how that's going to impact that, I really can't speak to that. But I don't see much of a difference in the way physicians will prescribe this compared to other analgesics.

Ashraf Habib Attendee

I agree. I mean I think the patients are discharged with a script for an analgesic of some sort, and this would follow the same pathway of the script being phoned to a pharmacy or depending on particular institution, or they can get the script from the hospital pharmacy as well. In some institutions, they can get their script from the hospital pharmacy. But it will be, I will see this being along the same ways of any script that being placed for the patients.

Todd Bertoch Attendee

I will add that over the over-the-counter drugs, Tylenol and the NSAIDs that are over the counter, obviously, patients can go acquire them at their own leisure, right? But if you're talking about maybe more difficulty getting suzetrigine than a prescribed opioid, believe me, it's getting harder and harder for patients to get a prescribed opioid postoperatively, there's long delays. So I don't see that impacting usage very much, in my opinion, anyway.

Ashraf Habib Attendee

And the other point about opioids as well, there are now restrictions of how many -- how much opioids you're allowed to give the patient in the script. So actually, the workload regarding we ordering opioids is much more than a non-opioid -- non-regulated medication where you can order a supply for a longer period of time compared to what we allowed now to do with opioids.

Duncan McKechnie Executive

And maybe I can add to your question with regard to retail and the payers, I can't quite see you at the back of that. As I alluded to earlier, we are working with retailers to ensure that there will be broad physical availability of suzetrigine. And we're also putting in place, as you'd expect, co-pay assistance and financial assistance programs to ensure that patients will be able to get it when they turn up at the pharmacy counter.

Susie Lisa Executive

Great. I think that's a perfect place to end. Dr. Bertoch, Dr. Habib, Duncan, Charlie, Paul, thank you very much, and thanks again for all of you being here in Philadelphia.

Todd Bertoch Attendee

Thank you.

Ashraf Habib Attendee

Thank you.