Trevena Business Update Conference Call

MELISSA: Greetings and welcome to the Trevena Corporate update. At this time, all participants are in a listen only mode. A question and answer session will follow the formal presentation. If anyone should require operator assistance during the conference, please press star-zero on your telephone keypad.

As a reminder, this conference is being recorded. I would now like to turn the conference over to your host, Mr. Barry Shin, chief financial officer for Trevena. Thank you. You may begin.

BARRY SHIN: Great. Thanks, Melissa. Good morning and thank you for joining us to discuss our proof-of-concept data for TRV045. With me today are Carrie Bourdow, our president and CEO and our chief medical officer, Mark Demitrack. We'll also touch on other business updates.

And as a reminder, Olinvyk was approved by the FDA in August 2020 and contains oliceridine, an opioid, which is a Schedule II controlled substance with a high potential for abuse similar to other opioids. It's indicated in adults for the management of acute pain severe enough to require an IV opioid analgesic and for whom alternative treatments are inadequate.

As with all opioids, serious life-threatening or fatal respiratory depression may occur in patients treated with Olinvyk as indicated in the boxed warning. The safety information, including the boxed warning and full prescribing information are all available on olinvyk.com.

We'll also be making forward looking statements under federal securities law, which are subject to risks and uncertainties related to our business, including those covered in our filings with the SEC. We undertake no obligation to update these statements beyond today. I'll now turn the call over to Carrie.

CARRIE BOURDOW: Thank you, Barry. Good morning, everyone. Thanks for joining us today. Trevena is a company with a novel platform focused on innovative new medicines for CNS disorders. All of our assets are new mechanisms wholly owned by us discovered in our own labs. Alembic was our first new chemical entity that we took from discovery to approval.

Today, we're focusing on the middle box on this slide, our novel S1P modulator program. And it's an exciting day, because we're here to review preliminary results from two proof-of-concept studies for TRV045, our novel S1P receptor modulator.

You may be familiar with other blockbuster S1Ps like fingolimod. And while TRV045 is part of this family, it has a unique mechanism of action that we believe will allow us to target a range of CNS disorders. Trevena has been doing work for the last few years with TRV045 as a non-opioid for chronic pain conditions.

The NIH has been studying 045 in their epilepsy therapy screening program known as ETSP and has generated interesting nonclinical epilepsy data. After we announced positive first in human phase I studies late last year, we initiated two proof-of-concept studies to gain further insight into the unique mechanism and to evaluate CNS target engagement.

I'm very pleased with these results because what we've demonstrated in both studies is evidence of CNS activity. And despite the small sample size, we showed a statistically significant analgesic effect in a validated model for neuropathic pain. The TMS study showed interesting changes in EEG results and early reduction in cortical excitability, as well as additional evidence of CNS activity that complements the target engagement pain card study.

We now have further insight into the novel mechanism of action of TRV045 and we believe these results support future development either on our own or with a partner. Let me now turn the call over to Mark to walk through the results after which I'll provide some additional business updates. Mark?

MARK DEMITRACK: Thank you, Carrie. As Carrie indicated, this has been an exciting quarter for our clinical development team. And today I'm pleased to report the preliminary findings from our two proof-of-concept studies for TRV045, our novel S1P receptor modulator.

Before discussing the data, I'd like to provide some context for why we are so excited about the opportunities we see in 045 and what sets it apart from other drugs in this class. This slide highlights one of the main features of TRV045.

We believe that because of how rapidly the bound drug receptor complex is internalized and recycled reflected in the step shown in the green box at the bottom, TRV045 should be devoid of any effect on circulating peripheral lymphocytes.

In our prior phase I study results we saw no reduction in lymphocyte levels, which we believe will lead to no long-term immunosuppression. This next slide shows another important property of 045, namely its targeted specificity for the type I S1P receptor. We believe this is important since the Type I receptor is highly expressed on cell targets of interest in the brain, astrocytes and microglia both implicated in brain inflammation.

This was a critical aspect of 045 properties which led us to investigate its potential application for disease targets like neuropathic pain and epilepsy since these cells are believed to play an important role in the regulation of brain signaling events key to the development of chronic pain and to play key roles in the physiology of how seizures develop and how they persist in causing epilepsy.

With that as background, we embarked on our clinical proof-of-concept study program with two key goals in mind outlined on this slide. First, we wanted to provide evidence that TRV045 penetrates the CNS and engages its target as demonstrated by appropriately chosen pharmacodynamic outcome measures in humans.

Second, we plan to measure plasma concentrations during these studies to help guide future development of our next generation drug formulation and to help frame our dose selection considerations for subsequent phase II development. Finally, we wanted to provide additional safety and tolerability data to support what we already saw in our prior phase I study.

To accomplish these goals we chose to pursue two different, but complementary proof-of-concept studies, each with different design features, pharmacodynamic measures, and clinical targets in mind to help guide our path forward. The first study, which we've referred to previously as the target engagement study, employed a variety of human experimental pain models to help probe the peripheral and central actions of TRV045 shown on this slide.

This study conducted in 25 male and female subjects used a placebo-controlled single dose, dose ranging crossover design. The dose is chosen based on the PK parameters we saw in our prior phase I study. The pharmacodynamic endpoints examined in the target engagement study are shown on the lower portion of this slide, an assay at a broad range of pain modalities, such as pressure, heat, electrical and cold pain, and also used capsaicin as a skin irritant, which serves as a model of neuropathic pain.

Second proof-of-concept study used transcranial magnetic stimulation, or TMS, to probe the potential effect of 045 on cortical excitability in the brain and was conducted in 25 male subjects. This study used a placebo-controlled multiple dose crossover design with 045 given over four days and measured outcomes using electroencephalography, or EEG, and electromyography, or EMG, to track changes in brain electrical activity after dosing with TRV045.

We announced the preliminary results from both of these studies today and I'm very pleased to report that the results provide us with a wealth of encouraging information and offer insights into the potential path forward for our future development efforts with 045. I'll summarize the most salient findings now.

While we expect to receive the final safety and tolerability data by early fourth quarter of this year, I'll note that there were no SAEs or discontinuations due to study drug-related adverse events in either study.

In the target engagement study despite the small sample size we saw a statistically significant dose-dependent treatment effect on the principal model for neuropathic pain, namely mechanical allodynia by Von Frey testing measured on skin exposed to topical capsaicin.

I'd like to note that the results seen with this model are important since capsaicin irritation of the skin is recognized as a valid, experimental model of neuropathic pain in humans and therefore, supports the hypothesis for the potential use of TRV045 for neuropathic pain indications.

The analgesic effect of 045 in this model is shown in two ways on this slide. On the left side, you can see that this analgesic effect was evident when measured in the area surrounding the region of skin where the capsaicin was directly applied, the so-called secondary allergenic area.

On the right, we also saw the analgesic effect when we measured the total surface area affected, which includes the area of capsaicin application or the total allergenic area. For each of these graphs, the surface area of pain is shown. So as the bars go down, this means that the area of painful sensation is shrinking.

In both analysis the results show statistically significant reductions in pain sensation or mechanical allodynia with both the 150 milligram and 300 milligram doses. Note also that the effect is evident beginning two hours after dosing and nicely followed the trajectory of the plasma concentrations of the drug, which generally show maximal concentrations around four to six hours after dosing.

The PK exposure we achieved in this study was consistent with the levels seen at these doses in our earlier phase I work and the half-life was comparable to the prior phase I study, which would support anticipated once daily dosing.

To summarize, these data on the mechanical allodynia model were statistically significant, dose-dependent, and provide support for the hypothesis that TRV045 has the potential for use in neuropathic pain in patients. Also the outcomes at the 150 milligram and 300 milligram doses will help to guide future decisions about dose selection as we advance towards future clinical studies in patients.

In addition to the mechanical allodynia findings, additional trends were seen in several other pain models, including on the cold pain test, on measures of heat pain, and on one of two different measures of electrically-stimulated pain, though these results did not achieve statistical significance.

Some of the pain modalities studied, including pressure pain and conditioned pain modulation showed no statistically significant effects or trends. It's important to note that this pattern of outcome with a statistically significant effect on the most relevant model for our intended neuropathic disease target along with evidence of analgesic effect on select other pain measures is encouraging as it suggests specificity in the mechanism of pain relief.

Finally, results of the mechanical allodynia endpoint indicate that TRV045 is entering the brain since the pain signals in this model depend upon central pain signaling processes, sometimes referred to as central sensitization. We've had the opportunity to discuss these top line results with several of our external advisors all of whom agree that the results are very exciting.

Results from the second proof-of-concept study using TMS to probe brain electrical activity using both EEG and EMG methods were also encouraging. While many of the outcomes did not achieve statistical significance, the results did provide additional statistically significant evidence indicating CNS penetrance of TRV045 as shown through measurable changes in select measures of brain electrical activity on the resting state EEG power spectral analysis.

Among the EEG-related endpoints measured in the study resting state EEG obtained before and after administration of 045 on the first and the last or fourth day of dosing demonstrated statistically significant increases in the power spectral density in several of the middle to higher frequency bands including alpha, beta, and gamma waves. These changes were evident on day one and became more prominent on day four of dosing. The changes on day four are shown on this slide for 045 compared to placebo.

With 045 an increase in alpha waves was the most notable observation with increased power evident in the frontal region and in the parietal regions in the back of the brain in both the left and right hemispheres. The increase in beta and gamma wave power spectra were noted over the frontal regions only.

Alpha waves are generally considered to be associated with conscious arousal and alertness, while beta waves are thought to be associated with GABA-mediated inhibitory corticospinal neurotransmission and gamma waves are generally associated with cognitive processing learning and memory.

In addition to these changes, we also studied the slower brain wave spectrum in the delta and theta wavelengths. These EEG wavelengths are generally associated with sedation, and sleep. And activity in these power spectra are increased with some antiepileptic drugs and are thought to correlate with their reported adverse effects on cognitive function in patients.

Therefore, we noted with interest that unlike the changes in the mid to higher frequency brainwave bands, there was a statistically significant decrease in the slow delta brainwaves, again, in the frontal region and no difference in slow theta brainwaves.

Among the EMG-related endpoints measured in the study, TRV045 demonstrated evidence of reduction in cortical excitability on day one of drug dosing in response to single pulse TMS. The difference in mean peak motor evoked potential or map amplitude was minus 304 microvolts, though this result did not achieve statistical significance.

This outcome for 045 is shown on the left of this slide. For context, on the right side are the results rich study guide in the same laboratory also using TMS-EMG to monitor amplitude change in a different population of subjects. The map decrease we observed in our study is of a magnitude similar to that seen with other known antiepileptic drugs in the other study shown here.

Although we can't directly compare these outcomes as there have not been head-to-head comparative studies, they do provide some context for interpreting what we are seeing in our results. There was no difference in mean peak amplitude on day four and no differences in resting motor threshold on day one, or day four, or on other EMG-related endpoints.

In our study, we examined only one dose of 045 and measured amplitude and resting motor threshold only at one post-dose time point due to the complexity of the testing demands of this study. Overall, we believe these early results are encouraging. We are very pleased with the results of these two studies. And as I mentioned, above we've received positive initial feedback from discussions with our advisors on both of them.

Taken together, we believe these data show that TRV045 gains access to the CNS and engages the brain in a manner consistent with the results we observed in our animal models in both neuropathic pain and epilepsy.

In addition, we demonstrated a statistically significant treatment effect in the mechanical allodynia model, which is particularly noteworthy since it is considered to be a valid experimental model of neuropathic pain and central sensitization processes in the brain.

We also showed interesting statistically significant effects on brainwave activity that may be relevant across indications. And finally, we showed promising evidence of early reductions in cortical excitability.

We'll study these preliminary results in more detail in the coming months and also expect additional data from the ETSP, which is studying TRV045 as a potential disease modifying therapeutic for epilepsy prevention. We plan to continue to advance toward future clinical studies in patients either on our own or with a strategic partner and look forward to updating you soon. I'd now like to open the call for questions. Operator?

MELISSA: Thank you. If you'd like to ask a question, please press star-one on your telephone keypad. A confirmation tone will indicate your line is in the question queue. You may press star-two if you'd like to remove your question from the queue. For participants using speaker equipment, it may be necessary to pick up your handset before pressing the star keys. Our first question comes from the line of Jason Butler with JMP Securities. Please proceed with your question.

JASON BUTLER: Hi, thanks for taking the question and congrats on the results. Maybe just at a high level, can you just give us some thoughts here on next steps? How are you going to prioritize the two different settings chronic pain versus epilepsy? How you're thinking about the different epilepsy populations you could study. And then on the funding side of things just how you're thinking about prioritizing partnerships versus go alone and different indications. And I have a follow-up. Thanks.

CARRIE BOURDOW: Hey. Thank you, Jason. I appreciate the questions. Yeah. So we are very excited about this data. And as you heard, we're thinking about how we're going to approach next steps. First, I think we need to see the full safety and tolerability data on the epilepsy side. We're waiting for the NIH data on seizure prevention.

We're a little bit further ahead as a company on neuropathic pain and I think this data then could lead to a more definitive studies in patients a little bit more quickly. But the NIH has been really interested in this compound and has been accelerating some of their work in epilepsy.

So I'd like to see what the seizure prevention data looks like before we would declare, I think, on what models we might be wanting to do in epilepsy, but Mark certainly has been thinking about it. As you heard, he's meeting with KOL both in neuropathic pain and in epilepsy to prioritize and think about next steps.

As it relates to partnerships or doing on our own, I think that was your question, there are certainly phase II type studies that we could do on our own, very targeted studies that could bring forward the 045 and advance it. So those are some of the things that we're thinking about and we'll be back out with our plans here relatively soon. Mark, anything you want to comment around the patient populations you're thinking about?

MARK DEMITRACK: Well, we've talked in the past about the epilepsy targets of interest. And the data that we've assembled to date we think certainly points us in the direction of refractory epilepsy. A lot of the basic models that ETSP has studied are modeled in that direction.

And more importantly, the changes that we've seen that 045 appears to exert on immune mediators in the brain is one aspect of it that's particularly excited our advisors as it may play a potential role in actually modifying the cause of the disease and also for some often types of epilepsies where inflammatory process or immune-mediated events play a role in the propagation of those illnesses.

So there are a couple of different avenues in front of us. And I would say for neuropathic pain it's similar. We've learned and we are learning a tremendous amount from the data that we've generated here that point us to particular understandings about the mechanism of 045.

The efficacy and the mechanical allodynia model, for example, does suggest that receptors like TRPA1 may be an important target for us to think about. That narrows down a bit the way we might shape inclusion criteria or even delete disease selection targets in the neuropathic pain space.

Small fiber neuropathy, for example, comes up as an area that is, I think, a pretty fruitful for us to dig into. Even in some of the larger targets like OA, for example, or other neuropathy targets, even though large, based on the mechanism we may be able to narrow down our focus so that we can have an efficient understanding of proof-of-concept in that work moving forward.

CARRIE BOURDOW: I think because Mark and his team studied so many different aspects of pain it really helped us think about and derisk frankly other studies that we might want to take on. So I there's some orphan pain indications you're also thinking about it in addition--

MARK DEMITRACK: That's right.

CARRIE BOURDOW: Yeah.

MARK DEMITRACK: That's right. There are some orphan pain indications where the literature suggests that central sensitization may play an important role in things like sickle cell disease. Even some subsets of patients with Ehlers-Danlos syndrome, for example, are areas that we've been interested in our discussions.

JASON BUTLER: Great. And then just on the capsaicin data capsaicin model data, could you just the magnitude of change into context used for neuropathic pain like gabapentin? And then I know it's still early, but can you maybe frame the size and scope of a phase II study in patients that would be informative or could be a next step? Thanks.

MARK DEMITRACK: Sure. Well, I can comment on the size of the effect in a couple of ways. One is just the shear strength of the statistical signal. When you look at it as a stand alone piece of data it is of a magnitude that in statistical terms we would consider large. You have effect sizes that are approaching on the order of 0.9 or 1 here, that's a very meaningful change in statistical terms.

The capsaicin model has been used in a variety of ways and including with gabapentin. And when we look at data from comparable models of capsaicin irritation with drugs like that, with opioids, these are the kinds of changes that we see in those models. I'd also point to some of the more recent data even with some of the compounds like the nave inhibitors that use similar types of neuropathic pain model targets. So we're pretty pleased with the results we've seen here.

In terms of the phase II, like I was saying earlier, our approach know in the near-term is going to be to build on the understanding we have as to where this data points us mechanistically and then to think efficiently about clinical targets. So again, think more selected populations where we can get a homogeneous patient sample and get a very robust signal in a quick manner. So those are the kinds of things we're beginning to think about at this stage.

CARRIE BOURDOW: Yeah, our plan is or our thinking is to have a very targeted study to get this drug into patients, that would be the next steps and so that's why Mark's been spending time with KOLs. Obviously, we just got the data so he's been thinking about models, but presenting the data now to the KOLs and think through next steps to get it a targeted phase II study in patients. And as I mentioned, we're further ahead with neuropathic pain, but I'm really anxious to see the NIH's data on seizure prevention as well.

JASON BUTLER: OK, great. Thanks for taking the questions and congrats, again, on the results.

CARRIE BOURDOW: Thank you, Jason. Appreciate it.

MELISSA: Thank you. Our next question comes from the line of Douglas Xu with H.C. Wainwright. Please proceed with your question.

DOUGLAS XU: Hi, good morning. Can you hear me?

CARRIE BOURDOW: Yes.

DOUGLAS XU: So congrats on the data. I'm just curious starting on the pain side, is your inclination to start in broader indications and then potentially narrow down or take the opposite because that could potentially be a faster course? And I guess a similar question in terms of epilepsy, what are the immediate next steps? I mean, is there anything that you can do or are you really waiting to see what NIH comes up with? Thank you.

CARRIE BOURDOW: Yeah. Doug, so good questions. And as I said earlier, let me take on the pain side. So there are subsets in the broader markets, as Mark talked about. So if you think about OA, or back pain, some of these large markets there are subsets of patients within those markets that we think based on the mechanism of action and the area where we're headed towards neuropathic pain would be very interesting for 045. And then as Mark described, there's even potentially some orphan area like Ehlers-Danlos.

On the pain or I'm sorry on the epilepsy front, I think it's going to be important for us to see the seizure prevention. We certainly could move forward without seeing the ETSP data, without seeing the NIH data. And so we're talking with our advisors on next steps on epilepsy as well. Mark, I don't know if there's some specifics you want to give on that.

MARK DEMITRACK: Well, I can echo what I had mentioned earlier. I think for us right now we've learned a tremendous amount we believe about the mechanism here particularly from the pain data. So it points us in a more targeted way when we think about selection of subjects in our first step into patient-based studies.

So our goal here is to get a clear, unambiguous convincing signal in those next step studies. So linking the mechanism in that way to selection of patients is critical and it's an analogous type of approach when we think about epilepsy.

I think the remaining data has been informative, but don't forget that we've already discussed with you in the past that we have tremendous amount of data that has already generated that we believe is quite informative. Carrie?

CARRIE BOURDOW: Yeah, the only other comment I want to make is what Mark commented on and I did as well, is that we were talking about this on our own or with potential partners. And so some of those larger indications both in pain and in epilepsy we think based on the discussions that we're having with partners that would be really interesting for a partner to take this forward.

And now that we've shown CNS target engagement activity, those are going to make those conversations even more fruitful. So think about partners potentially taking on some of those larger indications and Trevena thinking about more of a targeted advancement into a phase IIA type study. Does that help, Doug?

DOUGLAS XU: Yeah, that's helpful. Then I guess, Carrie, just maybe be helpful for everybody just to outline the timelines that you're thinking about for next steps and milestones.

CARRIE BOURDOW: Yeah, great. So the NIH data, the epilepsy data, we're expecting that in the second half of this year. The full safety tolerability data, we're expecting that early next quarter or early fourth quarter. So those are the two data sets. We actually have also a non-clinical study running in infantile spasm, we're expecting that in the second half of this year. Those are the, I guess, three big data sets.

And then we announced preliminary data today, we're not expecting too much more from this study, but that's that part of it. Mark is already speaking with advisors, showing them the data, and talking about what we've seen, and looking at the CNS target and engagement and moving forward on that. And so that gives you a sense that we're not talking about long time frame here before we would get back to everyone and let them know next steps.

DOUGLAS XU: OK, great. Thank you.

CARRIE BOURDOW: Thank you.

MELISSA: Thank you. Ladies and gentlemen, that concludes our question and answer session. I'll turn the floor back to Ms. Bourdow for any final comments.

CARRIE BOURDOW: Great. Well, thank you, again, for joining us this morning. And as you can hear, we've generated evidence that supports TRV045 innovative mechanism of action in CNS target engagement. As we've talked about in part in the Q&A the market opportunity for once daily novel solutions in both chronic pain and epilepsy is large.

And so our next steps as we've described, first, we'll provide updates on the full safety and tolerability results, which we're expecting early fourth quarter. We have promising evidence of the therapeutic potential of TRV045 in neuropathic pain. Statistically significant EEG data, we have that now in hand. And as I mentioned, we're waiting for the NIH-ETSP data. We're already working with our KOLs and potential partners to plan the additional clinical studies in patients.

Before closing, let me also call your attention to the business update we issued this morning where we announced that our partner in China, Nhwa, achieved the milestone of first commercial sale of Olinvyk. As a result, we are now in receipt of the $15 million tranche that was part of our ex-US royalty-based financing with our bridge. That funding is in addition to the 28.1 million in cash we previously reported at the end of the second quarter.

We also expect new Olinvyk data from the volition study in the coming weeks. And we announced new abstracts that will be presented at the American Society of Anesthesiologists next month. So thank you, again, for calling in today.

MELISSA: Thank you. This concludes today's conference call. You may disconnect your lines at this time. Thank you for your participation.