**DOUG TSAO:** OK. Good afternoon, everybody. Thanks for bearing with us. I'm Doug Tsao, Senior Analyst at HC Wainwright. Thanks, everybody, for joining us. Up next, we have Trevena, represented by Carrie Bourdow, the CEO, and Mark Demitrack, the Chief Scientific Officer or Medical Officer?

**MARK DEMITRACK:** Chief Medical Officer.

**DOUG TSAO:** Medical Officer. So I know you just recently presented some really interesting data last week?

**CARRIE BOURDOW:** Last week, right.

**DOUG TSAO:** So we'll get to that, but Carrie, I did want to give you a chance to maybe just provide a quick overview on the company and where you are.

**CARRIE BOURDOW:** Great. Well, first off, thank you, Doug, for inviting us to the conference. We're really pleased to be here. And for those of you that don't know Trevena, we are a CNS-focused company. All of our assets are new chemical entities, wholly owned by us, discovered by us in our own labs. And IV OLINVYK was the first new chemical entity that we took all the way from discovery to approval.

Just a quick reminder that IV OLINVYK is indicated in adults for the management of acute pain severe enough to require an IV opioid and for whom other alternative treatments are inadequate. All of our safety information, including our boxed warning and our prescribing information, is on OLINVYK.com, so I encourage you to look at that as well. And we will be making forward-looking statements, so I encourage you to review our regulatory filings, just a little bit of housekeeping before we get started.

But as you mentioned, the exciting news was last week for us. One of our other new chemical entities, one of our pipeline assets, TRV045, which is a novel S1P receptor modulator, we announced data from two proof of concept studies. Quick history before I turn it over to Doug. TRV045, we were looking at TRV045 as a non-opioid treatment for chronic pain.

And the NIH, through their epilepsy therapy screening program, started looking at TRV045 for epilepsy. So they ran the program through their non-clinical studies. A lot of the current antiepileptic drugs that are on the market went through this program. This was part of the NIH as their own resourcing. We didn't pay for this.

And so then we initiated these to proof of concept studies. They read out last week. And the reason why we're so excited, in the first study, which was a series of pain endpoints, statistically significant differences showed CNS activity. The second study, which used Transcranial Magnetic Stimulation, or TMS, really as a proxy for epilepsy, also very exciting data, statistically significant differences. And both studies demonstrated CNS activity.

So we were very excited. It was an incredibly busy week for us, a long, long holiday for the team.

**DOUG TSAO:** OK, Carrie. So we'll get to TRV045. But maybe as a starting point, just a brief update on OLINVYK. You did launch the product a couple of years ago in the midst of COVID, which obviously presented challenges, and you sort of repositioned the commercial footprint and your efforts. So maybe just tell us exactly where you are. I know there might be some data upcoming, and what you think that might help you accomplish.

**CARRIE BOURDOW:** Great, yeah. So as you mentioned, we launched OLINVYK-- it's a hospital-focused product-- at the beginning of the pandemic. So we all know what was going on in hospitals. OLINVYK can be used in the inpatient setting and also in ambulatory surgery centers in the outpatient setting.

And really, for us the bulk of the opportunity is in the inpatient. But with formulary committees for the most part shut down during the pandemic, we shifted our efforts to the outpatient setting, where physicians can get experience with OLINVYK and then bring that experience back into the inpatient setting. So we're starting to see that happen now.

Certainly, we're not where we'd like to be with OLINVYK. We do have new data coming, as you said. This data is coming out of the Cleveland Clinic and Wake Forest Baptist Health. So we've announced some of the data already. We announced GI tolerability data, delirium data, and this new data that's coming is in respiratory depression.

As with all opioids, serious, life-threatening respiratory depression, potentially fatal, can occur with OLINVYK and that's one of the reasons why we thought this was important to do this study. The Cleveland Clinic wanted to do this study. So we're looking for that data this quarter, third quarter, so obviously, just right around the corner.

And you asked me, what do we think this will do. So it's important that you study new drugs in a real world setting, and so that's what the Cleveland Clinic took on, this real world studies looking at this data set, as I mentioned. And we think, because this data is being done at two of the largest academic medical centers, top academic medical centers, that this will really help us get back into that inpatient setting and help us with formulary committees.

**DOUG TSAO:** And I know when you first started, you were not necessarily as interested in the outpatient setting. But as you've turned to that focus a little bit, what has that enabled you to accomplish so far and what are some of the early returns been?

**CARRIE BOURDOW:** Yeah, so a couple of things. As I mentioned, the first is really getting physicians to get experience with the drug in the outpatient setting. The other thing that I'll say is, if you've looked at some of the outpatient trends, you see that more and more complex patients are shifting to the outpatient.

In the old days, they wouldn't do spine surgeries, for instance, in the outpatient setting. That's now happening more and more, and patients are staying longer in the outpatient settings. Some outpatient centers are actually shifting to two-day centers. And so that complex patient, really where we've positioned OLINVYK, is starting to shift into the outpatient.

So you're right. In the beginning, those patients were only treated in the inpatient. Now we're sort of seeing not quite an even mix, but a lot more opportunity in the outpatient setting than what we saw previously. OK.

**DOUG TSAO:** And maybe we'll turn to TRV045 because that's obviously become a big focus for the company. There obviously have been several other S1P modulators approved for different indications. What makes your molecule different and what has that potentially set you up to do?

**CARRIE BOURDOW:** Yeah, I'll start and then I'll turn it over to Mark. So as you mentioned, there are other S1Ps out on the market, drugs like fingolimod, large, blockbuster drugs. TRV045 is part of that family, but is also very distinct mechanistically. And so I'll let Mark talk about some of the exciting--

**MARK DEMITRACK:** Yeah. I can sort of boil it down into three major facets of the compound that really set it apart from other drugs in the class. The first is the way the receptor drug complex is handled once internalized in the cell. Ordinarily, that complex would lead to disposal of the receptor through the lysosome, which leads to long-term absence of the receptor on the cell surface. That's one of the reasons why lymphopenia is a characteristic of drugs in this class.

Our compound is different in that, once internalized, that drug receptor complex rapidly disengages, so-called more rapid recycling process, which makes the receptor almost immediately able to transit back to the cell surface, so no long-term loss of the receptor on the cell surface. So you get the benefit of agonist activity at the receptor, but without that loss of cell surface signaling, as a result, no lymphopenia. We haven't seen that in any of our animal studies to date, we haven't seen it in the clinical studies, and we believe that would need to know long-term immunosuppression associated with the use of 045, important because it opens up the potential application of an S1P modulator for targets that are not traditionally open with the use of these agents where we've been studying it in chronic pain, and with NIH's collaboration with epilepsy.

Another key feature that differentiates it is its specificity for the subtype of S1P receptor. There's five different subtypes. Ours is targeted at the type 1 receptor, and the reason for that being that that's arguably the most plentiful receptor on cell targets of interest for us in the brain. And the brain is ultimately a clinical target for us.

And those S1P1 receptors are very plentiful on glial cells, astrocytes, microglia in the brain, which have important regulatory functions on neuronal activity, which leads me to the third differentiating feature of the compound is that, by virtue of its ability to act on astrocytes and microglia, it actually can modify the output of immune mediators or really modify the inflammatory state of these non-neuronal cell elements. And we've demonstrated that in a preliminary study in cultured mouse astrocytes, where we've demonstrated by assessing a variety of cytokines and chemokines in the fluid that are coming out of the astrocytes. When incubated with 045, the net pattern of output is an anti-inflammatory signal. So those three aspects of the compound are really what set it apart and we think make it pretty unique within this class.

**DOUG TSAO:** And Carrie mentioned you recently released some proof of concept data. Why don't you just provide an overview about what you learned, both in terms of the pain models as well as potentially implications for epilepsy, and more broadly, other potential CNS conditions.

**MARK DEMITRACK:** Sure. So as Carrie was mentioning, two studies, and they really exploit the two different paths that we're on right now, one, all the animal data that we've generated aiming towards chronic neuropathic pain, and then the more recent pathway towards epilepsy. So we chose to pursue two different studies.

The first one used a variety of a whole panel of experimental pain models in healthy humans that looked at both central and peripheral nociceptive function. We were most interested, and we chose one model in particular in this array that tapped into neuropathic pain modeling. It uses capsaicin as an irritant on the skin, which produces a phenomenon called allodynia, or pain that normally wouldn't be perceived as pain, in this case, mechanical allodynia. So we're hoping to demonstrate activity in that target.

We also looked at a variety of other pain models, temperature, electrical, heat pain. That experiment paid off very nicely for us in that we had very nice, highly statistically significant results in the mechanical allodynia model. So it fit pretty much hand in glove with the data that we had already collected in animals. So it points us really kind of several steps ahead on the pathway towards chronic neuropathic pain.

Also, I'd point out that model is one of the key pieces of evidence that tells us that the drug is getting into the brain, modifying neuronal function, in this case, the process sometimes referred to as central sensitization in the CNS, so pretty important result that we got in that study. The second study more speaks towards the potential in epilepsy, and this is fundamentally a study that's asking, can TRV045 modulate the electrical properties of the functioning of the brain. So it gives us another way of demonstrating that we're getting into the brain and modifying its functional state.

And we did that by measuring two different methods of outcome. One is using electromyography in response to TMS, or Transcranial Magnetic Stimulation of the brain. The other is to use Electroencephalogram, or EEG as a pharmacodynamic measure of drug activity in the brain.

Let me start with the EEG outcomes first. We measured the power spectra across the range of frequency bands that are seen in the EEG, from slow wave activity in the delta and theta range, all the way to fast frequencies, alpha, beta, and gamma ranges. What we saw is a statistically significant increase in the power spectra for the alpha, beta, and gamma, so sort of the mid-range to higher frequency bands, important because those are the range of the spectrum that is generally associated with, in the case of alpha, arousal and alertness, in the case of gamma, usually associated with higher order cognitive functions like learning and memory. And the beta spectrum is thought to be a reflection of GABAergic inhibitory tone in the brain, so pretty important insights into potential functional consequences.

At the other end of the spectrum, the slower end of the spectrum, a typical finding for many antiepileptic drugs is that they increase slow wave activity, and that is thought to be associated with some of the sedating properties of antiepileptics. We didn't see that. With delta, we saw a slight decrement in the power spectra. With theta, it was essentially neutral.

Whether that has implications for the future in terms of the potential adverse event profile of the product, it's a pretty important area that sort of would guide us in terms of future studies that we might do. The other aspect to the study was to use TMS, which provides a pulsed magnetic field that induces an electric current in the cortex of the brain. And so you can measure, essentially, the excitability of the cortex. This is a maneuver that's used quite commonly early in antiepileptic drug development as a way to screen for whether or not these drugs have a likely reduction in cortical excitability. Virtually all antiepileptics that are out there do, and that's been helpful to us because we sort of have a target that we're aiming at in terms of the magnitude of the reduction in the electrical excitation.

And what we saw in this study, though not statistically significant, was a signal that was of a magnitude, electrically, that is right smack in the middle of the neighborhood where you see the electrical changes with known anticonvulsants. So that marries up very nicely with some of the animal data that we've generated with the NIH's input that shows us that 045 modulates the convulsive potential in animal models. So both of these studies together, it was a good outcome for us because it gives us two different clear demonstration instances that we're entering the brain, we're modulating the properties of the brain, in the case of the pain study through that pain model that's reflective of neuropathic central pain signaling, and then in the TMS study, changes in electrical excitability of the brain. So couldn't have asked for a better outcome from this work.

**DOUG TSAO:** And from the pain studies that you did, obviously you saw a really strong signal in allodynia. But you didn't necessarily see as strong signals in some of the other models that were tested.

**MARK DEMITRACK:** Right.

**DOUG TSAO:** And what does that tell you?

**MARK DEMITRACK:** Right. It tells us that we are seeing a mechanistically specific outcome. So that specificity is pretty important. You don't want to see a shotgun effect, if you will, when you do an experiment like this. That may suggest you're having some nonspecific influence that's causing you to appear to be detecting a pain signal.

Here, you're looking for an effect in a model that's reflective of your hypothetical underlying mechanism, and that's exactly what we saw. So seeing effects in some, but not all of the measures is really the kind of signature that you'd like to see coming out of a study like this.

**CARRIE BOURDOW:** And so when you sort of pull all this together and you think about, as we started, a non-opioid treatment in chronic pain, huge market where there's tremendous unmet medical need, epilepsy, where you have this potential signal where you may not have the sedating effects that other antiepileptic drugs have, and we mentioned the NIH. They're continuing to study TRV045. They're looking at it right now in seizure prevention in some of their non-clinical models. That data is expected second half of this year, so that makes a very interesting picture for us.

And anticipated once daily dosing novel mechanism of action, that's sort of the ticket of entry for both of those huge markets. And then on top of that, either potentially better efficacy, better safety, tolerability, or at least better safety, tolerability is where we're thinking about things.

**DOUG TSAO:** And so I guess maybe provide some perspective in terms of what are next steps, both in terms of development for neuropathic pain as well as epilepsy. What will that new data from NIH tell us? And at what point does that help you refine your strategy, because obviously, in epilepsy you can go in a lot of different directions.

**CARRIE BOURDOW:** Sure. I'll start, Mark, and then I'll have you have you jump in as well. So I mentioned the data sets that we're waiting on. We're also waiting on the full safety and tolerability. We know from this study, these two preliminary proof of concept studies, no serious adverse events, no drug-related discontinuations, but we'd like to see the full safety, tolerability that as I mentioned already, the NIH seizure prevention data.

So as it relates to neuropathic pain, we're a little bit further ahead because, in our hands, in Trevena's hands, we have been looking at that for a while. Mark is already talking to key opinion leaders about next steps. And so when you think about neuropathic pain, you think about things like OA, low back, big indications where potential partners might be interested, targeted areas for us could be in something like small fiber neuropathy or fibromyalgia, some of those other areas. As you mentioned, epilepsy, there's a lot of places that we could go, including some orphan areas as well that we're thinking about. But Mark?

**MARK DEMITRACK:** Yeah, I think the next step logically for us is to move as promptly and as quickly as you can into patient-based studies. So we're using the data that we obtained from these proof of concept studies to help us refine that design and targeting strategy. So that's really what's next up for us.

**DOUG TSAO:** And so, Carrie, I know we're out of time, but just quickly, at what point would you be positioned to give us an outline of or sort of advance into those patient studies?

**CARRIE BOURDOW:** As Mark said, we're looking to do that as quickly as we can. We just got the data last week, so more to come, but a really exciting time for the company.

**DOUG TSAO:** OK, great. Well, with that, thank you.

**CARRIE BOURDOW:** Thank you, Doug. Appreciate it.