11 - 06 - 2025

Skye Bioscience, Inc.

Q3 2025 Earnings Call

Skye Bioscience, Inc.

Q3 2025 Earnings Call

CORPORATE SPEAKERS:

Bernie Hertel
Skye Bioscience; Head of Investor Relations
Kaitlyn Arsenault
Skye Bioscience; Chief Financial Officer
Punit Dhillon
Skye Bioscience; President and Chief Executive Officer
Christopher Twitty
Skye Bioscience; Chief Scientific Officer
Puneet Arora
Skye Bioscience; Chief Medical Officer
Tu Diep
Skye Bioscience; Chief Operating Officer

PARTICIPANTS:

Michael DiFiore
Evercore ISI; Analyst
Unidentified Participant
William Blair; Analyst
Ananda Ghosh
HC Wainwright; Analyst
Jay Olson
Oppenheimer; Analyst
Unidentified Participant
Citizens; Analyst
Unidentified Participant
Piper Sandler; Analyst

PRESENTATION:

Operator^ (Operator Instructions) At this time, I would like to welcome everyone to the Skye Bioscience third quarter 2025 Financial Results and Business Update Call. (Operator Instructions) I would now like to turn the conference over to Bernie Hertel, Head of Investor Relations. Please go ahead.

Skye Bioscience, Inc.

Q3 2025 Earnings Call

Bernie Hertel^ Hello. Thank you, all for participating in today's call. Before we begin, I'd like to caution that comments made during this conference call will contain forward-looking statements under the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995 including statements about Skye's expectations regarding its development activities, timelines and milestones.

Forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially and adversely.

And reported results should not be considered as an indication of future performance. These forward-looking statements speak only as of today's date, and the company undertakes no obligation to revise or update any statements made today.

I encourage you to review all of the company's filings with the Securities and Exchange Commission concerning these and other matters. I'll now turn the call over to Kaitlyn Arsenault, Skye's CFO.

Kaitlyn Arsenault^ Thanks, Bernie. After the market closed today we issued a press release and filed Skye's Form 10-Q with the Securities and Exchange Commission, outlining our quarterly financial results. We encourage you to reference our filings for the details of our financials and the risk factors described therein.

I will now provide a brief overview of our key financial results for the third quarter ended September 30, 2025. We ended the third quarter with cash and cash equivalents and short-term investments totaling $35.3 million.

We expect our current working capital to fund operations and key clinical milestones into 2027. This includes the completion of the extension of our Phase IIa study for nimasimab and certain manufacturing and preparatory clinical activities needed to initiate the next study.

In addition, our runway continues to include a modest discovery R&D budget and the dose concentration and process intensification work required to support our expected TPP and scale and support later-stage studies for nimasimab. R&D expenses for the three months ended September 30, 2025, were $9.4 million as compared to $4.9 million for the same period in 2024.

The increase was primarily due to contract manufacturing, clinical trial costs associated with our obesity study for nimasimab, discovery R&D expenses, salary and stock-based compensation expense and consulting advisory and professional fees.

General and administrative expenses for the three months ended September 30, 2025, were $3.9 million as compared to $4.6 million for the same period in 2024. The decrease was

primarily related to decreases in consulting, advisory and professional fees, recruitment fees, salaries and stock-based compensation expense.

Our net loss for the three months ended September 30, 2025, totaled $12.8 million including noncash share-based compensation expense of $1.9 million compared to $3.9 million for the same period in 2024 with noncash share-based compensation expense of $1.9 million. Now I'll turn the call over to our President and CEO, Punit Dhillon.

Punit Dhillon^ Thanks Kait. So today and during this quarter and the subsequent quarters, we're really focused on what matters most, turning the answers from our CB1 study into the logical next steps.

We're going to walk you through what we've learned from our Phase IIa CB1 study so far and how that data has really sharpened our focus, maintained our focus on our clinical path and strengthened our conviction in the nimasimab opportunity. From the start, we said that the next step for nimasimab would be to determine an optimal dose for nimasimab.

And to that end, the top line data from the Phase IIa study provided us with a wealth of information that we continue to mine for further insights. Most importantly, it gave us evidence in the biological activity of nimasimab and the clarity on the PK to move forward confidently on our combination development pathway while simultaneously planning to further understand nimasimab's benefit in a monotherapy setting.
On today's call we'll walk you through the progress that we've made over the past 90 days, the data that we've generated and the path that we're really focused on in terms of charting forward. We're going to cover four key areas today.

One is clinical development, specifically what we've learned from the CB1 study, how those insights are shaping the potential for future next studies. Number two is CMC and product economics, how we're designing nimasimab for scalability and long-term market penetration.

Number three is R&D and the work we're doing there, the science that continues to validate that peripheral CB1 antibody and -- sorry, nimasimab or peripheral CB1 antibody is differentiated and it's a durable mechanism.

And four, the continued emphasis on just really strong accountability and consistency, how our actions this quarter measure against what we said that we would deliver. I'm going to conclude with an outline of what's next.

I look ahead at the key milestones and the catalysts over the coming 90 days. So first, let's get into clinical development. We'll start with what we said last quarter and where we are now. In Q2, we committed to three different things.

One was deliver top line data in Q4 from CV1. Two was to use that data set to inform the dose-ranging strategy for the next clinical phase; and three, maintain operational and regulatory milestones and readiness to move efficiently into the next study. We've delivered on each one of those commitments. At Obesity Week last week, Dr. (Lou Aronei) presented the late-breaking results from CV1 and the findings are both clear and very encouraging.

We showed synergistic efficacy with nimasimab plus semaglutide and achieved an additional approximately 3% weight loss at 26 weeks compared with semaglutide alone. This is with a p-value of 0.0372 on a modified intent-to-treat population. That's nearly a 30% improvement with this combination with no observed plateau at 26 weeks.

We also showed quality of weight loss that the combination of -- the combination of nimasimab and semaglutide improved lean to fat mass ratio of 0.26 versus 0.13 with a p-value of 0.0126 and reduced weight circumference by an additional 3.17 centimeters with a p-value of 0.0492.

We also showed durability that in the 12-week post-treatment follow-up, nimasimab plus semaglutide blunted weight regain with only an 18% regain or 2.3 kilograms versus 50% regain or 4.7 kilograms on the semaglutide alone arm, and that's with a p-value of 0.006 versus placebo. The safety signal has also been very positive. There's been no neuropsychiatric signal and no additive GI burden.

And so this overall data really confirms that nimasimab is biologically active, clinically meaningful in combination and exceptionally well tolerated. They validate our long-held view that the mechanism is sound and that the value now lies in refining really the dose to unlock the nimasimab true efficacy window and fully capture the therapeutic potential of a peripheral CB1 antibody.

Additionally, in September, we completed enrollment of the 26-week extension study. A total of 43 patients were enrolled with 19 and 24 patients in the combination and monotherapy cohorts, respectively.

Retention in the extension study has been very strong, and the data from the 26-week extension study is expected in late Q1, early Q2 of 2026, and we will provide information on the potential for full treatment duration of 52 weeks, followed by a 12-week follow-up period.

This long-term follow-up from the extension will be a new inflection point with a richer data set and a more complete understanding of nimasimab's clinical potential. In parallel, we're going to continue moving up the dose.

So the monotherapy extension study is evaluating a slightly higher dose where we've stepped it up from 200 milligrams to 300 milligrams weekly, but our current plan is to even go higher. Analysis of our preliminary PK/PD model showed that patients achieving higher systemic levels

of nimasimab corresponded with a greater weight loss. That aligns with the range where we expect to show clinically significant results.

Our PK/PD model based on the clinical data and the preclinical dose ranging really gives us confidence that the higher dose -- a higher dose of nimasimab can potentially achieve better monotherapy efficacy and drive even further weight loss when combined with semaglutide.

The parallel approach that we're taking with further clinical data from the extension study for the durability and then evaluating a higher dose ranging in a well-powered Phase II focused combination study with understanding a better characterization of the monotherapy dose will really keep the development of nimasimab on track, and we're really focused on that.

And we think that that's the next logical step for understanding our next important decision points. Next, I'll move to CMC. So another area that we've continued to make progress in has been all of our manufacturing and CMC work that includes our high concentration formulation strategy.

And that remains on track. We believe a path to achieving the formulations that really align with our clinical protocols and expectations for our TPP as well as patient convenience remain on track. This isn't simply like a technical milestone for us.

It's really rooted in a commercial TPP. Our focus is on reducing overall injection volume, lowering costs per gram and ensuring we can compete as pricing pressures on incretins continue to intensify.

This aligns, we believe, perfectly with our titration-free target product profile, and that's a key advantage over the incretin-based injectables that require a step-up dosing for tolerability.

To clarify, nimasimab has shown no additive GI burden at the 200-milligram once weekly dose, and we expect to evaluate any higher dose without the need for titration, making it easier for both prescribers and patients. Equally important, we're continuing to evaluate and manage and execute on measures that can significantly impact our cost of goods.

This process includes optimization of the upstream and downstream manufacturing steps for nimasimab and scaling up into high fermentation volumes, and we're continuing to evaluate multiple delivery devices including auto-injectors that will improve the patient experience. Together, these activities will have a significant impact on reducing our cost of goods to support an eventual pricing model that aligns with Medicare and is rapidly influencing the obesity market.

We're ultimately designing a product that is potentially not only clinically differentiated, but commercially durable from a manufacturability and real-world affordability. Next, we'll move into R&D.

So beneath all the clinical data sits an increasingly powerful scientific base. The preclinical and translational work continue to show that nimasimab reduces fat mass while preserving lean mass, improves insulin sensitivity and glucose control, lowers leptin and increases GLP-1, reduces hepatic steatosis and inflammatory markers and maintains weight loss durability after treatment stops. This is consistent with what we're seeing clinically.

Combination studies in DIO models with tirzepatide and semaglutide show greater than additive weight loss and minimal rebound, confirming that peripheral CB1 inhibition complements incretin biology mechanistically. And collectively, these results reinforce why nimasimab is really the right molecule, the right mechanism and the right program to move forward.

Our message to investors ever since we began development on the nimasimab program has been about discipline and delivery, and that remains true to today.

In Q2, we said we'll complete the top line readout by late Q3, early Q4, and we did that, and we presented late-breaking data at Obesity Week last week. We also said we're going to continue with the current data set to guide our dose ranging, and that's what we're doing.

We're going to continue advancing our CMC readiness in parallel, and we continue to improve manufacturing capability as well as process improvements are going to continue to be ongoing.

We're focused on the higher concentration formulation path, and that's on track and synchronized with our clinical development planning.

We ultimately expect our monoclonal antibody to be the best way to target CB1 inhibition to enable confidence in the safety and this pathway will ultimately show the clearest mechanism validation in terms of targeting this particular pathway.

With our Phase IIa data, we have now provided an important initial demonstration of nimasimab's utility that does offer the validation of the mechanism. And notably, we did that by showing that there is no neuropsychiatric adverse events or other unexpected adverse signals across the different cohorts that received nimasimab.

And we've just completed the fifth DMC meeting this past week with no concerns. So every commitment that we've made, we've made it on time we've made it with precision, and we're going to continue doing that.

Skye Bioscience, Inc.

Q3 2025 Earnings Call

Over the next 90 days and into 2026, our focus is on converting what we've learned from the clinical data into further execution. We're going to generate a more complete picture of nimasimab's potential using insights from our PK and PD modeling and the ongoing extension study.

We're finalizing the next Phase II design, we're concentrating on combination and also in the maintenance indications where the data already point towards a really strong direction.

And we're continuing to advance the formulation and manufacturing work so that nimasimab can be delivered practically at scale and with the cost discipline that the market demands.

We'll also be presenting at several investor conferences beginning next week and into December and gearing up for sharing new preclinical and clinical data at all the major scientific conferences and meetings in 2026. Across each of these fronts, the through line is really about consistency.

We've said what we would do, and we've delivered on the data and on the timelines and on the execution. Our next steps are an extension of that same discipline, and we're interested in continuing to focus on translating all of this into momentum and the momentum into value.

So this concludes the prepared remarks and comments today. We thank you, everyone, for joining the call and we'll now open the call for questions from our covering sell-side analysts. Operator, over to you.

Operator^ (Operator Instructions) Our first question comes from the line of Michael DiFiore from Evercore ISI.

Michael DiFiore^ Just two for me. Now that you've had some time to further digest the data from the trial, have you gained any additional insight between weight loss and exposure? I recall at the time that the data were revealed, you only had PK exposure versus weight loss up to 16 weeks.
So that's my first question. My second question is regarding the 26-week extension. Simply, are there enough patients, 43 patients seems sort of low. And do you have enough patients to draw any statistically significant insights?

Punit Dhillon^ Michael, thanks for dialing in and asking the questions. So I'll take the first question and kind of hand it over to Chris because you can further elaborate. But as you kind of indicated there, obviously we showed a really strong validation of the mechanism in the combo efficacy.

The monotherapy dosing, I think has been evident in terms of the issue was dose, not the biology. The exposure response really has demonstrated that the observed concentrations at

the 200-milligram dose didn't achieve the efficacy that we would expect because they were -- patients were underdosed.

But Chris, yes, can further elaborate in terms of what we've seen now based on the 26-week data set as well as anything he wants to point to from the preclinical data.

Christopher Twitty^ Thanks, Punit. Yes. So to that point, we have, in fact, looked at a more complete PK data set. I would just note that the final PK/PD analysis, which is still underway likely won't be available probably for another few more weeks to months.

But we do have a more robust build-out and we looked at a mixed effects model, both controlling for the placebo effect as well as doing a similar type of modeling where we controlled for the semaglutide effect and looked at that in the combo setting. In both instances, we see that there's really no bias in the residual.

So the models fit well. They align with the observed weight change that we saw in the trial. Importantly, they point to the point you're making, that is we're seeing a nice slope, a very believable, credible slope that demonstrates this response related to exposure. So we feel very comfortable that the PK data is holding.

We'll again have the final PK/PD model, but we feel very confident that, in fact, there is a dose response. And as we get to better and better exposures, we will see better and better weight loss as both monotherapy and in combination. The other thing I've just pointed briefly since we've last talked, Michael, the translation of the DIO data has been further validated.

We've done some important biodistribution studies looking at where the compartments and how those fill relative to what's in the serum and using that along with some other approaches to really get a good fit in terms of how the DIO data, which demonstrates very clean dose response as well how that translates to the clinical doses.

So both those pieces are really supporting this concept of higher dosing in the clinic to see better weight loss.

Punit Dhillon^ Michael, would you mind just repeating your second question? Or did we answer it?

Michael DiFiore^ So my second question is regarding the 26-week extension data. I just -- it seems that only 43% -- 43 patients are enrolled, it seems kind of on the low side. I was wondering if that's enough patients to draw any statistical significant insights when the trial wraps up.

Bernie Hertel^ Yes. So the good news on the extension is that enrollment has been -- obviously that was good that we saw good interest in the study and then retention has continued to stay really strong. it is a smaller number of patients relative to the core study, the first part.

But we do believe that there will be a clear separation that we would be able to see, especially if you recall in the 26-week time point. The first 26-week time point in the combination, we did see a really strong difference and then the slope wasn't plateauing.

It continued. So we hope that we're going to continue to see that separation between semaglutide alone.

On the monotherapy, as we've indicated, we believe that there's still room to go higher in terms of dose. So we'll see what the data reveals. But at this point, it's a little tough to comment on that because we don't have that separation that we expected on the first 26 weeks.

Operator^ Your next question comes from the line of Andy (inaudible) from William Blair.

Unidentified Participant^ We have two. One is more on the regulatory side. So we're curious very provocative data looking at the weight rebound. Do you need to have a monotherapy approval before a potential maintenance approval? Just trying to get a sense of the sequence and requirements based on your regulatory discussions with the agents.

So that's number one. Number two is we looked at comparative kind of randomized withdrawal studies, in particular, step four with semaglutide. It seems like in that study, the weight regain was about 50% out to one year.

In this study, the weight regain was much faster. So I'm curious if there is any sort of patient baseline characteristics that you want to highlight that could explain the more rapid than expected weight regain from the semaglutide arm.

Punit Dhillon^ Yes. I think these are both great questions and interrelated. I can pass it over to Dr. Arora to take those and then might come back with some additional commentary on the maintenance setting.

Puneet Arora^ Andy, to address your first question, yes, if we were to do maintenance therapy with nimasimab as a monotherapy, that would require monotherapy approval, although if that is the strongest suit for the drug, then the approval could be as maintenance as well.

And we are -- as part of our plan as we go forward is to continue looking at the monotherapy to find that optim dose and frequency on how to dose monotherapy for varying indications including maintenance.

So that's a question that we will be discussing with the agency, and I think that will be part of our continuing interaction with them as to how to push both monotherapy and combination forward and what differential path each one may need. So I'm sorry, what was your second question?

Unidentified Participant^ It's just on the regain piece (inaudible).

Puneet Arora^ Yes. So if you look across -- if you look at the weight rebound data across a bunch of studies, there was a (inaudible) withdrawal study. I think it's one of the ones you had some and then tirzepatide did some randomized withdrawals. In one year, the weight regain is about. It does tend to be somewhat accelerated in the first half because the weight regain is faster initially and then tends to plateau a little.

We do see a somewhat faster regain in this study. We don't know why. It's we don't know particular characteristics that we're seeing in the demographics in this study are frankly the same as you see in most other studies.

So we don't know why these patients regain their weight this quickly, but they did and being a randomized trial, we figure that both the cohorts are effectively similar.

Punit Dhillon^ Yes. If I can just elaborate on one thing, Andy. So look, the durability data that we've showed last week with the only 18% regain versus 50% for semaglutide alone is, I believe, a real cornerstone of our strategy, and it really validates what we saw from an R&D preclinical perspective.

It shows that peripheral CB1 inhibition can provide a durable effect after treatment stops, which is a significant issue for the incretin-only therapies. I noticed coming from Obesity Week, there has been a growing emphasis of the incretins or companies that have incretin pipelines focusing on the maintenance market as well.

We believe that this comment we made at the last earnings call and we stand by it is we do believe that we really have an interesting opportunity for nimasimab to aggressively pursue a maintenance indication, which we can formally kind of look at once we finalize our dosing strategy.

But we see a massive commercial opportunity that's differentiated because it's more likely and doctors will confirm this, that they would treat with a differentiated mechanism rather than maintenance with another incretin after induction of incretin is completed.

And Tu investigated that from a commercial standpoint from the survey that we've done and that's been confirmed. Tu, do you want to just expand on that?

Tu Diep^ Yes. No. I don't -- I think you kind of covered it pretty well. I think it is important to understand that the maintenance approach therapy is something that's being looked at a lot, not just by Skye, but from investigators and clinicians as well as obviously other companies. And as Puneet said, right now there's not a lot of options other than another GLP-1 for patients to go on.

And so physicians are generally either reluctant or, in fact, at least the ones I've spoken to generally actually put them on something else other than the GLP-1, like phentermine or something like that, that to them makes more sense because it's a different mechanism of action, even though phentermine may have some other comorbidity issues as well as maybe not be as effective. So I think again in that space, I think there's a real market for a drug like nimasimab that we think -- where we think we can win.

Operator^ Your next question comes from the line of Ananda Ghosh from HC Wainwright.

Ananda Ghosh^ Congratulations on the combo data looks really impressive. One of the question I have is like what kind of the magnitude of data do you believe can be clinically and commercially viable when you are thinking about the combo potential? And I was also curious to know what was the quality of weight loss in terms of the lean mass that would be helpful.

Punit Dhillon^ Yes. I think that's a great -- thanks, Ananda. I'll turn it over to Puneet Arora. He can take both those questions.

Puneet Arora^ Yes, Ananda, thanks for that question. You've seen that a lot of the effective weight loss indications that we out there cluster in around the 20%, 22% range.

In fact, if you speak to most obesity physicians, they'll tell you that a lot of patients don't even need 20% weight loss. Frankly, once you start exceeding about 10% weight loss, you can reverse a lot of comorbidities.

But in so far as the benchmark today is about 20%, semaglutide or a generic GLP-1 usually gives you about 15% and then we start seeing the other combinations adding up to another 5%, 6% like you see with tirzepatide.

That's a differential that we would hope for. We're already seeing in our protocol set here a 14-point-something percent weight loss at 26 weeks, which is 3.5% more than semaglutide alone. So it's about a 35% increase.

And we think that when we do a full 52, actually a 68-week treatment, which is where all these are measured, we will have a combination treatment effect that will be in the range or better than what we are seeing with all these other combinations. We are actually seeing

improvement in body composition along with this 30% extra weight loss. So we have printed this at Obesity Week as well.

What we're showing is that if you just look at the accrued numbers, semaglutide alone has about a 72% fat loss and 28% lean mass. When you add nimasimab to it, this actually becomes a 76% fat loss and only 24% lean loss. So there is a transition towards fat mass loss. When we break this down, we see that -- as you know there is 30% extra weight loss, right?

But the fat loss goes from 15% for semaglutide to more than 20% when we look at the combination, whereas the lean mass loss almost doesn't change. It goes from about 5.5% to 6%. That is what is and that is the effect that we are seeing in the lean to fat mass ratios and why the body composition is improving.

So all of the additional weight loss that we're seeing is almost all fat mass loss. Our secondary endpoint to be specific was lean to fat mass ratio, and that ratio should increase with weight loss.

And the more the increase, the better your body composition is. In our trial, semaglutide increased that lean to fat mass by 0.13. The combination improved it by 0.26, which is twice the improvement, and this number was actually significant. The p-value was 0.01.

Operator^ Your next question comes from the line of Jay Olson from Oppenheimer.

Jay Olson^ We have two questions. Our first question is about your current thinking around the potential for studying a combination of nimasimab plus semaglutide for induction of weight loss versus maintenance of weight loss.

While acknowledging the regulatory considerations, it seems like they both may offer potentially significant commercial opportunities. So how are you weighing the pros and cons of induction versus maintenance? Then I had a second question, if I could.

Punit Dhillon^ Yes. Thanks, Jay. Thanks for joining the call today. That's a key question. We are certainly focused on the induction side.

When we are seeing this improvement that we've showed over the course of this early data set with no observed plateau at 26 weeks, it really demonstrates a synergistic activity, and it's been very encouraging. We're looking forward to seeing what the 52-week data reveals.

But the current focus for the Phase IIb is on evaluating the right and optimal dose in combination with sema. I think there's a little bit of other supportive data that we've seen from a preclinical perspective that Chris might be able to point to in terms of why we feel confident of dosing higher can lead to a better, deeper weight loss.

In sema because of the data that we've seen so far with tirzepatide and sema in combination. Chris, do you want to discuss that?

Christopher Twitty^ Sure. To that point, we directly asked that question in light of our recent clinical data. It is important to understand as we get better exposure moving from what we've modeled to be something very similar to our CD1 nimasimab dose, which we're calling sort of a suboptimal dose in this DIO preclinical model and then a more active dose, an active dose represents something that we're looking towards potentially using in future trials.

So comparing the difference between the active and the suboptimal, you can, of course see that as a monotherapy in terms of weight loss.

But importantly, when we look at this in the setting of combination, we see while the additive effect is there, we really see a large improvement beyond the magnitude you might expect with the monotherapy.

So it seems to really unlock the combo potential as well and maybe even beyond what we see as a monotherapy. So it's important, we think to really get the dose right as we look towards sort of that induction of that combination approach in the clinic.

Punit Dhillon^ And I think it's just important for us to emphasize that it's really relevant in terms of being a truly differentiated alternative or orthogonal approach to what's out there in terms of current combinations.

So although the data is early in the 26-week data is very encouraging. When you do stack it up across these other combinations, it's really interesting to see how deep that response is initially.

So like we're all excited to see what -- how that reveals in a longer 52-week data point. But it makes -- at the moment, it makes a very compelling case for us to evaluate this in a Phase IIb combo.

Puneet Arora^ Roger, this is too. I just want to sort of also add in the relevance of this sort of this rebound data and what I think that also means potentially for a market opportunity, not just in the maintenance setting, but also more in the combination setting where you can get that induction of weight loss.

And if in the real world where patients need to go on a dosing holiday for whatever reason, maybe they're actually going on holiday. They just don't want to bring their drug with them or maybe they have other things, maybe there's access issues, things like that.

What our data suggests is that, that's not going to be as big of a problem as it has been when patients do either lose access to their GLP-1 or lose or have to go on vacation or have other reasons that they're not going to have a significant rebound like we're seeing and like the STEP one data has shown and that you can have this sort of holiday without sort of losing the gains that you've achieved through the treatment.

So I think that's really meaningful. I think a lot of physicians are looking at that and what that means as well how you can manage patients' weight over a much longer period of time than just sort of these sort of compressed times you're seeing in clinical trials and what that really means in the real world for patients.

Jay Olson^ Okay. Great. That's super helpful. If I could ask a second question. Can you please talk about any KOL feedback you've received following the top line CB1 Phase IIa data? And also any feedback you may have received at Obesity Week.

Punit Dhillon^ Yes. I think Chris -- or sorry, two and Dr. Arora, you guys can take those questions.

Christopher Twitty^ Yes. Thanks for the question, Jay. I'll say that I think the reaction was positive. I think they see the combination data as very intriguing. They think that the responses that they're seeing are different.

And they definitely look forward to us looking at much at sort of the dose-ranging study. They obviously see that, that's a key, and that's going to be really important for us to establish that sort of baseline what that optimal dose is going to be.

In terms of the blunting of the rebound data that also has kind of resonated with a number of physicians and KOLs that we've spoken to, to the point that I actually just brought up earlier, one specific physician actually brought that up and said, this is really cool data. If this means that a patient can go on a dosing holiday and not have to worry about gaining their weight back, then this could be really meaningful for their practice.

So yes, I think ultimately, positive. And again from a monotherapy side, I think they recognize our need to dose higher and -- but they don't see that as necessarily a deterrent for the future of the program.

Punit Dhillon^ And I think that...

Puneet Arora^ Some of the leading physicians out there had experience with CB1 before. So it's a pathway they've had interest in for a long time. The neuropsychiatric events has been a source of problem. I think they're really enthusiastic about the idea that you can get these effects and get them in a safe and tolerable manner.

So there's a rekindled interest now that we are showing that there's biological activity and you can do that with an antibody without crossing the blood-brain barrier and getting these neuropsychiatric effects.

Punit Dhillon^ Yes. That's great that you emphasize that, Dr. Arora. I mean I think that was the biggest immediate takeaway once the data hit the tape that we saw when we spoke to our Clinical Advisory Board and other investigators that a lot of folks had just recognized that this was a big leap forward for the class. This is the first time that any data set has been shared with no neuropsychiatric adverse events.

So that's a really important kind of step for us in being able to give us the comfort to be able to dose higher, and we feel confident that there's going to be biological activity.

Operator^ Your next question comes from the line of John Wolleben from Citizens.

Unidentified Participant^ This is Catherine on for John. I kind of a quick question about what you expect from the monotherapy arm in the 26-week update. What do you want to see in order to give you confidence in kind of choosing the path forward? I know that we talked a lot about the combo arm just wondering about that.

Punit Dhillon^ Catherine, thanks for joining the call and stepping in for John. We -- yes, so from the next 26-week data, the differences here is that we've added -- increased the dose from 200 milligram to 300 milligram.

What we have emphasized, obviously to our clinical sites is really making sure that there's strong follow-through in terms of the, not only from a patient retention standpoint, but ensuring that if there's any noise here regarding compliance, we rectify that.

So at the end of the day what we're really looking for is a better understanding for our PK model at this dose. In terms of efficacy, it's really hard to predict at this point in terms of what that's going to be relative to what we've seen so far in the first -- based on the 26-week data.

We are obviously encouraged by the PK/PD modeling that we've done at higher doses that we should be able to reach the 5% or higher bar, but we need to see that data, and we want to make sure that we have improvement in terms of our sensitivity around the PK/PD understanding.

Puneet Arora^ Just to clarify, we did use a slightly higher dose in the extension.

But as Punit said, it's primarily to help us refine our PK models -- we will be -- when we do a Phase II study, we will look at meaningfully higher doses and different exposures, and we think that will give us a more positive result.

Unidentified Participant^ And I know that in the past, you said about -- you will go up to 1,000 milligrams. Have you changed your thinking at all on that on the target for the higher dose?

Punit Dhillon^ Yes. We're still working through that, Catherine. For monotherapy, we expect basically to unlock efficacy at higher doses. So we've -- like we said, it's in line with our exposure and response modeling, and it hasn't necessarily ruled out that the 200 and 300 are effective doses as well. I think we had some lack of consistency in terms of what we saw in the phase -- in the first 26 weeks.

And in our slides that we shared during the top line data review, I think we showed some indication of what the optimal dosing would have revealed and those patients that had increased exposure response, they tended to do really well versus the patients that were suboptimally dosed or had lower exposure response.

So I think what we need to see is if that is kind of course correcting in what we're evaluating, and then we have confidence that dosing higher is definitely going to show a higher likelihood of efficacy signal that we expect to see, and we expect that to be over 5% at 26 weeks at these higher doses that we want to evaluate.

Operator^ Your next question comes from the line of Ted (inaudible) from Piper Sandler.

Unidentified Participant^ And I wanted to maybe dig into the other side of going higher on dose. And from the combination of earlier studies, preclinical data and then the initial C beyond results, obviously we're going to keep a close eye on potential CNS side effects. Is there anything else that we should be really focused on or that could sneak up on us from a safety standpoint of taking the doses to these substantially higher levels?

Punit Dhillon^ Thanks, Ted. Yes. I think we feel really confident about the safety signal and allowing us the room to go higher in terms of dose, especially from the standpoint of any concern of neuropsychiatric adverse events.

So in this study, based on our Phase I data, based on our tox data, there's a substantial amount of room relative to where we're at in terms of dosing.

In terms of other safety concerns, I think we have to see. So we don't have the data to -- yet at higher doses over a longer period of time whether that's a change in terms of GI tolerability.

But we feel at this point, based on the data that we've seen in the Phase II that there wasn't any concerns to be able to go higher. But across the class, it seems to be a little bit different.

Some small molecules have had only about 30% GI issues and then the (inaudible) data recently showed about 60% GI issues. We don't know if that's linked to CB1 yet or if it's -- or it's like it's molecule specific. At the moment, though, there still seems to be substantial room for us to be able to evaluate that.

And mechanistically, it's not the same -- it doesn't -- the mechanism is different than what the GLP-1 drugs are doing. So we feel that we shouldn't have any exacerbated GI burden. But Dr. Arora, sorry, you might want to take that further.

Puneet Arora^ Yes. It's been my sense that even with the data, if you go back to rimonabant that even though they showed 30% GI effects, there was a certain placebo effect as well that's worth comparing to, which seem to suggest that the GI effects that you see with the CB1 pathway are not that significant.

And of course with nimasamab, we are showing even better results at this dose where essentially there is no difference between placebo and what we are seeing with the drug.

With the GLP-1s, which is where all the attention comes from, I believe that a lot of the GI effects tend to come because of the central action on area -- on places near the hypothalamus like the area (inaudible), which whose job is to see what's going on in your blood and cause you to have nausea or vomiting if they think that there is something that's deleterious and stimulating receptors is causing that.

And it's very possible that the CB1 mechanism doesn't actually do that. That's why you see GI effects being so much more muted with this mechanism and especially with the antibody nimasimab.

We will test this, as Punit said, with higher doses, but we're pleased to see that at least with the dose that we've tested, we are seeing really neutral effects.

Unidentified Participant^ Yes. That's great. In the next study, how long do you think you'd be able to dose?

Puneet Arora^ Go ahead, Puneet.

Punit Dhillon^ Go ahead.

Puneet Arora^ So in a Phase II study, I mean we would -- we want to dose people all the way out to a year or 52 weeks, but we haven't -- we're still looking at what the primary structure of

the study should be. What we'd like is to design a study that will move us meaningfully towards doing pivotal studies.

So we may still read out data at, say 26 weeks where you can get a substantial indication of how individual doses are working and get a lot of safety information. But we do want to design studies in the end where the patients that we recruit get longer-term treatment and can be treated for a year or even longer.

Operator^ There are no further questions for the Q&A session. Thank you for attending Skye Bioscience's third quarter 2025 earnings call. You may disconnect.