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<<Michael DiFiore, Analyst, Evercore ISI>>

Welcome, everybody. We're going to get started. So welcome to the second day of Evercore ISI's Healthcare Conference. With us today right now is Skye Biosciences. I had the pleasure of hosting Punit Dhillon, CEO; and Tu Diep, Chief Medical Officer. Gentlemen, welcome. Thank you so much for coming down and spending time with us.

<<Punit Dhillon, President and Chief Executive Officer>>

Yes.

<<Michael DiFiore, Analyst, Evercore ISI>>

But listen, before we delve into Q&A, there's a lot to cover. We'd love to have you guys give a kind of a state of the union of the business and what we could look forward to, perhaps, in the next year or so.

<<Punit Dhillon, President and Chief Executive Officer>>

Yes, thanks, Michael. Again, it's always a pleasure to be at the Evercore conference and meeting with investors. We've really used this week to kind of come out and speak to investors ahead of the New Year, especially with where our last data set came out, so just for grounding everybody, we're a metabolic company. We're focused on metabolic therapeutics. We have a lead asset that's developing a CB1, a peripherally restricted CB1 antibody. We have moved that into Phase 2 development, and we just reported the first 26-week data from a 52-week data set. The next data set, which is a part of this extension that we're running for an additional 26 weeks, will be reported in Q1, so it does set the stage for what did we learn from the initial data, and where do we go from here?

Well, the takeaway that is important for us is that the biology and the proof of concept of this, the intent of this trial, has really allowed us to have conviction in terms of a real clear path forward. The data revealed that there was a suboptimal dose in the monotherapy, which basically established a floor of a 200-milligram dose does drive a limited efficacy. From there, there's a pretty linear kind of equation of being able to have higher dosing improve the weight loss response overall. So that's what we expect to kind of see with monotherapy. But where the other part of the data that was really interesting is what the combo revealed. And the combo revealed an increase of about 30% weight loss when combined with semaglutide. So that has been an interesting trajectory at 26 weeks.

What we'd like to see is that trajectory continue and start getting into that 20% mark at 52 week. And we believe that this is a very unique product profile then when you compare that against

CagriSema, against tirzepatide, and some of the other combinations that are already being – that are in the market are being developed.

<<Michael DiFiore, Analyst, Evercore ISI>>

Excellent. A lot to dig into here. But just in light of these initial Phase 2a result, granted suboptimal exposure, not a high enough dose, what makes you confident that your large molecule approach is still the best angle or a way to treat this disease as opposed to small molecule approaches?

<<Punit Dhillon, President and Chief Executive Officer>>

Yes, and I can cover kind of a couple high points here, and maybe Tu can talk about some other kind of safety considerations. But there's three, I think, important takeaways when you think about a large versus small molecule. One is just the physics of it, right. The large molecule is better situated to stay out of the brain or not cross the blood-brain barrier. The second, in this context, in terms of targeting CB1, we do have a differentiation in terms of the way that the mechanism actually engages with the receptor. And we believe that the allosteric modulation that we offer has a distinct mechanism that kind of leads to the third point of having a really high, large window of safety relative to what the small molecules endure.

So small molecules, unfortunately, we've seen the data to-date still crossing into the blood-brain, crossing into the brain, and exacerbating neuropsychiatric concerns. We don't have that challenge with what we have experienced so far with the profile of what nimacimab is. And so that's the important third point, is that the safety to-date does give us confidence that we have an ample therapeutic window to be able to dose higher and not have any of those same concerns. So I would say that those are kind of the three kind of distinct mechanisms.

<<Tu Diep, Chief Operating Officer>>

Yes, I mean, I would just add that I think the small molecule data actually is what gives us confidence that our drug is going to work, and the peripheral CB1 inhibition is going to be effective. If I say that because rimonabant was sort of the first clinical evidence of it showed limited weight loss with real safety issues. And when we look at that data, we believe the limited weight loss was basically affected by the fact that the drug was mostly in the brain and not in the periphery. You flip that script with monlunabant, where they truly are more peripherally restricted. I don't think anybody can argue that. And they have demonstrated significantly better weight loss at 16 weeks than rimonabant did. And so you kind of see what the potential is with peripheral CB1 inhibition with monlunabant.

And then you also see the added issue, which is even with the small molecule peripheral restricted molecule, you still get the neuropsychiatric side effect. So we think that monlunabant is already kind of saturated. That's kind of, I think, what you may see as your maximum weight loss. And you're not seeing a dose response because they've already saturated the receptors with the small molecule. So you're going to see a dose response with monlunabant if they decide to go

to those lower doses and continue to develop it as a monotherapy. We have the reverse issue. We just didn't dose enough, and we're just on that early sort of dose response curve.

And so if we can dose higher, and we feel very confident now that we can, and still maintain that safety profile, then we think we're going to see those similar dose responses and weight loss responses that monlunabant demonstrated.

<<Michael DiFiore, Analyst, Evercore ISI>>

Makes sense. Makes sense. So just to highlight the combination therapy in the first 26 weeks, just semaglutide alone, patients lost around 10% over 26 weeks. By tacking on nimacimab, they lost 13%. So an extra 30%, just mechanistically, what do you think explains that? Given that nimacimab was a suboptimal dose, just when added on, all of a sudden you have the synergy. What's happening there?

<<Punit Dhillon, President and Chief Executive Officer>>

Yes, so there's a – I think we're still understanding what the biology is in the clinical results. If we go rewind back to some of the preclinical results, there was a really strong kind of body of work that we established during this year, where it shows that there's truly kind of what we've tried to coin as a rewiring that's happening in terms of there's multiple things that are at play. What we believe what is happening and hopefully should play out with the biomarker data that's still pending from this trial is that the GLP-1 mechanism is really kind of reducing the intake, it's caloric restricting. But the CB1 is taking the brakes off the storage of fat. So there could be this energy expenditure component that is in play that we think – we'll still be working on generating that data. But truly, this is an interesting situation where we're getting a one plus one equals three type of situation with both these mechanisms working together.

I think the other part is the…

<<Tu Diep, Chief Operating Officer>>

Well, yes, the ceiling. I think there's a leptin sensitivity improvement. Leptin sensitivity has certainly been shown with the DIO data, including our own DIO data. Improvement in insulin uptake also I think is meaningful in the muscles in particular, given that GLP-1 actually increases insulin secretion. So I think some of those mechanisms appear to be complementary even at the lower dose. I mean, there might be some synergy there at a suboptimal dose.

And again, I think that gives us a lot of confidence in the combination, given that it's a suboptimal dose. We did significantly improve weight loss without significantly increasing adverse events. And if we can continue to see better weight loss over the additional 26 weeks that we're evaluating, the extension study, I think that's a really meaningful outcome for us.

<<Michael DiFiore, Analyst, Evercore ISI>>

Got it.

<<Punit Dhillon, President and Chief Executive Officer>>

One other thing I would add, we've been talking about this with some of the KOLs in terms of really trying to understand this question of what's happening here physiologically. The interesting thing is with the incretins, though, when you look at the incretin and incretin combos, what's evident in the front lines is that there is probably some sort of kind of ceiling to weight loss. Obviously there's going to be the laws of physics involved in how much weight loss. But generally, in terms of this pathway is truly an orthogonal pathway to what's out there, even amylin or the CagriSema combo. Amylin's more or less a similar mechanism to GLP-1. So we do believe that here CB1 has an interesting role to play based on these pillars that we described as the differentiation from GLP-1. So that's where it's going to be interesting to see if that trajectory holds at 52 weeks, then I think we really have a competitive product.

<<Michael DiFiore, Analyst, Evercore ISI>>

Got it. Got it. Now just back to monotherapy, again, focusing on that initial 26 weeks. In your deck that day that you presented the top down, you had some swimmer plots of some patients, and some of those patients on monotherapy lost 8% to 15% of their body weight. So do these patients, in fact have high serum exposure? And I asked, because the scatter plot elsewhere in the deck at 16 weeks shows two patients who had near maximal serum exposure but lost like 2% body weight. What explains that?

<<Tu Diep, Chief Operating Officer>>

So I will say in that swimmer plot, there probably is above like one, maybe two patients that had pretty decent weight loss that had lower exposure. I think that's just kind of what happens sometimes you get some patients that respond really well to the drug and some that just don't respond very well. But in general, and I think what we're seeing in the trend is that those patients that had really high exposure tended to do a lot better.

And the way we've started to look at it differently, and the graph that you're referring to is actually looking at concentration – drug concentration at a specific time point, which is week 16. And that was kind of our initial look in our top line data showing that those patients at week 16, we should have expected them to reach a certain concentration at that point. And there was a handful of patients that did. And when we did that correlation, it looked like there was a pretty good correlation there.

Since then we've looked at it a bit more deeply where we truly looked at area under the curve, AUC, which is a bit more true to the actual exposure of the drug. And again, we see very similar trends. And what we actually see is there's a cluster of patients that actually did kind of get to the exposure you would expect, and you kind of see a relatively even distribution of patients. Some of those patients did well, some of those patients didn't do so well.

But then when you kind of track over a little bit further to the exposures where some patients actually got extremely high exposures to the level that we think would be actually effective, now

that we understand the PK/PD relationship a bit better. And those patients that received those exposures did really quite well.

<<Michael DiFiore, Analyst, Evercore ISI>>

Got it. Got it. Just when I think about your pre-clinical experiments, it showed great efficacy in mice and those mice were dosed anywhere from like 75 mg/kg up to 750 mg/kg. So it turned out in the Phase 2 that the 200 milligram Q weekly dose only equated to maybe mid teens mg/kg dose in mice. That was the translation. Or like it was really 5x to 50x below the successful mouse dose. So for future human dosing, would it be as simple as testing 5x to 16x to 200 milligram dose that was used in Phase 2a, which would be around maybe 1,000 milligram to 3,200 milligram or will allometric scaling kind of just dictate otherwise?

<<Tu Diep, Chief Operating Officer>>

Yes. I'll take that one. So we have continued to refine the model. I think what I was telling Oscar earlier is that we're getting a lot more – like way more confident just around our dosing strategy for this next study. And what I mean by that and why that's important is because since we have this data, we have the DIO data, we have our clinical data now we've refined our PK modeling from something that was a bit more simplistic from a one compartment model to something more sophisticated.

So I guess to answer your question more directly, I don't think we need to go as high as 3,200 milligrams. I think we could from a safety perspective, I think that could be a safe dose. But from an efficacy perspective and just from a practical perspective, I think what we're looking at is something more like a half a log increase, at least to start, which we think will be effective, and something closer to the 75 mg/kg dose that we see in the DIO model. And then evaluating doses higher than that and potentially evaluating less frequent dosing with higher doses as well.

<<Punit Dhillon, President and Chief Executive Officer>>

One thing that we can expand on here is that in the deck that we just put on the website, there was a recent DIO experiment that we did where we looked at these differences, and this is partially why we can elucidate a lot more confidence around dosing is the – we looked at the 24 mg dose and a 75 mg dose in mono, and then we looked at that in combo as well. And 24 mg dose right now is more or less equivalent to what we believe is the suboptimal dose in the clinic, the 200 mg dose, the CBeyond clinical trial dose.

Whereas the 75 mg dose is where we think is the kind of the sweet spot. And you can actually tell the difference in this experiment where the 24 mg dose actually had a non-significant. It did have separation, but it was non-significant. Whereas the 75 mg truly showed significance. Same thing correlated to the combo, 24 mg with sema was non-significant, but 75 mg was significant, like almost about 40% weight loss in DIO mice. So if you take that to what Tu just kind of explained, our sweet spot is more or like in the 600 mg to 1000 mg in the clinical setting.

<<Michael DiFiore, Analyst, Evercore ISI>>

Got it. And you mentioned you're doing a lot of formulation work to kind of just optimize hyper concentration of this drug. I mean, maybe talk about that for minute or two?

<<Tu Diep, Chief Operating Officer>>

Yeah. I mean, obviously, the doses we just laid out are going to be higher volume injection. So we are – we have looked at multiple technologies, both formulation technologies and delivery technologies as to how we're going to deliver these – this drug subcutaneously because ultimately we don't think this is something that you're going to want to do an IV infusion with or you're going to want patients to come in to do sort of a long infusion. You want to be able to have these patients do these at home. And so we're quite confident. We have technologies available to us and formulation activity that we've already put in place where we can one, both increase the formulation from our current concentration 100 mg/mL to also deliver much higher volumes either through a device technology or through other formulation technologies.

<<Michael DiFiore, Analyst, Evercore ISI>>

Got it. I recognize it's still very early in the game, but at this stage, I mean, might nimacimab be better suited for combination therapy versus monotherapy or still TBD?

<<Punit Dhillon, President and Chief Executive Officer>>

Yeah. So we haven't closed the door on monotherapy despite the top line result. We believe obviously that monotherapy has a role to play if we can get to that 5% to 8% weight loss, which is where our target was, I think, where we had limited PK information going into that study. Now we have a more robust understanding. So monotherapy, if it hits those types of targets, then there's a separate market that's maintenance, that's people that are looking for lower weight loss, that are looking for a tolerable treatment that is still open. And I don't think we're ready to close the door on that. But the near term, there's certainly an opportunity in the combo for the same reasons as well, but also potentially as a competitive alternative in the first line setting in weight loss. So we think both are still open. We're prioritizing the combo and obviously we're looking forward to seeing what the 52-week data reveals.

<<Michael DiFiore, Analyst, Evercore ISI>>

Yeah. I was just about to, that kind of segues nicely into my next question. Just when you think about the 26-week extension data coming up, that's due with Q1, correct?

<<Punit Dhillon, President and Chief Executive Officer>>

Correct.

<<Michael DiFiore, Analyst, Evercore ISI>>

Okay. So just based on the design of that study, some patients enrolled in the extension will have a gap in treatment.

<<Punit Dhillon, President and Chief Executive Officer>>

Yeah.

<<Michael DiFiore, Analyst, Evercore ISI>>

I think patients on monotherapy could theoretically have as long as a 13-week gap.

<<Punit Dhillon, President and Chief Executive Officer>>

Correct.

<<Michael DiFiore, Analyst, Evercore ISI>>

And whereas patients on the combo therapy would have a much shorter gap.

<<Punit Dhillon, President and Chief Executive Officer>>

Yeah.

<<Michael DiFiore, Analyst, Evercore ISI>>

So how might this gap affect the interpretability of the results when they come later on?

<<Tu Diep, Chief Operating Officer>>

Yeah. I think you make a great point. Definitely a bit of a challenge and definitely going to be a bit of a nuanced look at that data in particular with the monotherapy patients that were on nimacimab and then had a long break and then continued on nimacimab. I think in that case we'll probably have to be a bit more nuanced, maybe look at patients more individualistically versus as a group because pooling those patients together as a group might be a challenge.

I think more interestingly, there's going to be a group in the placebo population that was not on drug and then went on to a higher dose than the original nimacimab group, but they went on to the 300 mg dose group. That group will be able to look at more as a group rather than individual. So I think that's how we're probably going to have to look at the monotherapy group. The combo group I think is going to be more interesting because again these patients had very little time off, basically went transitioned straight to continuing on therapy. And I think seeing that weight loss that we saw at the first 26 weeks was very exciting and very competitive to other combination therapies. And so if we can see with the additional 26-week data something in the range of a 20% weight loss, I think that's going to be very exciting given again that we were at a suboptimal dose and we didn't drive any additional AEs.

<<Michael DiFiore, Analyst, Evercore ISI>>

Got it. Last question, because we're coming up on time. In terms of your longer-term development goals like you had initially maybe planned for a Phase 2b CBeyond too, is that still going to start the first half of next year and when might that trial wrap up?

<<Punit Dhillon, President and Chief Executive Officer>>

Yeah. So right now our first priority is the execution on the extension study and the data from that, from the monotherapy understanding as well as the combo understanding is going to only hopefully validate and inform what that final Phase 2b looks like. Our goal is still intact in terms of the original timelines for Phase 2b, but we are kind of making a sequence decision on that based on the extension data.

<<Michael DiFiore, Analyst, Evercore ISI>>

Got it.

<<Punit Dhillon, President and Chief Executive Officer>>

Yeah.

<<Michael DiFiore, Analyst, Evercore ISI>>

Well, unfortunately we're out of time, but gentlemen, this has been very helpful. Thank you so much for spending time with us.

<<Punit Dhillon, President and Chief Executive Officer>>

Thank you.

<<Tu Diep, Chief Operating Officer>>

Thanks a lot Michael.

<<Michael DiFiore, Analyst, Evercore ISI>>

Yeah. Okay.