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CORPORATE SPEAKERS:

Bernie Hertel
Skye Bioscience, Inc.; Head of Investor Relations
Punit Dhillon
Skye Bioscience, Inc.; President, Chief Executive Officer
Puneet Arora
Skye Bioscience, Inc.; Chief Medical Officer
Tu Diep
Skye Bioscience, Inc.; Chief Operating Officer
Chris Twitty
Skye Bioscience, Inc.; Chief Scientific Officer
Louis Aronne
American Board of Obesity Medicine; Former President of the Obesity Society, Former Chairman
Sean Wharton
University of Toronto; Wharton Medical Clinic

PARTICIPANTS:

Jay Olson
Oppenheimer; Analyst
Michael Fiore
Evercore ISI; Analyst
Kristen Kluska
Cantor Fitzgerald; Analyst
Andy Hsieh
William Blair; Analyst
Albert Lowe
Craig-Hallum; Analyst
Jonathan Wolleben
Citizens; Analyst
Ananda Ghosh
H.C. Wainwright & Co.; Analyst

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PRESENTATION:

Operator^ Ladies and gentlemen, thank you for standing by. At this time I would like to welcome everyone to the Skye Bioscience's Conference Call to discuss Phase 2a Topline Clinical Trial Results.

I would now like to turn the conference over to Bernie Hertel, Head of Investor Relations. Please go ahead.

Bernie Hertel^ Good morning. 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 the company's findings with the Securities and Exchange Commission concerning these and other matters.

I will now pass the call to Skye's CEO, Punit Dhillon.

Punit Dhillon^ Good morning, everyone, and thank you for joining us today. We appreciate you taking the time this morning as we review the top-line results from our Phase 2a CBeyond clinical trial of nimacimab in obesity.

Before we begin, I want to acknowledge everyone on the panel today. I'm joined by several members of the Skye leadership team, Dr. Puneet Arora, our Chief Medical Officer; Tu Diep, our Chief Operating Officer; and Dr. Chris Twitty, our Chief Scientific Officer.

I'm also very pleased to welcome two of our key external experts who are with us on the call, Dr. Lou Aronne, former President of the Obesity Society and former Chairman of the American Board of Obesity Medicine, who also served as Principal Investigator for the CBeyond study.

And Dr. Sean Wharton from the Wharton Medical Clinic and University of Toronto, and he's a leading clinician and thought leader in obesity medicine. We're grateful to both of them for joining us this morning to provide their clinical perspectives on the data and its broader context in obesity treatment.

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Skye Bioscience Conference Call: Transcript

Okay, so here's what we're going to cover today in the call. I'm going to begin with an overview of the top line results and what we've learned from this Phase 2a study. Dr. Arora, Dr. Twitty, and Mr. Diep will then walk through the efficacy results as well as information on the exposure response findings that were talked about in our press release today.

They're going to also talk about that in more detail as well as a safety profile. And we'll continue to emphasize that the safety profile remains a really important cornerstone of this program. I'm going to return at the end to summarize the key takeaways and outline our next steps.

And finally, we're going to open the line for questions and answers where both our management team and obesity KOLs will be available.

Okay, so let's begin with the key results. As stated in our press release this morning, the 200 milligram monotherapy arm did not meet the primary endpoint compared to placebo. In the modified intent to treat population, the least square mean change from baseline was negative 1.5% for nimacimab versus negative 0.3% for placebo.

And we acknowledge that outcome directly and transparently. However, we believe we understand the reason for this result. Our PK and exposure response analysis showed lower than expected drug exposure at the 200 milligram dose. In other words, the amount of drug achieved in circulation was lower than predicted from our Phase 1 model. And most participants did not reach the steady state levels.

Moreover, both our PK and PD and preclinical data inform us that nimacimab efficacy may be impacted by not only a less than ideal exposure, but also by a selection of a minimally effective dose at the 200 mg weekly dose.

It's important to emphasize that some of these insights are still preliminary and partly qualitative. So the full PK modeling and exposure response analysis which we're working on -- and we're also reviewing compliance and dosing -- this is going to take additional time and we'll continue to go over that over the next several weeks.

What we can say now based on the data that's available is that the directionality is consistent with lower than predicted drug exposures, which is driving the modest monotherapy effect. And the higher dosing is a logical next step really to test this hypothesis further.

There's going to be a few things that I want to cover to really set up the call before I turn it over to my colleagues. So I'm just going to walk through a couple of those things right now. Number one, is what we've learned about exposure response and dosing from the CBeyond study.

So we've observed a directional exposure response pattern for weight change values clustered more favorably in participants with higher drug exposure. And although these are preliminary results and are descriptive, the consistency of the trend gives us a clear hypothesis to test higher doses.

When we overlay these human exposures observed at 200 mg dose onto our preclinical DIO model, they align closely with the lower exposure ranges in mice, which produced relatively minimal weight loss.

Overlay these human exposures observed at 200 mg dose onto our preclinical DIO model, they align closely with the lower exposure ranges in mice, which produced relatively minimal weight loss. This translation gives us confidence that higher dosing and therefore higher exposure could yield increasing efficacy while remaining within the safety and tolerability limits.

The analyses we've conducted so far support this hypothesis and the additional work is underway to quantify the magnitude of underexposure, understand the variability across participants, as well as assess any potential relationship between the observed exposure and the compliance behavior in a patient basis.

Importantly, these are analyses that are now being performed using the final PK – the final PK dataset from the study, and they're going to help refine our dose selection model ahead of any potential future trial. So, in simple terms, we believe we were on the ascending portion of the exposure response curve and any potential future trials will be designed to reach that active part of the curve.

Okay, number two is moving to the kind of encouraging combination results. In the combination arm, we observed a clinically meaningful additional weight loss, approximately negative 14.3% at 26 weeks compared to negative 10.8% for semaglutide alone in the per protocol patient population. Importantly, no weight loss plateau was observed at week 26, indicating potential for additional weight loss, which we're evaluating further in the 26-week extension study.

The responder profile was also encouraging. Based on per protocol analysis, 100% of participants achieved at least 5% weight loss and two-thirds achieved at least 10%, and we believe that is a clinically interpretable signal that supports further combination development.

The question this data raises, and something we've discussed internally, is how can the same 200 mg dose show a modest activity alone, but stronger results in combination? And we believe the simplest answer at the moment, based on the data that we have, is rooted in the biology of these two distinct pathways.

So, mechanistically, the two pathways are complementary. Semaglutide acts through central and gastric mechanisms, while nimacimab modulates peripheral metabolic and lipid processes. Even at the suboptimal exposure, the peripheral CB1 inhibition appeared to be sufficient to add to the semaglutide effect.

And this combination result is both biologically and directionally consistent with what we've observed pre-clinically, where nimacimab has produced a dose-dependent and additive effect with incretins in our DIO models.

To be clear, the combination effect was nominally statistically significant on a descriptive basis, but given the small size of the exploratory cohort, we're treating it appropriately as hypothesis generating. And nonetheless, when we look at the data, the 3.5% incremental delta at 26 weeks is both clinically meaningful and consistent with what we would expect mechanistically.

The third point is safety. This is the foundation for dosing higher. So, at the tested exposures, nimacimab showed a favorable safety and tolerability profile. As a monotherapy, its adverse event profile was similar to placebo, and in combination, it did not increase the GI side effects relative to semaglutide alone.

There were no nimacimab-associated neuropsychiatric adverse events reported, and we've looked into a few cases of the vomiting reported in the combination arm. This doesn't appear to be a signal.

To put that into context, those data reflect a very small number of events. And when examining the overall GI adverse event profile there is no meaningful difference between the combination and the semaglutide alone arms. So the broader takeaway is that nimacimab did not increase GI burden at the 200 mg dose, and that remains one of its most important potential different differentiating features.

We believe this clean profile is meaningful because it's potentially differentiating nimacimab from prior CB1 approaches, which were limited by the central nervous system effects. And we spent time discussing this ahead of today's call. And it'll be fair by some to note that the 200 mg dose was likely underexposed. And that's precisely why any potential future trial will test higher doses to fully characterize that exposure-safety relationship.

However, what we'll cover today is that even in participants who achieved a higher end of the observed exposures in the study, we did not see any neuropsychiatric adverse events. And there's been a completely clean 200 mg starting point, which is, we believe, a strong foundation to build from.

And it really enables us to escalate the dosing safely and systematically in any potential future trial. So overall, we want to reiterate that this is a big step for the class. And we believe that nimacimab has moved the field forward on safety.

Finally, I just want to touch on the bigger picture for a second. When you take a step back, and what we take away from this data set, it provides some valuable insights. It demonstrated clinical activity and complementarity in combination. It confirmed favorable safety and tolerability at the 200 mg dose. And it provided an understanding of our PK model and exposure response direction that's actionable to dose higher and confirmed that the dose exposure response for any future clinical study, we can model that in the future,

In terms of a broader comment about the obesity landscape, where we recognize that GLP-1s dominate, but have potential challenges with GI burden, lean mass loss and rebound, we believe nimacimab's profile -- peripherally acting, showing orthogonal biology, as well as the clean safety profile, based on the data to date--really positions nimacimab with a potentially competitive and complementary product profile.

So with that, I'm going to turn it over to Dr. Arora, our Chief Medical Officer, to begin the presentation of the clinical data in more detail.

Puneet Arora^ Thank you, Punit. I'm going to start today with a quick overview of CBeyond, Skye's Phase 2a study to assess the safety, PK, and efficacy of nimacimab, both alone and in combination with semaglutide.

The primary endpoint of the study is weight loss. CBeyond is a placebo-controlled, randomized, blinded study that is being conducted across 16 sites in the United States. The study has two parts. In the first, we compare nimacimab with a matched placebo. The second part compares nimacimab in combination with semaglutide with a placebo in combination with semaglutide.

Participants were randomized 2:2:1:1 to these four study cohorts and treated for 26 weeks to the primary endpoint. This was followed by a 13-week follow-up period of therapy after the last dose of the study drug.

We subsequently added a treatment extension to the study. Participants were offered the opportunity to continue the study drug for an additional 26 weeks. In the monotherapy arm of the extension, all participants received a 300 milligram open-label nimacimab every week with the purpose of further refining our PK and safety models. The combination participants remain on the blinded therapy as assigned during the initial treatment period.

I will now hand it over to Tu to briefly discuss the rationale for dosing in CBeyond.

Tu Diep^ Thanks, Puneet. I wanted to take this opportunity to provide a historical perspective on how and why we chose the 200 milligram once-weekly dose for the CBeyond study.

As a reminder, when we acquired nimacimab from Bird Rock Bio, we were fortunate enough to have data from a completed phase one SAD/MAD study in healthy volunteers and NAFLD participants, as well as a phase one biodistribution study that compared IV versus subcutaneous dosing.

From that, we developed a pharmacokinetic model from these studies that established our basis for two key things. First, that nimacimab as a peripherally restricted monoclonal antibody should not enter the brain in significant amounts, and as such, should be safe and not result in the serious neuropsychiatric adverse events that have plagued this class of drugs for decades.

Second, a 200 milligram once-weekly dose should significantly accumulate enough drug in the periphery over time and reach a steady state between 14 to 16 weeks such that we would expect weight loss at this dose.

Importantly, I want to point out the amount of drug that we would have expected at 16 weeks of dosing that you see here in the slide. That is 83 micrograms per ml at the Ctrough, which is highlighted here.

The significance of this value is important as we walk through the CBeyond data, especially when Dr. Chris Twitty highlights what we learned from the PK, the actual PK exposures from the participants in CBeyond.

However, with these critical learnings combined with the additional data from the CBeyond study to further refine our PK model, we certainly are more confident in the dose ranging strategy for future potential studies with nimacimab.

I'll hand it back over to Punit to go over the remaining top-line data review.

Puneet Arora^ Thanks, Tu. Moving on to top-line data from the primary analysis of the study, this is a look at the key data sets. The mITT, or Modified Intention to Treatment subset, has all participants who were randomized and received any study drug.

Study participants are classified by the treatment they actually received. This is significant because seven participants early in the study were randomized to monotherapy based on an erroneous instruction, which led them to be treated with semaglutide as well, similar to combination participants. These seven participants were then allowed to continue semaglutide throughout the study and are therefore classified as combination-armed participants.

The per-protocol subset includes all participants that adhere to the protocol. They completed 26 weeks of treatment with adequate compliance and did not have a major deviation that affected study results.

A treatment policy strategy was used to handle data. All observations were used in the analysis without adjustment. This is an overview of the data we will be reviewing today.

So, here, yes, we can go back to the last slide a moment. Yes, so no explicit imputation for missing observations was performed.

Let's move on. So this is an overview of the data we will be reviewing today. The 26 week primary efficacy data for both monotherapy and combination therapy, safety and tolerability data, top line data from the body composition DEXA scans will be presented. The biomarker data is not yet available for review.

136 participants were randomized to the four study cohorts. 37 participants were viewed from the primary study treatment prior to 26 weeks. This was largely balanced across cohorts. The mean age was 45.6 years. The mean BMI was 36.8. 85% of the participants were female.

The nimacimab cohort had a higher mean weight at baseline, 107.3 compared to 101.7 kilograms for placebo. The nimacimab with semaglutide cohort also had a higher mean weight of 101.3 kilograms compared to semaglutide with placebo control arm at 93.3 kilograms.

Of the 37 withdrawals. The next slide.

Punit Dhillon^ Yep. Having a problem here with. The technicals here. Does that work? Yes.

Puneet Arora^ Yes, of the 37 withdrawals, only five were because of an adverse event. 20 withdrawal by participant included those that started another weight loss medication, withdrew because of life events like moves and jobs, or withdrew because of lack of weight loss.

The primary endpoint of weight loss with nimacimab versus placebo was not met. The placebo adjusted weight loss at 26 weeks was 1.26%. The combination treatment had a placebo subtracted weight loss of 12.94% in the mITT analysis, which was meaningfully greater than the semaglutide and placebo mean of nine point 9.99%. The P value for this comparison was 0.03.

In the protocol subset combination cohort at a 3.51% additional weight loss over the semaglutide only treatment cohort, with a P value of 0.014. The placebo subtracted weight loss at 26 weeks for the combination treatment was 14.29% at 26 weeks. As a reference in the step one trial for semaglutide treatment, the placebo adjusted weight loss at 68 weeks was 12.4%.

On the next slide here, we see the weight loss data plotted by time in the study for monotherapy treatment, showing the trajectory of change in weight. On the next slide, the same data is plotted with adjustment for placebo, which is now represented by the flat black line with zero change, allowing us to see the trajectory of weight change that is attributable to nimacimab clearly.

Here we see a waterfall plot with individual participants represented in the nimacimab and placebo arms. In the mITT analysis, 13% of participants on the nimacimab treatment alone achieved at least 5% weight loss and 4% achieved 10% or greater weight loss compared to 7% and 2% for placebo.

Now moving on to the combination treatment, this plot shows the trajectory of weight loss for nimacimab and semaglutide combination therapy in red compared with semaglutide and placebo in blue and the placebo treatment only in black.

The following plot is showing the placebo-adjusted weight loss for the combination therapy and the semaglutide treatment with placebo. Placebo is represented by the black line above with no change now shown.

In the next plot, we see the combination cohorts now represented with the weight adjusted for the control arm which is semaglutide treatment with placebo. This now helps us to see the time-based trajectory of change in weight that is attributable to the addition of nimacimab. These plots show a trajectory of continuing weight loss with the combination treatment without any plateau in weight during this 26-week treatment period.

Now, as before, we are seeing a waterfall plot representing individual participants receiving combination therapy and the semaglutide control. In the per-protocol population, 100% of combination participants lost at least 5% of weight compared with 85% for semaglutide alone and 67% lost at least 10% compared to 50% for semaglutide alone.

Now we'll move on to the body composition DEXA scans. The top-line data shows that the combination arm lost 76% of the total weight loss as fat loss compared to 72% with semaglutide. For lean mass, the loss was 24% compared to 28% for the semaglutide alone treatment.

This represents a healthier weight loss, more predominantly fat mass, and this is reflected in the change that we see in the lean-to-fat-mass ratio at 26 weeks. The ratio increased by 0.13 for semaglutide alone and 0.26 for the combination treatment, with the P-value for this difference being 0.01.

In summary, following 26 weeks of treatment, the primary endpoint for CBeyond, weight loss with nimacimab compared to placebo, was not met. However, the combination of nimacimab with semaglutide showed a meaningful difference in weight loss as compared to the treatment with semaglutide alone.

The placebo-adjusted weight loss for the combination treatment was higher at 26 weeks than that seen with semaglutide alone at 68 weeks in the STEP-1 trial. An improvement in the lean-mass-to-fat ratio was also seen with the combination treatment compared to semaglutide alone.

Chris is now going to talk about the exposure level seen for nimacimab in this study.

Chris Twitty^ Thanks, Puneet. We are clearly focused on understanding the relationship between nimacimab exposure and efficacy. I'd briefly note that the PK data we are able to share with you today is preliminary data and not the final PK dataset, which will be delivered subsequently and analyzed over the next few weeks.

Since the week 26-week measurements were not readily available, we initially focused on evaluating the relationship between weight loss and exposure by using week 16 Ctrough measurements shown here.

While this analysis has less than half of the data points that will be available with our final analysis, we are still seeing an interesting association between weight loss and serum concentrations of nimacimab.

With an R-squared value of 0.038, we are cautious to not over-interpret this data, but we're encouraged by the trend towards increased efficacy with increased exposure. This data, coupled with multiple dose titration for clinical studies, suggests that higher dosing will likely drive more meaningful efficacy.

Both Puneet and Tu will provide their perspective on higher clinical dosing strategies. A separate observation with this dataset relates to the relatively wide range of Ctrough values observed at this week 16 time point.

Specifically, when we overlay the percentiles of predicted Ctrough levels based on our previously modeled PK curves derived from our Phase 1 clinical data that Tu previously discussed, we see a few participants with serum nimacimab concentrations in the highest percentile as well as a few at the median level.

Unfortunately, many of the participants had nimacimab concentrations at or even below the lowest predicted levels. While a less than ideal exposure for many participants can be observed in this figure, stepping back to examine exposure from the beginning of the trial reveals this issue more clearly.

In this next figure, we highlight PK curves with observed Ctrough values from baseline through week 16 for a few representative participants. The PK curve seen on the left is an example of a participant with an optimal exposure of nimacimab.

In contrast, the PK curves in the middle and the right are representative of suboptimal exposures. I would note that monotherapy and combination participants both had these types of curves, although our preliminary analysis suggests that the combination group had slightly better overall exposure than the monotherapy group.

Our final PK analysis will provide a more detailed examination of this observation. I would note that any potential difference in nimacimab exposure between monotherapy and combination groups is distinct from the suboptimal nimacimab exposure that is evident in the majority of our participants.

Additionally, our initial anti-drug antibody analysis suggests that ADAs are not driving nimacimab clearance. A final PK analysis, which will include evaluation of participants' clinical diaries, will help us better understand potential compliance issues that are likely to be key drivers in these suboptimal exposures.

Moving beyond the observed suboptimal exposure in our CBeyond trial, I'd like to take a moment to further address nimacimab's potential for increased efficacy. While we cannot show the Emax for nimacimab today, we plan to develop this using the full PK dataset in the near future.

Separately, it is relevant to consider how learnings from our preclinical data may translate to our current clinical observations, particularly as they relate to dose response. Skye has a robust preclinical diet-induced obesity model, which has been used to run multiple independent dose response studies.

While there are potentially small differences in biology and behavior of a DIO model, CBeyond biology is highly conserved and a reasonable translation for the clinic. The tables we're looking at, the table we're looking at this slide, summarize various independent dose titration studies in our DIO model, which cover multiple logs of nimacimab dosing.

Additionally, PK analysis in this model enables us to understand the relative exposure as measured by AUC analysis for each dose, as noted in the second column from the left. The table also describes an extensive range of weight loss associated with this wide range of dosing.

Using preliminary AUC modeling to calculate the average week 26 clinical exposure allows us to translate the CBeyond dosing to a corresponding preclinical dose at the end of the dose titration curve. This is at the low end of the dose titration curve. This is indicated to the right of the table with the arrow.

Collectively, CBeyond's position in this relatively ineffective preclinical dose range suggests that with higher clinical dosing strategies, there's an opportunity to significantly increase the efficacy of nimacimab.

I will now hand the presentation over to Tu who will discuss how nimacimab can be safely dosed higher.

Tu Diep^ Thanks, Chris. This is a great overview of what we've learned from our DIO mouse models, and ultimately, how we can translate it to our human studies.

While we didn't have the luxury of these data prior to starting CBeyond, we can certainly use them to inform our next steps for dose ranging in future clinical trials. As Chris noted, the 200 milligram once-weekly dose in humans is predicted to be between the 7.5 milligram per kilogram and 24 milligram per kilogram dose in mice.

While using the same approaches to translating these doses, we could assume that the 75 milligram per kilogram and 240 milligram per kilogram doses would approximately be 600 milligram once-weekly and 1,000 milligram once-weekly of nimacimab in humans.

We believe these doses could potentially provide a similar stepwise increase in weight loss observed in the DIO mouse studies, while still maintaining a substantial safety margin well below the NOAEL dose we observed in our non-human primate toxicology studies.

As I noted earlier, we expected the 200 milligram dose to have extremely low concentrations in the brain. As you will hear from Dr. Arora shortly, this proved to be true, as we saw little signs

of neuropsychiatric issues in participants treated with nimacimab. Even more, when we looked at participants who had high exposures to nimacimab, we did not see any correlation with increases in safety concerns, including gastrointestinal and psychiatric adverse events.

I'll turn it back to Puneet to discuss the safety and tolerability data.

Puneet Arora^ Thank you, Tu. Safety and tolerability of nimacimab is a key endpoint in CBeyond. Overall in the study, 81% of participants reported a treatment emergent adverse event. These were largely balanced across the study arms. 82.5% of participants on nimacimab, 75% of placebo, 78.6% on the combination, and 91.7% on semaglutide reported adverse events. 95% of these participants who reported a TEAE reported them as mild or moderate.

Here we now see the reported TEAEs by system, organ, and class. The most frequent TEAEs are general disorders, including injection site reactions, followed by GI disorders, infections, and infestations. No study arm shows a greater incidence of GI or nervous system disorders as compared to others.

When we look at TEAEs by preferred terms, nausea followed by dizziness and injection site erythema are the most frequently reported events. Dizziness was reported by placebo arm participants more than by those treated with nimacimab and by semaglutide-only participants as compared to those on combination treatment. Rates of participants reporting nausea and injection site erythema were not different across the arms.

Taking a closer look at GI-related events, the overall incidence of participants reporting TEAEs was not meaningfully different between placebo and nimacimab and between the combination treatment and semaglutide-alone treatment.

Given the small size of these cohorts, some differences in reporting individual events were noted. Placebo participants reported diarrhea more frequently than nimacimab. In turn, nimacimab participants reported more constipation.

Combination treatment participants reported more vomiting, but less constipation than semaglutide only. Notably, of the 40 participants in the nimacimab arm, only one incidence of vomiting was reported.

We looked at whether GI-related events were seen more frequently in participants that had higher exposure levels of nimacimab, which you can see in this slide. No such association was seen in either the monotherapy or the combination therapy arms.

Finally, let's take a look at psychiatric disorders. Only four patients in the study reported five events that were classified as psychiatric-related disorders. There were three reports of insomnia, one of anxiety, one of depression that were recorded. The patient with depression was reported from a low PHQ-9 score on a single visit and did not report any symptoms. Only one of these cases, particularly of one incidence of insomnia, was in a nimacimab-treated study arm.

In summary, nimacimab at the tested dose of 200 milligrams every week appeared to be tolerable and safe, both as a monotherapy and in combination with semaglutide. GI-related events were not significantly different with combination treatment compared to semaglutide and as monotherapy compared to placebo.

Neuropsychiatric events of significance were not reported with nimacimab treatment.

Thank you. Over to you, Punit.

Punit Dhillon^ Thank you, Dr. Arora. Okay, so let me close by summarizing what this data tells us and how it positions Skye moving forward.

First of all, the key learning from this data is that at the 200 mg weekly dose, we confirmed that drug exposure was lower than expected based on our preliminary pharmacokinetic data, and we believe that was why the efficacy was limited. Importantly, this data tells us how to potentially improve dose higher, reach therapeutic exposures, and confirm the exposure-response relationship in a future study.

We also recognize that while the 200 mg dose result produced a clean safety profile, this is at an underexposed dose. So that's kind of, for us, the right problem to have. It gives us room to move forward safely as Tu articulated, and in the context of dose optimization, we see the current safety findings as a strong starting point and supporting our regulatory strategy rather than any limitation.

The combination arm, meanwhile, delivered what we hope to see, a clinically meaningful magnitude of added weight loss versus semaglutide alone and an improvement in body composition with no additional safety burden.

So when you put this data in context of the broader obesity landscape, there are three points that I'd like to highlight that matter strategically in today's overall obesity management medicine environment.

First, this is clearly an orthogonal add-on without the extra GI burden. In a market that's dominated by GLP-1s, where we believe GI tolerability and discontinuation are real constraints for weight loss and management, the combination of nimacimab and semaglutide delivered a clinically meaningful incremental benefit without adding any GI side effects and with no neuropsychiatric events at the tested exposures.

That supports nimacimab as a potentially clean orthogonal enhancer, not a competing incretin, and this is differentiated from tirzepatide as a combination of GLP-1/GIP and clearly differentiated from semaglutide alone, as Dr. Arora pointed to the STEP-1 data.

Second, body composition matters. Our DEXA data shows a favorable lean-to-fat-mass ratio improvement in the combination arm versus semaglutide alone at 26 weeks, and this is consistent with a healthier pattern of weight reduction. As the field increasingly focuses on lean mass preservation, we believe this could be a differentiating signal.

And third, this is an actionable dose insight and it's giving us a clear path forward. The monotherapy data, though unexpected, yields powerful insight into our clinical development plan for nimacimab, for which we already considered the need for a dose ranging study.

So while we did not meet the primary endpoint, what this data lays out is a clear, minimally effective dose for nimacimab, and it also provides guidance on how we can -- how we can and how we should go with our dose to achieve a more effective dose.

So, our path forward and what comes next. I just want to give you a kind of overview of how we move forward from here. The ongoing extension study is already evaluating a 300 mg dose, which should give us an additional PK dose exposure data point, as well as an efficacy data point in the first quarter of 2026.

We are currently completing additional PK analysis to determine the appropriate next doses for evaluation and we're evaluating the most efficient path to understand the dose and exposure response with more data.

One additional consideration, which we've been already alluding to in our development path and our development plan, is exploring a dose ranging combination-focused trial, pending additional capital, and our toxicology margins and clean safety profile observed at 200 mg give us the flexibility to move up safely and systematically.

The upper end of dosing, as just talked about today, will ultimately be guided by our PK modeling, the CMC feasibility and the commercial kind of design parameters. But those analyses are ongoing and we feel confident about that.

We believe our safety margins give us the flexibility to explore the higher doses, including the monthly dosing option, which is going to be enabled by our current drug supply. And just as a reminder, we're continuing to do parallel R&D activity to evaluate a higher concentration formulation.

A few additional points I want to touch on regarding milestones. So, the 52-week data point from the combination arm will be available in Q1 2026. This is going to help us characterize the overall durability of the effect, as well as inform any potential Phase 2 design. And we plan to have a deeper data cut based on the 26-week primary endpoint. Those results are going to be presented as a late-breaking oral presentation at ObesityWeek.

Our cash runway remains unchanged into Q1 2027. So, with this projection, it excludes the cost of any additional Phase 2 clinical study. But what that means is we have the resources to better understand our dose and exposure response, as well as plan for the next clinical study.

And with that, I'd like to thank the team for their tremendous effort to crunch the data in the time that we had and all of you for your engagement and thoughtful feedback, as well as continuing to build on these results.

At this point, operator we'll open the line up for any questions.

QUESTION & ANSWER:

Operator^ Thank you. We will begin the question and answer session. To prevent feedback disturbance, please mute your webcast audio when dialing in to ask a question. (Operator Instructions). Your first question comes from the line of Jay Olson with Oppenheimer. Please go ahead.

Jay Olson^ Oh, hey. Thank you for providing this comprehensive update. We have a few questions. In the context of the favorable safety data with no neuropsychiatric signals, can you talk about the optimal dose range of nimacimab that you're planning to test in the monotherapy setting, and the corresponding therapeutic profile? Especially with regards to maintaining clean neuropsychiatric safety and also the degree of weight loss that you're planning to achieve in the monotherapy setting?

And then we have some follow-up questions, if we could.

Punit Dhillon^ Yeah, Jay, thanks for that question. Clearly, this is a very important data point that you're pointing to. We believe this is, from the clinical trial perspective, this is the first study to really help de-risk CB1 safety in the clinic. And that's been a major historical overhang. So, we've, I think, had a big kind of contribution there from moving that whole field forward from that perspective.

In terms of doses that we're considering, Tu's talked about that in his remarks. So Tu, do you want to elaborate on that again?

Tu Diep^ Sure. Hey Jay, thanks for the question. You know, as I highlighted earlier, we're really taking all the learnings that we have, both from this clinical trial as well as the DIO studies. And as I pointed out from the previous slides, you know, we think that in terms of an exposure perspective, we're probably looking at, at least a half a log higher dose than 200 milligram dose. So that's probably a 600 milligram once-weekly dose and we could go as high as 1,000 milligrams as well.

From a safety margin perspective, we've looked at that. We've looked at our non-human primate studies where the NOAEL dose was about 75 milligrams per kilogram. So from an allometric

scaling perspective and exposure perspective, when we've modeled this, we are actually still well below that exposure. So we're still quite comfortable with dosing higher, and still quite comfortable that even at those, you know, I guess relatively significantly higher doses, we're still going to stay within the safety margins where we wouldn't expect any neuropsychiatric adverse events.

Jay Olson^ Okay, understood. And then, can you comment on the clinical meaningfulness of the semaglutide plus nimacimab weight loss you observed? And would you expect those synergistic effects to be even greater with higher doses of nimacimab? And then we have one more question, if we could, please.

Punit Dhillon^ Yeah, so, Dr. Arora, do you want to talk about a little bit of the orthogonal synergy that we're seeing in the combo results?

Puneet Arora^ So Jay, thank you for that question. I do want to say that I'm personally really pleased to see the additional effect that we are seeing, which I think is very significant, especially in light of the trajectory of weight loss that we are seeing along with it.

I think the key thing here is that these mechanisms are complementary. The GLP-1-incretin mechanism for weight loss seems to predominantly work through its central action, and a lot of what you see with the incretins is a reduction in appetite, whereas what you're seeing with the CV1 pathway and with nimacimab is a lot of peripheral action, which works on counter-regulatory mechanisms and changing metabolism in key organs that are related to metabolism in the periphery.

And these two are essentially coming together here, in a way where we are seeing a dose that may be suboptimal as a monotherapy for nimacimab, still potentiating the effect of semaglutide, in what appears to be a fairly significant manner in adding weight loss, and so that's really what we are seeing here. So I think the complementary nature of the mechanisms is really important, and I'm sure that Drs. Wharton and Aronne will have something to say about that too as we go along.

Jay Olson^ Yeah, I mean, that's a good segue. I think Dr. Aronne had a chance to talk about that with us. Maybe you can share your perspective, Dr. Aronne.

Louis Aronne^ Sure. One of the key things I want to point out is that if you look at these results -- with tirzepatide, when you look at the effect of GIP infusion in humans, it causes weight gain; but when you add it to GLP-1, you get much greater weight loss. You get 50%, at least 50% more weight loss. So there are unusual things that are going on in the background that we do not yet understand. So the result that we see today is entirely plausible to me, and it's very exciting.

The other thing that's exciting is when we look at the trajectory of the weight loss, it seems to be accelerating towards the end. Does that mean that this is just a more gradual effect and it's just beginning to pick up steam?

When you look at the magnitude, adding these together, I could imagine a result that is in the ballpark of tirzepatide over 68/72 weeks. I think that is entirely plausible based on what we're seeing right now. Thanks, Dr. Aronne.

Jay Olson^ Great, thank you.

Punit Dhillon^ Great, and also very quickly, what we're also maybe seeing is that if you look at some of those waterfall plots, there's always people who do not respond to these medications. Here we're seeing that we may be able to grab those people who didn't respond and push them into a response rate.

You see there's always some that are gaining a little bit of weight on the monotherapy, but then when you add in, you may start to see them losing weight.

We may even start to see difference in the mechanism in terms of maintenance, the ability to maintain these medications--someone stops medication for a week or two weeks, goes on vacation or whatever the case is. There seems to be some ability to maintain the weight loss during that timeframe before they restart the actual medication. So this combination therapy, which we don't exactly know how they all work, we don't know how GLP-1 and glucagon, GLP-1 and GIP work, and why they're making this synergistic action--but it's happening and it certainly is a positive thing. You can see people wanting to actually potentially have this combination effect to get greater benefit.

Operator^ Your next question comes from the line of Michael Fiore with Evercore ISI. Please go ahead.

Michael Fiore^ Hi, guys. Thanks so much for such a comprehensive overview and for taking my question. Just two for me. I was wondering, could the nimacimab construct just be too big, such that could it be a situation where perivascular sinks trap the antibody and limit distribution to key tissues? And if that were true, would increasing the dose yield any more significant results? And I have a follow-up.

Punit Dhillon^ Yeah, so it's a great question. I think, Chris, you should take that one. And I think, Chris, if you don't mind, also maybe elaborating here that this is truly a peripheral-driven response that we've seen now in terms of the efficacy. So I think it's worth mentioning there in terms of this debate that's constantly been had about the central engagement being a factor for weight loss. Here we're seeing that activity. But I think the compartmental question that Michael is asking is the first point.

Chris Twitty^ Yeah, hey Mike, thanks for that question. Yeah, it's certainly an interesting question, one that we've been thinking about for some time now. When we reflect back to the DIO model that we have, obviously, more granularity insight into, we do believe that the antibody is able to get into tissues and we can actually do biodistribution and see it readily

interacting with some of those key tissues and compartments that we think help drive this peripheral response, notably adipose tissue, GI tract, muscle, etcetera. Also, noting that it does stay out of the brain.

Now, translating that to the human can represent some challenges and have potentially different biology. And so there may be potential relative difference between the ability to access those compartments in a human and a mouse. But we believe with the correct dosing, we believe that we can get there. But I would acknowledge that it may be a bit different in terms of the applicability, the relative translation of the mouse to human dose. There may be a coefficient that requires potentially doubling or more than the preclinical dose.

So a fair question, but ultimately we believe that we can get there and demonstrate more efficacy with a higher dose. And we believe that the CBeyond clinical dose is really at the earliest point of that efficacy curve with the current 200 milligram flat dosing. But a fair question and one that we'll answer succinctly in upcoming trials.

Michael Fiore^ Thank you, Chris. And just a follow-up question to that. I remember seeing in one of your preclinical posters that the DIO mouse first received kind of an induction dose of nimacimab of 240 mg per kg for three days, but then switched to 75 milligram. Like the whole idea of an induction followed by a maintenance dosing, would that be kind of a possible route to go in humans?

Chris Twitty^ Yes, that's a great catch and something we're certainly looking at preclinically and considering clinically. And, you know, one of the keys, if you recall the slide before this, when we were looking at some of the individual PK profiles, one of the keys that we think may be relevant actually ties somewhat into Dr. Aronne's comment, is this antibody is different than a small molecule in many ways, but notably the time it takes to get to an equilibrium dose may be really important.

And so we're investigating strategies to try to compress that timeframe and allow for a more meaningful exposure in a shorter time period that can ultimately start making those productive metabolic changes and yield weight loss, as opposed to a bit more of the delayed kinetics we witnessed in this trial. So that idea of a load phase initially is certainly one approach and one that we're considering.

Michael Fiore^ Got it. And if I could just squeeze one last one in. Obviously, you guys are going to have the extension trial data in 1Q next year, but in terms of additional news flow that'll help get the stock moving again, will these different additional PK analyses and possibly Phase 2 trials, will that data be available next year, or is that something more of a 2027 type of event?

Punit Dhillon^ Yeah, so I'll take that one, Mike. We're obviously looking at things that we can do efficiently to understand this dose-exposure response with more data. There's a deeper dive that we still need to do ahead of the ObesityWeek presentation that we have, so we'll have more data to share there.

We have the ongoing clinical trial as you've alluded to. So we're evaluating opportunities that we have with the existing CBeyond study. But the additional data points that we have already planned for are intact, 52-week data on the combination and Q1, the 300 mg dose continues to inform our PK modeling, so those will be available shortly.

The other thing that we're looking at further is the durability of the response in the follow-up period. So there's that piece that we're going to have hopefully later this year as well.

Michael Fiore^ Thanks so much, Puneet.

Operator^ Your next question comes from the line of Kristen Kluska with Cantor Fitzgerald. Please go ahead.

Kristen Kluska^ Hi, good morning, everybody. Thanks for taking the question. On the exposure for the monotherapy arm, do you have any initial thoughts as to why the exposure levels were scattered? And then, do you think that potentially on the combination arm, these patients may have had better compliance, taking all their injections, since we're seeing weight loss, given the arm also had sema as well?

Punit Dhillon^ Yeah, thanks Kristen. That's a really important question. And well, I'll let Chris talk about it in the context of the initial modeling that he's built out based on 16 weeks of data.

Chris Twitty^ Yeah, thanks for that question, Kristen. It does appear that we have a certain skew that's evident in these Ctrough weight loss association curves here that we can readily see. Many of the patients in that, really low quartile, even beyond the fifth percentage, there's certainly patients that are just very low in terms of those concentrations. And the slide after that we were just looking at also clearly demonstrates this sort of PK curve that is frankly a bit concerning, whereby a majority of the patients, unfortunately, have that suboptimal type of PK profile.

And so when thinking about this, our initial thought was, could there be some type of clearance issue that might be driven through something like ADA, for example. And the anti-drug antibody analysis we've looked at, which is still preliminary (and won't be final until we release our final PK data sets), but the initial data sets suggest this is likely not to be a player, very minimal, very much in line with the Phase 1 data.

So outside of that, we're really focusing now in trying to understand better the simple compliance, which can be anything from patients missing some of those doses at home or potentially even mis-dosing one of the injections. And if that happens over a few weeks, you can start to see PK profiles similar to those on the right. So it is something that we certainly are appreciating, and we're considering different strategies to mitigate that type of compliance issue.

Dr. Aronne and Dr. Wharton have suggested some ideas, and our own internal team has thought about those as well, so we can address those in future trials. But it's a fair question, for sure.

Kristen Kluska^ Okay. Are there, like, patient diaries or anything that you can reference to kind of line up with some of these week-by-week data to see if there's something you can further gather from that?

Chris Twitty^ Absolutely. That'll be part of the analysis. So the diaries are being interrogated, and we're looking closely at matching diaries with some of the PK data. There's other approaches too that we can take purely with the concept that blood doesn't lie. We can do things where we can mitigate and extrapolate from the diary and look at the blood and sort of put that together to have a better understanding of compliance. But yes, diaries are part of the equation, for sure.

Kristen Kluska^ Okay. And then other than its -- (Crosstalk) Sorry, please go ahead.

Sean Wharton^ Sean Wharton here. Yeah, maybe I can comment on that, too. We're seeing this type of problem in many studies that we're having now. For some reason, the GLP-1, the weight management studies, exposures are not in line with what the doses that are actually given. Are people shooting the drug up into the air, or do we need to monitor them more closely in the clinic? Is something else happening? So it is a phenomenon that's not just a CB1 as the CBeyond trial, but we're seeing it more so. And the more patients you have in the trial, the better you can actually mitigate that, but I do see it as a bit of a challenge, and we don't have the answer, to be clear.

Kristen Kluska^ Okay. Thank you for that. And then just other than exposure levels, was there any other correlation you can make between the patients that responded the best to the therapy at the 26 levels? Thanks again.

Punit Dhillon^ I think that's what you're pointing to in terms of we're going to have to investigate this further in terms of compliance and adherence. That is a factor that we're looking into as well.

Tu Diep^ Kristen, we do have a planned biomarker analysis. That's still ongoing. That's going to still be some time. So hopefully something comes out of that, but I think that's also potentially what you're referring to as well. But at this point, no additional kind of biomarkers that seem to be pointing to any responders.

Operator^ Your next question comes from the line of Andy Hsieh with William Blair. Please go ahead.

Andy Hsieh^ Thanks for taking our question. So going back to some of the comments made by Chris, I'm curious for the design of nimacimab. Can you remind us the FC receptor binding activity as a potential explanation for some of the exposure that you are seeing?

Second part of the question is, on slide, I believe this is 23. Basically association weight loss and exposure. There's the IC90 value, which is basically slightly below 20 micrograms per mil. Just

trying to get your thinking in terms of how much higher than IC90 you need to derive additional weight loss there. So any sort of clarification on that front would be much appreciated.

And then lastly, I'm curious, you know, just to -- just when you juxtapose the STEP-1 study, it seems like in this trial, theCBeyond, Wegovy outperformed versus STEP-1 a little bit, maybe 1% or 2% at, you know, at week 24. But I'm curious if there's any sort of explanation for that. Thank you so much.

Punit Dhillon^ So Chris, you want to take the first two questions, and if you want me to move to the PK modeling slide on slide seven, I can do that as well. And then Dr. Aronne, maybe we can take the third question on the STEP-1 comparison.

Chris Twitty^ Sure. Thanks for the question, Andy. In terms of the antibody structure, the IgG4 comment, the FC region of the antibody being IgG4, you know, one of the things that we've looked at is the potential for you know, you have a 22 day -- 21, 22-day half-life. We've seen that very consistently now in multiple trials. When we looked at this, the performance of this antibody in the murine system, it certainly has a more truncated half-life, roughly two to three days. And we believe that the driver there is neonatal receptor recycling. So we're doing things to understand, such as crossing our human CB1 mice with the human neonatal receptor, to get something closer towards to the clinic in terms of the behavior of the antibody.

But ultimately, we do think that our nimacimab antibodies are quite stable and likely through FCRN recycling dynamics, that gives it its strong half-life. We don't believe class switching has any limitations that might be occurring without that. So we do have some small additions to prevent Fab switching with the antibody. Overall, I don't believe the dynamics relate to ADA or any FC concern--more than likely compliance issues, as Dr. Wharton was pointing to, we think might be the driver.

In terms of your follow-up question, you know, when looking at the relationship to IC90 here in this figure, we can see that there's a few of the participants have some observations that are very close to that IC90 threshold, and of course, some that are further away. You know, the actual level in terms of achieving relative to the IC90 is still up for debate.

When thinking about the previous question shared by Mike, you know, you really start to think about maybe serum nimacimab as being one important metric, but more than that, thinking about the compartmental concepts, getting nimacimab into adipose tissue or muscle, even into other organ tissue systems that can really help drive some of these peripheral modulators.

And so maybe what we need to be thinking more about not so much as it relates to the IC90, but how much, what kind of concentration is required to get into those compartments. And that may be more than a two or four or even six, eightfold. It may be, you know, something that's beyond that. And that's sort of one of the rationales we're thinking about as we look to a potential 600 milligram weekly dose that would be high enough to really clear that IC90 in a meaningful way

in the blood, but maybe give us something more in line with the concentration in the various compartments. So something we're actively looking at, Andy, and a great question.

Punit Dhillon^ So I forgot that we have both important authors on both the tirzepatide paper and the STEP-1 paper on the panel today. So maybe, Sean, you should take the question on the STEP-1 question that Andy asked.

Sean Wharton^ Yeah. So very quick answer to you, Andy. That was a good question. Every time we see another semaglutide trial at the week 16 or at whatever stage, it's at a different time, different timeframe. If the weight loss was a little bit less than what we have in STEP-1, a little bit more than what we have in STEP-1, it's all within the realm and within the zone. So we're not -- we're never looking for the exact type of timing. There's that type of result, because timing is all different and the patient profile is different, smaller number of patients, different space and time. So never a concern. Head-to-head is going to be the most important.

Andy Hsieh^ Do you mind if I squeeze one more question in?

Punit Dhillon^ Go for it. Thanks, Andy.

Andy Hsieh^ Sure. So for Slide 17, basically this is the waterfall plot. You do see some, you know, I would call it maybe super responders on a nimacimab arm, maybe two or three. I am curious, for those, you know, really deep responders, where would you find them in the exposure weight loss plot in Slide 23?

Punit Dhillon^ Yeah, I don't think we have that detail at the moment based on the preliminary data, but that is, you know, obviously a good observation. I don't know if you want to touch on the demographics relative to this, Dr. Arora, but to answer your question directly, we don't have, we don't have it broken down based on Slide 23 at the moment, to my knowledge. Chris, is that correct?

Chris Twitty^ Yeah. The preliminary data set that we had to build out the PK analysis we're showing today, had many, many patients that were not -- the data was not there for week 26 yet. So we're getting that shortly and we'll be updating the PK analysis to answer Andy's question directly. We do see a trend in the week 16 that you know potentially would answer that, but I don't want to speak out of school.

Andy Hsieh^ I see. Got it. Thank you so much.

Operator^ Your next question comes from the line of Albert Lowe with Craig-Hallum. Please go ahead.

Albert Lowe^ Hey guys, I was wondering, do you mention these potential for 600 to 1,000 once weekly and maybe connected to this potential compliance issues around administration? Can you mention, are these prefilled syringes that are being used here and maybe similarly for these

higher doses, whether there will be perhaps an injection burden here and maybe the status of this new formulation work?

Punit Dhillon^ Yeah, that's a great question. Tu do you want to walk through that and like what our CMC plan is for the next trial?

Tu Diep^ Yeah, sure. Thanks -- thanks for the question, Albert. Yeah, so to quickly answer your question, correct. These were what the CBeyond study was: the drug was formulated in prefilled syringes, concentrated at 100 milligrams per ml and filled to 1 ml.

So in order for us to get to the 200 milligram dose, patients were asked to inject two prefilled syringes. In the future, to get to the higher doses, yeah, we're certainly very aware of any potential injection burden, tolerability issues as it relates to injection. So, however, we're quite confident there's actually a lot of solutions out there for higher volume injections and higher volumes from subcutaneous infusions, whether it's from a formulation perspective or from a device delivery perspective. And there's lots of options out there that we have considered.

We've already been working this even prior to this data readout. So, you know, we're confident that there's going to be solutions for us to easily and tolerably deliver higher volume doses to these patients.

Punit Dhillon^ Yeah, and it's going to be in line, it's going to be in line with existing formats that we're that we're already seeing in the AOM [anti-obesity] landscape.

Albert Lowe^ Okay, do you still plan to, I guess, start this new dose ranging study potentially next year.

Punit Dhillon^ Yeah, that's the plan. So I think, like, that's a very important point that you're bringing up. You know, we've obviously generated, an actionable kind of understanding here from a dose exposure, understanding from this, this study, the proof of concept study.

So when I look at the big picture, the timeline for us has remained intact. This is -- this is the data point that we needed to understand what we're going to be doing for the next trial. I think there, there's a little bit additional learning that we're going to take a moment to understand in terms of how the combo path could look like. That's certainly encouraging.

So we're evaluating, from a development standpoint, a strategy that can support further review of what a combo path can look like. But we're also going to continue to evaluate what the dose ranging needs to be to better understand our mono therapy dose response.

Albert Lowe^ Great. One last question. Can you, can you give us any more color on what trends you saw in the nimacimab PK profile and the combo treated patients?

Punit Dhillon^ What trends we saw in the, sorry, was that safety you were asking about?

Albert Lowe^ No, in the PK profile.

Punit Dhillon^ In the PK profile, okay.

Albert Lowe^ In the combo…

Chris Twitty ^ Yeah, I could, I could -- I could speak to that. So the, by and large it was a relatively similar PK profile. The exposure overall did seem to be a bit more favorable in the combination. So our early analysis, you know, is looking like there may be a bit more. We're hesitating a little bit and being too firm.

So sort of waiting for the final PK data set where we can really make that claim. But that's something that's a bit soft and we're seeing, well, we don't know if that's because maybe you can imagine in a combination setting, there may be better compliance.

And maybe that patients are losing more weight and that could, it could impact, you know, how we look at exposure. So we want to be a bit hesitant to really provide too much color. But it's not, I would say night and day.

We don't see striking differences that would maybe argue why the combination effect is dramatic as it is relative to the monotherapy. We believe overall they're mostly in line, but we'll have that final data set in the next few weeks/months, and we'll share with you as soon as we can do that.

Punit Dhillon^ Yeah, we have a bit of a short time here. I think we're running over. So we want to get through the rest of the questions. Can we, um, take the next question from.

Operator^ Your next question comes from Jon Wolleben with Citizens. Please go ahead.

Jonathan Wolleben^ Hey, thanks for taking the question. Just one for me, for Dr. Wharton and Dr. Aronne. Wondering, if we think about, you know, offering two injections to your patients, are you seeing enough of this week 26 end point to say, hey, doing two injections is better than doing one. And if not, what do you want to see at week 52 in terms of separation or attributes to make that offering attractive to someone looking to lose weight.

Sean Wharton^ Lou, you are going ahead?

Louis Aronne^ So I think that when this would be commercialized, it would be one injection. And if you look at what we're seeing in the trials that we're doing right now, in my opinion, the big winner is going to be a lower dose of a GLP-1 plus another drug that enhances the weight loss but doesn't have the GI and other side effect profile.

And we've -- we're seeing that. So, a lower dose of GLP-1 plus something else that's giving greater weight loss, I think that that will be a very popular strategy, and it will be given as a single injection--not asking people to take two injections.

The second thing, I mean as far as the trial, a simple way to overcome this, the possibility that people aren't injecting themselves is to have them come in and in a small study, give them the injection to see what happens.

So doing a PK study, where you're actually injecting. So, there are ways to solve these riddles right now. We should be able to figure this out by next year.

Sean Wharton^ Yeah, I think as well here what people are looking to do is to find out about the body mass composition changes. Can we get better? Can we get better if we stop the medication for a period of time, if you're off for a week or two weeks or a month? Can you still stay on track, not lose lean body mass, not regain weight. Can you not get that side effect profile.

So the CB1 antagonists from back in the early 2000s showed remarkable efficacy and real great positivity, visceral adiposity loss. So this idea that we want to get back to all those positive aspects is still there.

We just want it without the side effect profile, and right now we didn't see any side effect profile. So it's truly staying in the peripheral area not going up into the brain. And so I think that we're seeing a really -- that's a positive aspect. We can get that, and we can get the weight loss, that'll be great and that would be the combination.

Jonathan Wolleben^ Got it, helpful color. Thank you.

Operator^ Your next question comes from the line of Ananda Ghosh with H.C. Wainwright. Please go ahead.

AnandaGhosh^ Yeah, hi, guys, thanks for the opportunity. I have two questions. One is, you know, given the suboptimal exposure of nimacimab, one still sees an additive effective synergistic.

How does it fit with the overall MOA of the drug and, you know a close follow up would be for Dr. Aronne, you know how significant is the lean mass data when you are thinking about with respect to the current landscape.

Punit Dhillon^ Thanks, Ananda. Dr. Arora you want to just talk about the synergistic--or Dr. Aronne, I guess you can you can touch on both aspects if you-- if you feel comfortable with that.

Louis Aronne^ Sure. I think that as far as synergy we've seen this, now, going back 20 years, that there is some type of synergy between certain compounds. The amylin analogs are another example where we have seen some synergy. But when it comes to the cannabinoid antagonists,

you know, we have cases of patients who had rimonabant back 20 years ago. And when we lost rimonabant and switched them to GLP-1, these are people with Type 2 diabetes who are on insulin, one of the things that was so interesting is that the GLP-1s didn't substitute for the cannabinoid antagonists. And I'm talking about a small number of patients, a handful, less than five, but it was really remarkable to me seeing the difference in efficacy profile.

The second thing is there is a difference. I mean, we're seeing older patients in particular, taking GLP-1s, have significant reduction in lean mass and also a feeling of less strength. That's something that every clinician is going to tell you.

Maybe not in a 45-year-old man, but in a 60-plus year old person, there is a significant difference. So the question is, if we're using a higher dose of this, will we get a better improvement in body composition? Which, by the way, we saw with GLP – with the earlier cannabinoid antagonists.

So, I'm confident that we get a better result.

AnandaGhosh^ Got it. Thanks very much.

Sean Wharton^ Yeah, and adding color to that as well, you guys want to know, will our patients want to take it? Do people want to take two injections? As Lou said, it'll likely be combination. And even so, people will take, people are interested. They're really interested in these answers and will push the envelope. Taking two injections, I mean, we found, we didn't think they'd take any injections. They'll take one, they'll take two, they'll take -- they're ready to go. So I think that this is something that we have learned about our patients is that we underestimate how much they're actually willing to do to get the impact that they are looking for, that they want.

AnandaGhosh^ Got it, thanks very guys.

Punit Dhillon^ Thank you, Ananda.

Operator^ We have no further questions in our queue at this time. I will now turn it back over for closing comments.

Punit Dhillon^ All right, thanks everybody. Well, obviously, from a proof-of-concept perspective, we came away with some real wins from the perspective of really proving that the orthogonal biology works. And thank you for highlighting that, Dr. Aronne and Dr. Wharton.

We've also de-risked CB1 safely in the clinic from the initial dose that we've tested. And then we've had an actionable kind of plan here from a dose exposure perspective to evaluate in a subsequent trial.

I want to take a moment to thank the team for their tremendous effort. I want to thank the patients and the physicians that have participated in the CBeyond trial. And thank you all for

your engagement today and your thoughtful feedback. And we'll look forward to providing additional updates later this year. Thanks, bye-bye.

Operator^ Ladies and gentlemen, this does conclude today's conference call. Thank you for your participation and you may now disconnect.