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EDITED TRANSCRIPT

Biomea Fusion Inc to Discuss Initial Phase II Clinical Data for BMF-219 in Subjects with Type 2 Diabetes- Conference Call

EVENT DATE/TIME: MARCH 28, 2023 / 12:30PM GMT

CORPORATE PARTICIPANTS

Ramses Erdtmann *Biomea Fusion - Chief Operating Officer & Co-Founder*
Juan Frias *Biomea Fusion - Scientific Advisory Board Member*
Rohit Kulkarni *Biomea Fusion - Scientific Advisory Board Member*
Steve Morris *Biomea Fusion - Chief Medical Officer*
Thomas Butler *Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder*

CONFERENCE CALL PARTICIPANTS

Joseph Pantgini *HC Wainwright & Co. - Analyst*
Joe Catanzaro *Piper Sandler - Analyst*
Yigal Nochomovitz *Citigroup - Analyst*
Hartaj Singh *Oppenheimer - Analyst*
Michael King *EF Hutton - Analyst*
Eun Yang *Jefferies - Analyst*
Eric joseph *JPMorgan - Analyst*

PRESENTATION

Operator

Good day and thank you for standing by. Welcome to the Biomea Conference Call and Webcast to Discuss the Clinical Data from the First Two Cohorts of BMF-219 in Patients with Type 2 Diabetes. (Operator Instructions).

I would like to turn the conference over to your speaker today, Ramses Erdtmann. Please go ahead.

Ramses Erdtmann *Biomea Fusion - Chief Operating Officer & Co-Founder*

Thank you, operator. Good morning, everyone, and thank you for dialing in at this early hour. We're excited to discuss with you the press release we issued earlier today and the initial top line data from the first dosing cohorts from our ongoing Phase 1/2 study of BMF-219 in healthy volunteers and Type 2 diabetes patients, also known as COVALENT-111.

Today marks a very big milestone for the Biomea team, as these are the very first ever clinical data we have reported as a company, the first of what we anticipate will be many clinical readouts.

Some quick introductions, my name is Ramses Erdtmann. I'm the COO, president and co-founder of Biomea. With me on the call today from our team and available to answer questions are our CEO and chairman Tom Butler, also co-founder of Biomea, as well as our CMO, Dr. Steve Morris, and our Executive Medical Director, Dr. Sanchita Mourya.

Additionally, we have Dr. Juan Pablo Frias on the call. Dr. Frias is currently the medical director and principal investigator at Velocity Clinical Research headquartered in Durham, North Carolina, with more than 80 sites in the U.S. and Europe. He is former clinical assistant professor of Medicine Division of Endocrinology at the University of California, San Diego School of Medicine, and a former CMO and SVP Clinical and Medical Affairs, Diabetes Care at Johnson & Johnson.

We also have Dr. Rohit Kulkarni with us on the call. He is currently a senior investigator and professor of Medicine at Harvard Medical School, and has been a faculty member of the Joslin Diabetes Center since 1999. Dr. Kulkarni's laboratory primarily focuses on the generation of beta cells, which are the insulin-producing cells that are primarily affected in Type 1 and Type 2 diabetes.

Both Dr. Frias and Dr. Kulkarni are members of the Biomea Scientific Advisory Board, and has been involved in diabetes and metabolism-related research for decades, and have authored numerous publications in this field. Dr. Frias and Dr. Kulkarni are both restricted from making any product endorsements. So they will focus their remarks primarily on the disease, the disease origin, the current treatment modalities, and other related factors. Thank you both for attending this call, and also for being available for questions.

Before we start, let me remind you that this non-confidential presentation contains forward-looking statements about the business prospects of Biomea Fusion, including expectations regarding Biomea Fusion's, clinical and preclinical results, and potential future

product candidates in different areas of therapeutic research and development.

Results may differ materially from those expressed or implied in this presentation, depending on the progress of Biomea Fusion's preclinical and clinical development activities, actions of regulatory authorities, availability of capital future actions in the pharmaceutical market, and developments by competitors, and those factors detailed in Biomea Fusion's filings with the SEC such as 10-Q, 10-K, and 8-K reports.

All forward-looking statements made during this presentation are based on the belief of Biomea Fusion as of this date only. And future events or simply the passage of time may cause those beliefs to change. Please be aware that you should not place undue reliance on the forward-looking statements made today.

I will now turn the call over to Dr. Frias.

Juan Frias ***Biomea Fusion - Scientific Advisory Board Member***

Thank you, Ramses. I'm glad I can participate in today's call. It's exciting to see this innovative new investigational agent, BMF-219, with a novel mechanism of action, demonstrating very encouraging data to date in patients with Type 2 diabetes. Let me provide a little background to help establish some context for these preliminary BMF-219 data.

As many of you know, there are many, many ongoing trials in diabetes. In fact, a search for active Type 2 diabetes trials on clinicaltrials.gov yields more than 1,000 studies. While these trials are assessing different treatment modalities, they're primarily focused on reducing hyperglycemia, which is the key clinical indicator of Type 2 diabetes.

Currently approved medications for Type 2 diabetes are also primarily focused on improvement of glycemic control. And none of the many agents approved today for Type 2 diabetes are designed to directly address a key pathophysiologic defect of the disease, which is the progressive decline in beta cell function leading to insulin insufficiency.

Let's take a closer look at the agents approved today. Newly diagnosed persons with Type 2 diabetes are typically prescribe an oral agent as first line therapy. The first agent used is generally metformin, which is thought to act primarily by reducing the amount of glucose produced by the liver. Unfortunately, less than half of the patients treated with first line agents have the necessary effect to achieve their individualized glycemic target, which generally means achieving a hemoglobin A1C below 7%.

The A1C is the standard we generally use to compare the level of glycemic control across treatments. It's an indicator of overall glucose control during the preceding two to three months. For the 50% or so of patient whose glycemic control initially reaches the target, the effect typically does not last. The patient has so-called secondary failure.

Data showed that after four years on therapy, with initial oral agents, of those patients who have a benefit initially up to three quarters, no longer have adequate glycemic control. Importantly, their poorly controlled diabetes can cause long-term damage to multiple tissues and organs, and reduce overall quality of life and general health.

Patients who do require intensification after initial metformin therapy generally have a second, and many times, a third oral agent added. This can be a sulfonylurea, a class of drugs to stimulate the beta cell to secrete insulin; a DPP-4 inhibitor, which act via increasing endogenous incretin hormone concentrations; or an SGLT2 inhibitor, which act to reduce plasma glucose by inducing glucose urea, causing glucose excretion in the urine, and have many other important benefits for both the kidney and heart.

Oral or injectable GLP-1 receptor agonist, which mimic the actions of the incretin hormone GLP-1 are also commonly used as second line agents due to their positive effects on glucose, body weight, and cardiovascular protection.

For many patients with Type 2 diabetes, despite combinations of various oral and non-insulin injectable agents such as GLP-1 receptor agonist, adequate glycemic control cannot be achieved, and many patients end up on insulin therapy. At first, basal insulin such as insulin degludec, or insulin glargine, and then if needed, rapid-acting mealtime insulin like one or more meals during the day.

Today, in United States, about 10 million of the more than 35 million persons that have Type 2 diabetes require insulin to manage their condition. The treatment modalities I've outlined here have led to over 60 different FDA approved therapies for Type 2 diabetes, as single agents or in various combinations. They can provide several years of good glycemic control to patients. But ultimately, due to the progressive decline in beta cell function, many of these patients will require insulin therapy to achieve normal or near normal glycemia.

While important to improve health and well-being of many patients with diabetes, these agents have one thing in common, they do not directly affect a root cause of diabetes, which is the progressive decline in beta cell function. Beta cells reside in the pancreas, and their main function is to produce, store and release insulin. As such, they play a critical role in ensuring that plasma glucose concentrations are kept within the range that is necessary for an individual to carry out their daily activities and to ensure that glucose will not go too high or fall too low.

Dying and declining beta cells are not repairable or programmed to regrow like other cells in the body, as liver cells can do, for example. Beta cells are quite unique in this regard, they're very long-lived. It turns out that by the age of 30, an individual is typically set with his or her beta cell pool, which can easily have a lifespan of 20 or more years, but with very little replication.

Multiple factors such as leading an unhealthy lifestyle with insufficient exercise, unhealthy diet, uncontrolled weight, and other factors place constant pressure on the beta cell pool and ultimately will start to exhaust them. When the beta cell exhaustion exceeds a certain threshold, insulin production is too low to maintain healthy blood glucose levels, and glucose may rise into the prediabetes range. And ultimately, some individuals will have further progression of beta cell dysfunction and develop Type 2 diabetes.

If a person's beta cell mass is low, and their body, therefore, is not producing sufficient amounts of insulin to reduce glucose production by the liver, and to stimulate glucose uptake by peripheral tissues such as skeletal muscle, glucose levels will increase, and over years, will then impact various vital organs, causing serious health problems and reduced life expectancy.

In the U.S. today, there are over 96 million persons with prediabetes and over 35 million adults with Type 2 diabetes. Worldwide, over 537 million adults have diabetes and this number is rapidly increasing. Diabetes is the seventh leading cause of death in the U.S. and one of the largest economic burdens on the U.S. healthcare system, with $1 out of every $4 in U.S. healthcare costs being spent on caring for people with diabetes.

Something that is often overlooked is just how deadly diabetes can be. 80% of people with diabetes will ultimately die from diabetes-related organ damage or other complications. We have a real problem that requires enormous amounts of funding to manage, let alone tremendous loss of productivity and life. Unfortunately, instead of going away, the problem seems to be growing and intensified.

In order to effectively change the progression of diabetes, starting with prediabetes, we need to reverse the loss of beta cells which, so far, has been elusive for researchers and has not been possible to achieve with current treatment modalities.

I'll now turn the call over to Dr. Kulkarni to discuss the up-to-date unattainable potential therapeutic benefits of restoring healthy functioning insulin-producing beta cells and beta cell mass. Rohit?

Rohit Kulkarni ***Biomea Fusion - Scientific Advisory Board Member***

Thank you, Juan. Let me start by congratulating the Biomea team for such an incredible accomplishment, as it continues to progress BMF-219 to clinical development.

Throughout my scientific career, I have looked and hoped for a treatment that could potentially preserve the decreasing number of functional beta cells, regenerate them, and ideally, even reactivate dormant beta cells again. BMF-219 is now clinically on its way to potentially achieving each of these attributes, regeneration, preservation and reactivation of functional beta cells. Exciting times. Let me pick up where Juan left off.

A lower number of functional beta cells has been correlated with higher HbA1c and poor glucose control, which may lead over time to diabetes. At the point a patient is diagnosed with Type 2 diabetes, that individual, in many cases, may have already lost around 50% of their functional beta cell mass, which is difficult to measure. So we typically describe this as a 50% loss of beta cell function. And as patients continue to progress, the beta cell pool has been observed to continue to decline over 5% a year, until the patient gets to only 10% of the pool remaining. And that's when the patient will become insulin dependent.

Potential therapy that can reestablish the pool of function beta cells through beta cell proliferation and beta cell reactivation to produce desired amounts of insulin, I'm afraid, do not exist at the moment.

Now, do we have any examples that beta cell growth can lead to more insulin and glycemic control? In fact, we do, the body's process for preventing gestational diabetes. As the pregnant woman enters the second and third trimester, the demand for more insulin is drastically increasing. Stanford and other researchers have demonstrated that at that stage, the body increases the levels of a key hormone, prolactin, which in turn has been observed to downregulate the protein menin, which in the pancreas will act as the brake on proliferation, keeping them in check.

When prolactin is upregulated and menin effectively loses its function, the proliferation of maternal pancreatic islets has been observed. This has been shown to increase insulin production and enable glucose control for the mother and growing fetus, which may prevent gestational diabetes. Prolactin has been observed to prevent menin from engaging in transcription so that there's less menin in the nucleus, which in turn stimulate beta cell proliferation.

Now, also, in pregnancy, we have, so far, not seen any validated mechanism capable of restoring function of beta cells. To date, this was considered a finite loss, potentially directly correlated to significant health problems. But it certainly makes sense that instead of focusing solely on managing downstream glucose levels, the scientific and medical communities should also focus much further upstream. In fact, what is thought to be a source of the problem, functional beta loss.

Now, turning to the BMF-219 data today, I have to admit, I was quite surprised by the effect size of BMF-219 after just one month of treatment, and this only at the first dosing cohort. Based on the initial data, downregulation of menin has led to initial improvements in glucose control for 90% of the patients on 100 milligram dosing, without food, with a median A1C reduction of 1%. Most notably, I find that these results were achieved already after four weeks of dosing. A1C, as many of you know, shows the average blood sugars over the past three months. So typically, an A1C reduction shows maximum reduction after an observation of 90 days.

Interesting to note is also the population of uncontrolled patients that enrolled in the study. Here, the patients enrolled had an entry A1C at the start of the study of only 7.8%. Typically, the lower the entry A1C, the lower the effect potential of a given diabetes treatment. I'm pleased by the data and look forward to learning more about higher dose levels, longer duration of therapy, and the overall product profile of BMF-219 as the clinical development progresses.

As larger studies are initiated to support these early results, I can see many ways to utilize BMF-219 to potentially support patients with various stages of diabetes, including those possibly with Type 1 diabetes. Beta cells are thought to be a key to proper glucose control, and their loss is considered the root cause of diabetes. I'm really pleased by the progress the Biomea team has made, and I look forward to watching the study progress and the future results to come.

I'll now turn the call over to Steve Morris, CMO of Biomea, to present the data announced today. Steve?

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Thank you for that very helpful context-setting, Rohit and Juan Pablo, about the treatment landscape for Type 2 diabetes and the potential impact of a drug that could restore healthy beta cell function and mass.

Before I dig into the study details and findings, I just want to formally introduce BMF-219. BMF-219 is an investigational covalent menin inhibitor discovered and designed via our FUSION System platform. We designed BMF-219 to inhibit menin's capacity to interact with transcriptional partners that drive the expression of cell cycle protein regulators, including those that prevent the replication and

expansion of beta cells.

BMF-219 has been observed to restoring balance the beta cell mass in multiple animal and preclinical diabetes models, as reported at prior medical meetings. Today, we are reporting initial top line data from our clinical study, COVALENT-111.

Before I provide a quick overview of the study design, I first wanted to provide a summary of the results observed related to glycemic control based on the reduction in hemoglobin A1C. As shown in the slide titled Summary of Results, we are reporting today two dosing cohorts, each comprised of 12 Type 2 diabetic patients. 10 patients in each cohort received BMF-219 at a dose level of 100 milligrams once daily by mouth for four weeks, administered with food, Cohort 2, or without food, Cohort 3.

COVALENT-111 is placebo-controlled, randomized, blinded study. Two patients in each cohort received placebo. In the second row of the table, you will note that with regard to PK parameters, administration of BMF-219 without food was associated with a threefold higher systemic exposure based on the Cmax and AUC than that observed when the small molecule was taken with food. With regards to the median and mean hemoglobin A1C at baseline in the two cohorts, the numbers were well matched, overall.

Now, the results, and what I show you here on the bottom row of the table is the median and mean reduction in HbA1c observed after four weeks of dosing with BMF-219 or placebo. In Cohort 2, in which dosing of BMF-219 with food was associated with low systemic exposure. We nevertheless observed a medium and mean reduction of A1C of 0.3% and 0.25%, respectively; compared to a 0.1%, median and mean reduction in the two placebo patients.

In Cohort 3, in which the administration of BMF-219 without food resulted in an approximately threefold higher exposure, a remarkable 1% and 0.8%, median and mean reduction in A1C were achieved. This compares to a median and mean reduction of 0.15% in the two placebo patients. This median and mean A1C reduction of 1% and 0.81% in Cohort 3 was observed at the first dose level, 100 milligrams and our dose escalation. These numbers rival A1C reductions observed after the same dosing duration of only the most effective standard of care diabetes agents such as the GLP-1R and dual GLP-1R GIP agonists, when those agents are administered at their optimal dose levels.

Now, let's take a more detailed look at the study design. COVALENT-111 is a Phase 1/2 randomized, double-blind, placebo-controlled trial. As shown on the left-hand portion of this slide, we began with single ascending doses of BMF-219 in 40 healthy volunteers at 100, 200, 400 and 600 milligrams in the Phase 1 single ascending dose or SAD portion of the study. This part of the study was designed to provide initial safety tolerability and PK data for the small molecule. These data are not reported today, but will be described at an upcoming medical conference.

The Phase 2 portion of COVALENT-111 examines multiple ascending doses or MAD of BMF-219 at first, again, with 16 healthy volunteers who received 100 milligrams orally once daily for 14 days. Like the healthy volunteer study in Phase 1, the goal of this portion of the study was to assess safety tolerability and PK of the investigational covalent menin inhibitor. We've already completed all healthy volunteer cohorts in COVALENT-111.

I will shortly describe the top line results from the 16 healthy volunteers referred to herein as Cohort 1, focusing on the observed safety profile of BMF-219. We are now dosing Type 2 diabetes patients at various dose levels. We started with 100 milligrams with or without food. These are the two patient groups referred to as Cohorts 2 and 3, respectively, that I introduced to you in the Results Summary slide earlier.

This 100 milligram dose is the beginning dose level of BMF-219 in the study. Going forward, we plan to dose also 200, 300, 400 and 600 milligrams each in separate sets of 12 diabetes patients, with two patients in each set receiving placebo. Today, we are reporting top line results from only the two sets of diabetic patients enrolled in Cohorts 2 and 3.

On the left-hand side of the next slide, we are showing a simplified schematic of the dose escalation in COVALENT-111 to illustrate the three sets of subjects we have dosed today, Cohorts 1, 2 and 3, for which I'm describing data today, all of whom received the lowest dose of BMF-219 in the study, 100 milligrams.

The schematic in the upper right-hand portion of the slide shows the four-week dosing period of BMF-219 administered to Cohorts 2 and 3. We are following all patients subsequent to the four-week dosing for an additional five months in order to assess longer term safety as well as the potential durability of glycemic control.

The study will enroll a total of 60 Type 2 diabetic patients, with a hemoglobin A1C in the range of 7% to 10%, indicating poorly controlled glucose levels despite being on standard of care diabetes therapy. Patients can be on up to three standard of care agents. They have to have been on these agents without change in their treatment regimen for a minimum of two months before enrollment. We also ensure that enrolled patients do not change whatever regimen they are on.

We are enrolling patients that have failed their standard of care treatments and who have been diagnosed up to 15 years ago. We are enrolling primarily relapsing patients, that is patients who are responding poorly to their diabetic regimen.

The next slide describes the baseline patient characteristics and demographics, time since diagnosis and con meds for the 24 diabetic patients enrolled into Cohorts 2 and 3. Of special note, I point your attention to the fact that we enrolled individuals diagnosed with Type 2 diabetes as much as 14 years ago. In these first two groups of patients, the majority were receiving metformin as a single agent.

The slide titled Observed Hemoglobin A1C Lowering of BMF-219 provides a visual representation of the downward trends in A1C seen in Cohorts 2 and 3, after 14, 21 and 28 days of BMF-219 dosing. You will note a progressive reduction of A1C observed in both Cohorts 2 and 3, with the greatest decrease evident in the final seven days of the four-week dosing period.

The following slide, COVALENT-111 HbA1c Summary Results at Week 4 provides additional details not previously discussed. Included here are the number and percentage of patients dosed with BMF-219 who experienced any reduction in A1C in Cohort 2. Those numbers were 7 of 10 or 70%. And in Cohort 3, those numbers were 8 of 9, 89%.

Also included here are numbers that speak to the magnitude of the A1C reduction in the two cohorts. For example, those individuals achieving a 0.5% or greater reduction in A1C in Cohort 2 were 3 of 10, 30%. Whereas in Cohort 3, there were 7 of 9 or 78% experiencing this magnitude of reduction.

And looking at an even greater magnitude of A1C reduction, a 1% or greater decrease, no Cohort 2 patients were observed to achieve such a decrease. However, in Cohort 3, 5 of 9 or 56% of patients dosed with BMF-219 experienced a 1% or greater decrease in A1C. These effects of BMF-219 on A1C are consistent with a positive dose response relationship given the approximately threefold higher systemic exposure of a small molecule in Cohort 3 compared to Cohort 2.

In the next two slides, I would like to present two case reports of Cohort 3 patients focusing on glycemic parameters indicative of the responses observed with BMF-219. The two multicolored images in the upper half of this slide show results of continuous glucose monitoring, CGM, at baseline and Week 4. The different colors represent various glucose ranges during these time periods.

The notable takeaways are that the time and glucose target range, the green portion of the images, at baseline, was 37%, and after only four weeks of BMF-219 dosing, had nearly doubled to 72%. Further, the average glucose declined from 205 at baseline to 169 milligrams per deciliter during Week 4.

Also shown here in the lower left corner are oral glucose tolerance test, OGTT, results performed at Days 14 and 28. The marked reduction in glucose levels following oral glucose challenge at Day 28 is readily evident. Finally, in the lower right corner of the slide, we show the reduction in A1C in this patient, which was observed to decline from a baseline value of 8.9% to 7.9% at Week 4 of dosing with BMF-219.

I would like to draw your attention to our Week 8 A1C determination, which showed a continued decline of A1C to 7.1%, even though the final dose of BMF-219 had been administered a month earlier.

In the next slide, the same glycemic parameters CGM, OGTT, and hemoglobin A1C are shown for another Cohort 3 patient case report. Note that the time and target glucose range for this patient was observed to increase fivefold from the baseline value of 12% to 60% at Week 4. Average glucose was observed to decrease from 234 to 174 milligrams per deciliter at the two time points. Multiple OGTT determinations are shown for this patient, demonstrating a progressive reduction in blood sugar levels post oral glucose challenge following 14, 21 and 28 days of BMF-219 administration.

Lastly, as with the preceding patient, this individual was observed to also have a substantial decline in A1C levels from baseline 8.4% to 7.7% at Week 4. Here, as well, the A1C reduction continued past the four -week dosing to a level of 7.2% at the Week 8 assessment.

The following slide describes the tolerability profile of towards observed in Cohort 1, the healthy volunteers. This slide shows that the healthy volunteers who received 100 milligrams BMF-219 once daily for 14 days, experienced only minor grade 1 treatment emergent AEs.

The subsequent slide shows a comprehensive summary table of all TEAEs observed in the 24 diabetic patients enrolled into Cohorts 2 and 3. All TEAEs were grade 1, with the exception of an asymptomatic lab finding of grade 2 elevated lipase. Other TEAEs of note, included grade 1 elevations in GGT, AST and ALT that occurred in a single patient. These elevations were asymptomatic and resolved during the four-week dosing period. Two patients on placebo experienced asymptomatic grade 1 elevation of plasma pancreatic polypeptide.

In short, BMF-219 was well tolerated, no patients discontinued treatment or exited the trial during the four-week dosing. All patients continue in follow-up to assess durability of the treatment effect. There were no dose reductions, SAEs or severe AEs. All treatment-related AEs were mild and infrequent. No subjects showed symptomatic hypoglycemia.

We are highly encouraged by these initial safety and efficacy findings, and very excited to continue our investigation of BMF-219 in the COVALENT-111 study. As we complete various dosing cohorts moving forward, the plan is to unblind and share updates on a recurring basis, similar to that provided today.

Thank you very much for your attention. And with that, I will turn it over to Biomea co-founder and CEO, Tom Butler, for closing comments.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Thank you very much, Steve. And in summary on Slide 16, BMF-219 demonstrated a well-tolerated safety profile. As mentioned, there are no dose discontinuations and all 20 subjects completed the four weeks of treatment and continue in the five-month follow-up period. No severe or serious TEAEs were observed, and no episodes of symptomatic hypoglycemia occurred in any patients.

And then to summarize Cohort 3, 89% of patients achieved a reduction in hemoglobin A1C. Plus, 78% of patients achieved a 0.5% reduction in A1C or more, and 56% of patients achieved a 1% reduction in A1C or more. We also saw a positive trend in OGTT and continuous glucose monitoring parameters.

Today marks an important milestone for the company and for BMF-219, the first and only menin inhibitor in the clinic for Type 2 diabetes. This is the company's first clinical readout to date, and the first clinical readout for BMS 219. Today's data readout was just the first glance at COVALENT-111 data.

We'll continue to execute the dose escalation, enrolling the 200 milligram cohorts, and we will select the two most promising dose groups from the escalation phase for the expansion phase. We look forward to providing further updates throughout the year, including a potential presentation at a medical conference later this year that Steve noted.

I cannot be proud of the results we achieved after only four weeks of treatment with BMF-219. You compare these results to any other agents out there, during the group of patients with a median A1C level of 7.8% on the onset of the study and looking at relative reductions in A1C and glucose control after the first 30 days, with the first dose tested and with an oral agent, you will not find many

agents with this treatment effects. And we are just getting started.

This is the first step for us in pursuing a promising agent for the treatment of diabetes, all forms of diabetes. And while the reduction of hemoglobin A1C is the near-term focus and the current hurdle, we are after something much more important.

Our goal is to develop a treatment that doesn't require any additional therapy, a treatment that doesn't need to be given chronically for the rest of your life, a treatment that restores long-term glycemic control while off therapy. This is what patients need. This is what will transform diabetes, an epidemic affecting over 500 million people worldwide.

There is no question, we have a lot of work ahead of us and we have a lot to learn about BMF-219 and about treating patients with diabetes. What is the right dose level for BMF-219? How long do you need to take BMF-219? And what is the durability of its effect? These are all very important questions we will need to answer as we carry out the COVALENT-111 trial and beyond.

The good news is we believe we have answered a lot of questions today. The early profile of BMF-219 displayed today helps provide the necessary foundation to fully explore the molecules potential as a treatment for diabetes. Our base case for development of BMF-219 has always been to create a complementary therapy to the standard of care, due to the potential novel mechanism of action.

We believe that if we can sufficiently regrow a patient's pool of functional beta cells, we may be able to make every other agent out there work better and work longer. However, given our initial observations in COVALENT-111, we believe that some patients from this study may be showing signs of a potential durable response, and we are hopeful that such patients can maintain glycemic control during the follow-up period of treatment with BMF-219. Our goal, our long-term goal is to be in a position to explore BMF-219's ability to allow patients to stop all therapy.

In closing, I want to thank team FUSION for achieving this incredible milestone, while pushing all of our other programs forward. My teammates here are incredible professionals. They are executing at a very high level. When we started Biomea, we had a dream to help millions of patients overcome their disease. Today, with our first clinical readout, we have made a significant step towards realizing this mission.

Thank you all for attending today's clinical update, and I thank you for your interest in our development and dialing in so early. Let's open up the floor for questions. Operator?

QUESTIONS AND ANSWERS

Operator

Thank you. (Operator Instructions) We'll pause for a moment while we compile our Q&A roster. Our first question comes from Joe Pantgini with HC Wainwright. Your line is open.

Joseph Pantgini ***HC Wainwright & Co. - Analyst***

Hi, everybody. Good morning and congratulations on a very exciting first look. So when you look at these actually pretty extensive data for only the first two cohorts here, obviously, there's a food effect. That looks pretty interesting here. But there's a lot going on, and I'm just curious, you know, how you can draw any potential hypotheses or conclusions from the time from diagnosis, combined with the food effect, combined with the concomitant medications as well, because there's a lot going on here.

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Excellent question. What I can say is that based on our preclinical studies for dosing diabetic animal models, we've shown dosing for as short as a two-week period is sufficient to increase the total beta cell pool, to increase insulin secretion and revert animals with very high glucose levels to normal glycemia.

The other important aspect is that those results in animal models translate, of course, as we've just described to you, now we know to patients. We predicted that with non-clinical studies as well, using human ex vivo beta cell explants, in which we showed increased beta

cell replication with BMF-219 exposure. An important finding from those human beta cell explant studies was that each individual has a different basal replication rate of their beta cells.

So speaking to your question, it could be the case that different individuals need perhaps, for example, a different optimal duration of dosing. It's even possible that each individual could require a different dose level. Again, we don't know the answers to those questions, but COVALENT-111 is designed to answer those questions.

Joseph Pantgini ***HC Wainwright & Co. - Analyst***

No. That's perfect. Thank you. And then I'll just have one more, please, if you don't mind. So Tom made a comment too, obviously, about, you know, looking to be complementary to other drugs.

So, Steve, when you combine your comments about these preclinical data, you know, seeing the increase in beta cells within two weeks, how you could ultimately and of course, you got a way to go here with additional doses, et cetera. You know, the ultimate profile of the drug here, where really it doesn't necessarily appear to be chronic drug if you could get the beta cells functioning again, and how that could translate to what a maintenance therapy might look like, of course, all hypothetically right now.

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Right. Another excellent question. You know, I guess one thing I'll say in response to your question is that the preclinical data suggested no drug-drug interactions with 219. And indeed, to date, in the clinic, we have not observed any DDI. So we think that given that, combining 219 with other agents will be very doable.

You know, as Tom mentioned, the base case scenario would be to make standard of care diabetic agents better when combined with 219. The blue sky scenario would be a situation in which 219 had a magnitude of efficacy in terms of glycemic control so that individuals would no longer have to take their standard of care agents. So again, you know, we don't know the answer to those questions, but COVALENT-111 is designed to address them.

Joseph Pantgini ***HC Wainwright & Co. - Analyst***

Okay. Thank you very much.

Operator

One moment for our next question. Our next question comes from Joe Catanzaro with Piper Sandler. Your line is open.

Joe Catanzaro ***Piper Sandler - Analyst***

Hey, guys, thanks for taking the questions and congrats on these nice early data. The early A1C data are obviously pretty provocative and I know some of the case studies provide some insight. But maybe can you speak qualitatively to some of the trends you've observed with some of the other glycemic PD markers like fasting blood glucose and insulin and others, and whether they're tracking alongside the reductions you're seeing in A1C? Thanks. And I have a follow-up.

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Well, as mentioned, during the presentation, we have seen reductions in glucose levels. I refer you back to those two case reports from the two Cohort 3 patients. Speaking to the other metrics that you just mentioned, we will report data on those metrics later, at an upcoming medical meeting. So today, we're not speaking to effects on C-peptide, insulin, et cetera, however.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Yes. Hi, this is Tom. Great question. We have seen those positive trends, in general, certainly within Cohort 3, due to the higher exposure. So trends that you'd expect, that you have increasing functional pools. You see an increase in insulin for patients who need additional insulin, C-peptide production, so forth. And we'll share all of these additional data, hopefully, at a medical conference coming soon.

Joe Catanzaro ***Piper Sandler - Analyst***

Great. And if I could just ask a follow-up, I don't know if the physicians are still on the call. I know this is a placebo-controlled study, but wondering, as we think about the activity observing Cohort 3, whether there are any, you know, external factors that can contribute to

some of the effects seen there like improved lifestyle, diet, background, therapy, compliance. And with that, is it possible to see a 1% reduction in A1C at Week 4, some of those external factors are improved? Thanks.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Yes, absolutely. I'll pass it over to Dr. Frias. But just important to know, obviously, we're maintaining the [placebo]. That's the beauty of having a placebo arm, so you can observe what effects the patient population is doing in general, and then measuring the against the performance of the placebo. Dr. Frias?

Juan Frias ***Biomea Fusion - Scientific Advisory Board Member***

Yes. I mean, I agree that the beauty of having the placebo. But I would say it would be very difficult in that period of time. In my understanding, you know, certainly the studies, that there was not any intensive lifestyle intervention as part of the therapy. But even if there was, to have that degree of reduction in A1C in that shorter period would be extremely difficult. So I don't think that would be a confounding factor here, particularly since it wasn't done by these patients.

Joe Catanzaro ***Piper Sandler - Analyst***

Okay, great. That's exactly what I was looking for. Well, I appreciate you taking the questions and congrats again on the data here.

Operator

One moment for our next question. Our next question comes from Yigal Nochomovitz with Citi. Your line is open.

Yigal Nochomovitz ***Citigroup - Analyst***

Hi. Great. Thank you so much for taking my question. Hi, Tom, Ramses, Steve. Very compelling data. I have a lot of questions. Hopefully, we can get through all of them. If not, we can take it offline.

So first of all, could you comment with the 5 out of 9 that got over -- greater 1% drop? What was the distribution looking like for those above 1%, if you have that specific data? Then were there any patients that got below the 7% cut-off into the normal range for HbA1c at this short four-week look?

And then obviously with this very, very good data, are you reconsidering whether you even need the 400 milligram at this point? I know you started at 200. But the 400, you haven't started yet, if I'm correct. So do you even need to do that? And then finally, can you comment on the variability in the HbA1c level pre-enrollment? Just getting a sense as to how much variability there was before they actually got into the trial. Thanks.

Steve Morris ***Biomea Fusion - Chief Medical Officer***

You know, all great questions you've got, and I'll try to make sure I hit it from the top. You asked about the range of the top performers or the 5 of the 9, I don't know what the distribution was, and we'll present more at a medical conference. What is the median change on that? I think it's in the 1.2%, 1.3% range, but don't quote me. We'll update you further as we disclose more data. But the range was really strong and towards the higher end.

And then patients going under 7%, yes, we do have examples of that. Again, we'll provide that at a medical conference, that patients did go below 7% which was great to see. And then you had a question about how stable their A1C was and the attribution of their baseline characteristics. That's a very important question and something that we pay close attention to, and that's why we didn't want patients changing their therapy so that we knew that their A1C was stable. So we take baseline measurement, and then take Day 1 measurement, make sure it's stable.

And do we need 400 milligrams? Yes, I mean, after this data, it looks like no. But we still want to go through [investigation], see how the 200 milligrams performs. But we agree with you, given the 100 milligram, that seems that 400 which would not be necessary.

Yigal Nochomovitz ***Citigroup - Analyst***

Great. Okay. And then just one other thing, I'm assuming there was never an expectation that you were going to show P values for this very small trial, right?

Steve Morris ***Biomea Fusion - Chief Medical Officer***

It's difficult. Yes, difficult with a small number. Again, back to the effect size, it's quite large.

Yigal Nochomovitz ***Citigroup - Analyst***

Yes. Okay. Thank you.

Operator

One moment before our next question. Our next question comes from Hartaj Singh with Oppenheimer. Your line is open.

Hartaj Singh ***Oppenheimer - Analyst***

Great. Thank you. And really nice data comes. As everybody said early, that's really, really nice. You know, just kind of going back to some of the comments, Steve, you're making on some of the preclinical trial work you've been doing both in rat models and ex vivo stuff. You know, how to think about safety? You're at the 100 milligram. You know, Tom just mentioned, go to 200, maybe don't need to go above that. But in terms of your modeling, you know, how to think about safety, the 200 milligram, would there be any case whatsoever to try the 400, maybe push the efficacy, see where safety goes?

And then just, you know, assuming you finish out the dose escalation components of the study, what would be your regulatory and clinical next steps after that? If you can just give us a general idea. And then I got just one quick follow-up.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Yes, I'll pass it on to Steve this time. Thank you for the questions, Hartaj. In terms of safety, I mean, the 400 milligrams, and even higher, we have optional cohorts that are slated to go into higher dose levels, if we need to. So 400 is not our top. We can actually dose higher than that. I think a 600 is the next option forward after, based on all of our preclinical modeling. But really these dose levels were schemes based on trying to generate the best efficacy, if that makes sense.

And then from a regulatory perspective, or what our next steps beyond this COVALENT-111 study, that's a great question. But next steps would have a discussion with the FDA because we're not trying to create another chronic agent out there for diabetes. So we have to understand what is the sizing, what does the development path look like for an agent like this. But one could imagine that there will be, you know, a few larger studies that we want to do that look at various combinations in various patient populations.

We try to keep COVALENT-111 as broad as possible. We want to try to capture really the heterogeneous patient population of diabetes so that we could see who responds the best to 219, but the 89% response looked like the majority do, which is great. But we want to see what other demographics, other characteristics of the patients that generate that higher efficacy, if there are. I hope that will answer your questions. And Steve, if there's anything you can --

Hartaj Singh ***Oppenheimer - Analyst***

Yes, great thought.

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Nothing.

Hartaj Singh ***Oppenheimer - Analyst***

Yes. No. That's great, Tom. And then just one quick follow-up. You know, it's a little puzzling to me, I think the KOLs didn't touch on it earlier, maybe they could answer, or Tom, you know, which is a beta cell loss, right. So A1C seems to be what people are looking at. But

that seems to be, you know, kind of not exactly the exact biomarker you want to try to aim for. Has there been any work, or is there a way to be able to measure beta cell loss as a direct impact or something like BMF-219, you know, to help with regulatory and clinical development going forward? Thanks for all the questions.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Yes, great question, Hartaj and I'll pass it over to Rohit to discuss that very point. I think for us, you know, that's why we implement continuous glucose monitoring because it's not just about A1C lowering, because it's about trying to get the patients into normal glucose range. And then OGTT helps us assess how much of a functional core is present in the patient. But let me pass it on to Rohit. Rohit?

Rohit Kulkarni ***Biomea Fusion - Scientific Advisory Board Member***

Yes. Rohit Kulkarni. That's a great question. You know, the entire medical field is still waiting for very appropriate biomarker to assess taking a blood sample and looking at beta cell mass and beta cell function. So far, it's only C-peptide and insulin. So as Tom mentioned, that will be forthcoming.

But going back to your question, HbA1c is still a pretty important marker because once you argue that beta cells are improving or getting reactivated, then ultimately they're functional, then they will improve HbA1c. So the bottom line still is HbA1c. But a biomarker is still lacking and hopefully we can get something in the field to allow that in humans. Thanks.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Great. Thanks for all the questions.

Operator

One moment for our next question. Our next question comes from Michael King with EF Hutton. Your line is open.

Michael King ***EF Hutton - Analyst***

Hey, guys, good morning. Thanks for taking the question, and let me add my congratulations for this unprecedented data. A couple of questions to follow up on some of the others.

First, I'm just curious, from a standpoint, maybe clinicians want to weigh in on this as well. But just what's the imperative -- I mean, clearly, a 1% reduction in A1C in 28 days is remarkable. But is there an imperative to drive the A1C down so rapidly? I'm just wondering if maybe go the other direction and rather than explore higher doses, can you, you know, explore maybe lower doses, but lower A1C more gradually? And is there any kind of clinical scenario where that might be preferable or more appealing to patients?

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Excellent question. Of course, that's a possibility. What I will say, as we've reported today, the safety profile at the 100 milligram dose level looks very favorable, so perhaps we don't need to go lower. If we think we do need to do so, of course, we will look at that in future clinical studies.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

And yes, I'll just add, like, you know, the consequence of the rapid reduction, we haven't seen. If anything, we see benefit, actually. We've had, you know, PIs and their patients come back actually communicating that they feel great, they feel better while on therapy, and encourage them to stay on drug. I think that feeling better actually results in them keeping and maintaining the regimen, and having high compliance and persistence to lead to a greater outcome.

I think, you know, what we've seen with patients, in general, is because we have the continuous glucose monitoring, you get to see how the reduction happens over time. And just if you go back to that graph, that very powerful graph, you can see that it's very gradual in the beginning. And then as patients come into near normal range, that's when you see that large reduction in A1C. But keep in mind, A1C is backward-looking. The continuous glucose monitoring gives you a sense of a nice gradual reduction of sugar on a continuous basis, if that makes sense.

Michael King ***EF Hutton - Analyst***

Yes. No. It sounds like I just felt like I needed to ask that question. But it reminds me of Mounjaro or Ozempic, where you do get those rapid reductions. And you're right, I think for persistence and compliance, those are great outcomes.

The other question I wanted to ask was on the food effect, just not to get into the weeds on it, but I'm just wondering, when you say taken without food, how did you define that? Was that after a certain interval? Like, could I have just immediately unfinished lunch and then had a dose, or do I have to wait an hour or two? How did you define without food?

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Sure. We use a standard clinical approach to this, specifically a two-hour window before and after dosing of BMF-219. The individuals had to refrain from eating during that two-hour plus/minus window.

Michael King ***EF Hutton - Analyst***

Okay. So how would you envision -- when did these patients typically take their dose? Did they take it between breakfast and lunch? Did they take it, you know, just before they went to bedtime? What was the typical administration? I'm just wondering, again, from a compliance and ease of use standpoint, what this -- how this might impact day-to-day usage?

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Yes, I think it's straightforward. The individual, for example, could take it the first thing in the morning when they wake up, and then refrain from eating thereafter for two hours. Alternatively, as you said, they could eat breakfast, wait two hours, take the dose, and then wait two additional hours to eat their lunch.

Michael King ***EF Hutton - Analyst***

Okay. But you don't have any studies reflecting that information, or any information to share on that right now?

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Not at the moment.

Michael King ***EF Hutton - Analyst***

Okay. One other clinical question, any changes -- I know, people were asking about, you know, C-peptide and other things, but I'm just wondering about weight and body mass, any effects there at 28 days?

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Yes. Again, as mentioned earlier, we will report that as well as much additional data at an upcoming meeting.

Michael King ***EF Hutton - Analyst***

Okay. All right, guys, thanks for indulging the questions. Appreciate it.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Thanks, Mike.

Operator

One moment for our next question. Our next question comes from Eun Yang with Jefferies. Your line is open.

Eun Yang ***Jefferies - Analyst***

Thank you. So in the study 28 days and you are following up to five months post the completion of the dosage. So why five months? Isn't on like pancreatic beta cells, once they are produced, they have a very long longevity as well as a very low turnover? So I want to ask you why five months of follow-up? And if A1C levels continue to be low sort of five months, so how would you determine how often you have to give the drug? So that's number one question.

Second question is on the commercial, the development side, and this is a pretty big trial when you are going into Phase 3. So are you thinking about a partnership opportunity after completing a dose escalation and when you move into Phase 2 and 3? Thank you.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Yes, great questions, Eun. For the first question, on why the five months, and you're right, there's no magic number here. I think when we set the trial for six months, we are thinking of the patients as well as, that allowing the patient finally continue participating in a follow-up. And I could imagine it's arduous to keep them on at Month 7, Month 8, you know, putting notes in your diary.

But, you know, at the end of it, as we observed, the data we're currently observing, longer follow-up makes a ton of sense. And we just don't know what that durability looks like. Beta cells are very long-lived, as we've mentioned before. So longer follow-ups do make good sense.

And then before I pass it on to Steve, for any additional comments, I'll cover the [VB] conversation. I think for us, you know, we have everything right in front of us in terms of executing COVALENT-111. Let's continue generating data with this study, and then understand what's the best optimal path forward would look like for 219 in diabetes.

Steve Morris ***Biomea Fusion - Chief Medical Officer***

The only other thing I'll add to what Tom said, with regard to the follow-up duration, as he mentioned, this was largely keeping in mind the convenience for the patients. We can easily increase the follow-up period. And you know, we'll look as we move forward, once we have completed or near completed that five-month follow-up in all of the individuals, and will indeed extend that, if warranted.

Operator

Thank you. One moment for our next question. Our next question comes from Eric Joseph with JPMorgan. Your line is open.

Eric joseph ***JPMorgan - Analyst***

Hi, good morning, guys. Thanks for taking the questions and congrats on these pretty compelling initial results. It's clearly having an impact on A1C here, and we'll learn more about other measures maybe that relate to beta cell function. But I'm just curious to know whether you've also looked at menin modulations at all, perhaps looking at sort of surrogate PBMCs, just as a way of sort of corroborating whether there's need to dose escalate.

Secondly, just given the interest in the duration of impact, particularly off treatment, can you, please, talk about when the earliest opportunity might be to look at that? That's something you can do in parallel with additional dose escalation. And then I'm also curious about whether there are any stopping rules as it relates to A1C lowering, is there a lower bound sort of threshold that you want to avoid, given that you might see further declines with longer time on drug? Thanks.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Thank you. Great question. I'll take the last one first, before I hand it over to Steve. We don't have any stopping criteria yet because we just have the full week or 28-day continuous dosing period. An expansion phase, ideally, would look at longer periods. That would be the goal for us to say, okay, what about six? What about eight?

But the interesting mechanism of action here is that BMF-219 proliferates beta cells only under hyperglycemia. So as patients fall into normal glucose range, based on our preclinical work, we don't anticipate further reduction. And that's why we haven't observed any hypoglycemia in our study. Steve?

Steve Morris ***Biomea Fusion - Chief Medical Officer***

Thanks, Tom. With regard to menin levels, indeed, we are examining those. Again, we are not at the point to discuss that, but we'll be reporting the results of those studies in an upcoming meeting.

With regard to your question concerning duration of impact and the ability to assess that, essentially, in real time as we move forward, indeed, as we complete each dose level cohort, we will be following for each one of those cohorts during that five-month period. So we'll get ongoing assessment at each dose level in real time as to the durability of glycemic control.

Eric joseph ***JPMorgan - Analyst***

Yes. Thanks. I guess sort of my question is really related to durability of effects off treatment. I guess are those assessments built into the protocol? Is it really sort of after the five-month period where we can begin to kind of see durable off-treatment effect on A1C?

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

It is absolutely, Eric. So what we built in during the follow-up period is monthly OGTT and continuous glucose monitoring so that we can do just that. We'll be able to see how the patients perform from a glucose perspective, but also from a functioning pool perspective with OGTT. We'll do that monthly with all patients, even off-treatment.

Eric joseph ***JPMorgan - Analyst***

Okay, great.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Yes.

Eric joseph ***JPMorgan - Analyst***

Okay. Okay, good. Thanks for clarifying. I appreciate it. Thanks for taking the questions.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Yes. Thank you.

Operator

Ladies and gentlemen, we're past our one-hour time block for the conference call today. So that does conclude the Q&A portion. I will now turn the call back over to Tom Butler for any closing remarks.

Thomas Butler ***Biomea Fusion - Chief Executive Officer, Chairman of the Board, Co-Founder***

Thank you, everybody, for dialing in. We look forward to providing further updates in the coming future. Goodbye.

Operator

Ladies and gentlemen, that concludes today's presentation. You may now disconnect, and have a wonderful day