Biomea Fusion

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Eric Joseph: Thank you. Good morning. I'm Eric Joseph, senior biotech analyst with J.P. Morgan. Our next presenting company is Biomea Fusion. Presenting on behalf of the company is CEO Tom Butler.

There's a Q&A session after the presentation. Just raise your hand. We'll get a mic over to you. For folks tuning in via the webcast, you can also submit questions via the portal. With that, Tom, thanks for joining us.

Tom Butler: Thank you very much, Eric. Good morning, everybody. Exciting to be here and kick off the 2024 year at the J.P. Morgan conference. I'll be making forward-looking statements during this presentation, so please note.

Our mission, we aim to cure, is at the center of everything we do at the company. We believe that our approach may lead to significant improvement and extension of life for our patients. That's really the driving force behind our efforts.

We had a very successful 2023, really reading out the first clinical data in both oncology and diabetes for BMF-219 and really putting together and working hard to set the pieces for large data set readouts in 2024. We believe to be a very successful year again.

The success is really coming from what is listed here. We have a very experienced management team. We have the novel FUSION System, our platform. We have a Phase 2 clinical-stage molecule, BMF-219, advancing.

We also have a Phase 1 clinical stage compound, BMF-500, which is also advancing well. We think the development of combination assets is really where we can reach paradigm shift.

Our team has had success, but also a lot of experience working together. It really goes hand in hand. The majority of the C-suite here has worked together for over 10 years.

We believe, with covalent chemistry, validated targets and proprietary combination set the path for long-term patient benefit. It starts with covalency. Biomea Fusion is a biopharmaceutical company focused on the discovery and development of novel covalent small molecules.

The power of covalency is illustrated here. Ramses and I actually made this chart while at Pharmacyclics. What it's highlighting here is the potential of the PD effect outlasting the PK effect and really delivering this incredible outcome.

What the green line represents is the ability to achieve occupancy of your target. In this case, it's BTK and ibrutinib. That occupancy is maintained despite only needing a few hours of exposure during a 24-hour period. That difference between the green line and blue line is patient benefit.

The benefits here, on the right-hand side, is highlighting high selectivity, specificity to your target, deep target and activation through covalent bond formation, and a greater therapeutic window because the patient doesn't need to have a certain concentration during a 24-hour period.

Our FUSION System, our platform, is what allows us to discover and develop these novel small molecules. We create all of our programs in-house. It starts with a novel target selection process, crystal structure-based drug design, and proprietary scaffold construction.

We do not use compound library screening techniques. We do custom scaffold construction to the target of interest. What that does for you is provide incredibly strong intellectual property. We spend the majority of our time, not needing to optimize specificity or selectivity to the target, but optimizing the ADME properties.

What we do is look at human genome-wide covalent pocket analysis and really understanding your target, like menin, can have multiple cysteines. Menin, as an example, has six cysteines, but you only want to target one of them. Only one of them is important.

You have to understand what is the location of the cysteine, what is the right distance to the cysteine that you need to achieve with your warhead that's on your small molecule to achieve covalent bond formation, and what is the right angle to make sure you ensure covalent bond formation. These are really key components of building this highly specific, targeted molecule.

Our platform has produced this robust pipeline. The pipeline is continuing to expand. With BMF-219, because of the broad potential of menin as a target, we have four clinical trials. COVALENT-101 and 102 is focused on liquid tumor and solid tumor development. COVALENT-111 and 112 is

focused on type 2 diabetes and type 1 diabetes.

BMF-500, our FLT3 covalent inhibitor, is focused on acute leukemia. We have a third program that we expect to announce this year, in 2024.

Some of the upcoming milestones I'm highlighting here. In type 2 diabetes, we'll be at ATTD in the first quarter. Starting in the second week of March, we'll be announcing the completion of our dose escalation.

In 2024, we'll be announcing initial proof of concept in type 1. With solid and liquid tumors, we'll be completing the dose escalation and determining the recommended Phase 2 dose. For COVALENT-103, we'll also be completing the dose escalation and determining the recommended Phase 2 dose in 2024.

At the end of August last year, we hired a new CMO, Dr. Juan Pablo Frias. This was at the cusp of delivering the first clinical data set with BMF-219 in diabetes. As we were building out the company and increasing our internal expertise in diabetes, Juan, we thought, was an incredible cornerstone for this effort.

Juan has served as principal investigator on over 250 clinical trials with diabetes. Over half of these studies were Phase 3. He's been part of clinical development of more than 20 approved diabetic agents.

Diabetes continues to be a significant unmet need. It's the biggest epidemic of the 21st century. Two in five Americans will develop diabetes during their lifetime. What's astounding is that in 2022, the US spent over $400 billion to handle diabetes. Clearly, we have a lot of work to do.

Even though the number of approved agents and the number of innovation that continues to be seen in diabetes -- we continue to get newer SGLT2s, newer GLP-1s -- what we're highlighting here is that the number of patients with diabetes relying on insulin continues to rise.

Starting from the top, you see that those who are becoming diagnosed with diabetes, the number of patients depending on insulin, continues to rise at a similar rate. The percentage of patients who are controlled has not changed in the last 18 years.

It's because we're not addressing the root cause, which is the depleting pool of beta cells. We think BMF-219, as a novel mechanism of action, can start to change the paradigm here.

With 219, we have a unique value proposition of focusing on beta cell health. It's a first-in-class potential with a differentiated profile. We think having an oral small molecule that's complementary to an SGLT2, complementary to a GLP-1 and other treatment options...

Non-chronic dosing, meaning we think this is a short-term treatment regimen for patients. Disease-modifying, so that patients are no longer living with diabetes. They're done with diabetes. We think the addressable market may include all diabetic patients, because both type 1 and type 2 patients suffer from beta cell loss.

Beta cells do indeed proliferate. They've been shown to proliferate in obesity, as well as pregnancy. There are also several very strong literature support, decades ago, showing that menin controls beta cell proliferation and beta cell mass.

This is a very important diagram to understand and beta cell compensation in physiological and pathophysiological states. What we're highlighting here is both beta cell mass, beta cell replication, and beta cell size. Some of these parameters are very important to learn.

As you age from neonate, child, adolescent to adult, what you see in the normal condition is that you really establish your beta cell pool by the adolescent stage. It stays steady well into adulthood, and with a slow decline as you age.

During pregnancy and obesity, you see an increase in beta cell mass, in replication, and beta cell size. It's important to note that the majority of people who are obese do not develop diabetes. It's only the minority. The minority that develop diabetes are those that have a decrease in beta cell mass and beta cell replication. They're not able to keep up with the continued demand in insulin.

With BMF-219 focusing on beta cell proliferation as the core mechanism of action, we believe, if we can selectively increase the beta cell mass, we can restore insulin secretion and overcome the insulin resistance and the beta cell workload that's been subjected for the patient.

Some of the important work that we did from a translational perspective was focused on the human islet work and looking at how 219 elicits beta cell proliferation.

What's important to note -- this is something that we highlighted at the World Congress in December last year -- is that 219's proliferation is glucose-controlled, meaning under standard glucose or normal glucose conditions, there is no proliferation exhibited by BMF-219. It's only

under stimulated glucose.

It's important to note that the time and the concentration matters in the level of proliferation that's exhibited. Understanding the dynamics of dosing a patient for 4 weeks, 8 weeks, and 12 weeks is also critical. What we didn't show at the World Congress but is also important is that we only see beta cell proliferation. We don't see proliferation of other cellular components within the islet.

We've seen with our preclinical work, both in vitro, ex vivo, and in vivo, that BMF-219 shows preservation, reactivation, and regeneration of beta cells. What's important to note is that all of these components are important for a healthy islet.

BMF-219 is a potential first-in-class diabetic agent addressing, again, the root cause of disease.

On the left-hand side, what we're highlighting here is the different agents that are currently approved and how they're aimed at treating the symptoms of diabetes and really trying to go after the hyperglycemia, whether you increase the kidney flow rate, whether you suppress your appetite as well as increase insulin secretion from the existing pool.

What we're trying to do with 219 is get the pool back and rewind the clock on the disease.

Here's a little bit on the study design for COVALENT-111. Keep in mind, with COVALENT-111, we're enrolling type 2 patients that are currently failing their standard of care. The standard of care that they can be on is any combination of metformin monotherapy. They can be on an SGLT2. They can be on a GLP-1, a DPP-4, and any combination, up to three anti-diabetic medications.

The dose escalation, or Part 1, on the left-hand side, features four weeks of dosing with 219, followed by 12 weeks of follow-up. In the healthy volunteers, we had 16 patients. We have 50 mg, 100 mg, with and without food. We have 200 mg QD, as well as 200 mg for QD for two weeks followed by 400 mg for two weeks.

This allows us to really understand the dynamics. We really created an all-comers dose escalation trial so we can understand the four corners of how BMF-219 works. The important thing to note is that four weeks is intended to help us in a dose selection.

The important component becomes now the dose expansion phase, the Part 2, where we're treating patients up to 12 weeks. We have four cohorts designed for the expansion phase.

The first three are listed here, arm A, arm B, and arm C, where we're treating patients for 100 mg for 8 weeks, 100 mg for 12 weeks. The third is 100 mg for eight weeks, followed by 200 mg for four weeks. These are all QD dosing.

Back to the islet data that I just showed, you can see that everyone has a different proliferation and background rate. We want to understand how do we convert those who need just 4 weeks compared to 8 weeks and compared to 12 weeks.

Some of the baseline characteristics and demographics are highlighted here. You can see that with age 52 and the 100 mg without-food, 51 and 100 mg with-food cohort. The placebo is 46 years old.

We're highlighting here the sex, the duration of diabetes, varied between the with- and without-food. Without-food was four years on average, with diabetes. With-food was 8.7. Placebo had a similar 4.2. The baseline characteristics of A1C was fairly similar. The majority of patients on the without-food cohort were on just metformin alone.

The glycemic results that we highlighted here at week 26, keep in mind, these are patients who took therapy for only four weeks. Now we're following them five months off treatment to see how the durability in the response and the durability of this new pool has realized.

What you can see here, the mean change in A1C for those taking 100 mg without food was -.5 percent and a placebo-adjusted mean of -.8 percent. 20 percent of patients in both cohorts had at least a one percent reduction maintained at week 26. Great proof of concept here.

Looking at the placebo, it's a positive .3 percent. It's important for folks to know that on the placebo arm is really what's happening in the real world, that despite the start of a new anti-diabetic medication or despite being on standard of care, your A1C is going to increase over time because the pool continues to deplete. The pool, again, continues to deplete at about five percent a year.

Here's our exposure and PD effect. The AUC is really what we use to guide our drug development and really is the key exposure for a covalent inhibitor. The 100 mg without food had an AUC of about 224. The 100 mg with food had about a third of that.

What's nice to see is you see this nice dose response with the without-food had a .5 percent

reduction at week 26. The with-food had a .1 percent increase on average. The placebo had .3 percent increase. These are all at week 26.

Also pointing out, you see the variability is high between each cohort. Again, the variability is high, as I mentioned before, as everyone has a different background proliferation rate.

Since we're only treating for 4 weeks, we want to understand who are the patients, what are their baseline characteristics in driving long-term durability with just 4 weeks of treatment, and then how do we catch the remainder of those patients when we dose for 8 and 12 weeks.

Our patients who responded with just 100 mg had a tremendous increase in HOMA-beta and also had a tremendous increase in C-peptide AUC.

What's important to note is that we're looking at a baseline characteristic of a HOMA-beta below 200. 200 really represents the upper limit of normal. We're focusing on patients who are "beta cell-deficient" and who would have a chance to actually have an increase in their pool and respond because of it.

On the right-hand side, the change in C-peptide AUC, as a reminder, this is during the conduct of an OGTT experiment. This is a controlled experiment where every patient has the same amount of glucose that they take. Now we're seeing how their new pool responds to this glucose over time. This is the week 26 time point.

Want to highlight a case study. This was a 29-year-old man with a four-year history of type 2 diabetes. This patient was on metformin and an SGLT2. They had been on this therapy for several years. They came onto our trial with a hemoglobin A1C of 9.5.

Again, this is normal course of business for diabetes. Again, it doesn't matter if you're on an SGLT2 or metformin or a GLP-1. Your A1C, again, is going to continue to rise. This patient was at 9.5 coming into our study. If you look at their CGM, they had a time-in-range of about 30 percent, when guidelines and ADA treatment guidelines are suggesting you need to be 70 percent-plus.

When you look at the change in A1C within the first four weeks, it's a very robust change of about .6 percent reduction, but you can see the reduction continues while off treatment. What we're looking for when we're studying these patients is how long does the pool take to mature. Everyone has a different maturation process. We know that maturation can take up to 12-plus months.

It'll be interesting to see, in our expansion phase, how patients now followed up to week 52 perform over time. An important component is that you cannot proliferate and produce insulin at the same time for a beta cell. Once they're finished proliferating, they have to go through a maturation state in order to produce insulin again.

What you can see is just within 12 weeks of the study, this patient went from about 30 percent time-in-range to almost 80 percent and now is, at week 21, which was the last time point for this patient, in 90-plus percent time-in-range.

You can see their HOMA-beta increase dramatically, 190 percent increase from baseline to week 26. Their C-peptide production during the OGT experiment increased 71 percent.

Our accomplishments in 2023 were quite broad. Just highlighting here what we achieved with COVALENT-111, these are patients, again, failing standard of care on a number of agents. 84 percent of patients responded to 219 while on treatment, which gives you a really good understanding of the importance of menin inhibition in diabetes.

74 percent of patients continued to respond while off treatment at week 12. 20 percent of patients achieved at least a 1 percent reduction with 100 mg, five months off treatment. 36 percent of patients had at least a 1 percent reduction five months off treatment when they took 200 mg.

The expansion phase had initiated towards the end of last year and currently enrolling and exploring the 8 and 12 weeks of dosing.

COVALENT-112, type 1 diabetes. Because of what we're showing with beta cell proliferation increasing the capacity and the function of the pool, we think 219 can be a great agent for type 1 diabetes. We had the IND and CTA cleared from FDA and Health Canada.

Then in oncology, with COVALENT-101, relapsed/refractory acute leukemia, we had initial Phase 1 topline data with first complete responses and including MRD-negativity. With COVALENT-103, which is also in relapsed/refractory acute leukemia, we had the IND for BMF-500 accepted. Our first patient enrolled in the study.

Then with the FUSION System, we built out an expansion to our lab facilities to expand our in-house capabilities and then also continued development of the FUSION platform technology.

For 2024, a ton of excitement coming for our anticipated milestones.

For COVALENT-111, it's to complete the dose escalation, transition to the expansion cohorts and fully enroll them, as well as open up 112, which we announced on Monday, for FPI, and get the open-label cohorts, which is an N of 40, fully enrolled this year, and establish initial proof of concept in this indication for type 1 diabetes.

For oncology, for liquid tumors, dose escalation completed and recommended Phase 2 dose established is our goal. For COVALENT-102, it's the same. Also, for BMF-500, we think we can complete the dose escalation and also determine the recommended Phase 2 dose established.

Again, for us internally, we're really excited about the 219 and BMF-500 combination for acute leukemia. Lastly, we expect to announce our third pipeline asset from the FUSION platform technology this year.

Our development plan, the next four years for BMF-219 in diabetes. Of course, this is success-based and predicated on the success of our expansion. Based on recent FDA feedback we received, we think that we're in the driver's seat for accelerated path for 219 in type 2 diabetes.

We expect the expansion phase to complete in 2024 with proof of concept established again in type 1 diabetes. We expect to initiate two pivotal studies in 2025 for type 1 diabetes and for type 2 diabetes. That puts us on path for our first NDA filing in 2026 and for type 2 diabetes in 2027.

Here's a snapshot of our financials as of Q3. We ended Q3 with $200 million on our balance sheet with a burn of $25 million.

We'd expect that burn to stay pretty consistent and really be great stewards of our cash spend and really understand, out of all the indications that we're pursuing with 219, where do we see that breakthrough-type data and then focus on those indications that are generating the breakthrough-type data. Thank you very much. I'll open it now to questions.

Eric: I'll ask the first question that's submitted via the portal here. It really is one around mechanism of action and distinguishing how 219 is promoting beta cell function, truly trying to decipher between replication or just stimulated function.

Can you talk a little bit more about how you are interrogating that preclinically and the evidence supporting perhaps real repopulation or replication of cells within beta islets?

Tom: It's a great question, Eric. We really spent a lot of time and effort working in vivo in animals to understand that 219 resulted in an increase in not only the number of islets but also the size of the islets to drive responses in our preclinical studies.

The important component was in transitioning to human tissue and looking at the human islet work. The human islet work is quite extensive and looks at not only the impact from a cellular component perspective, looking at how beta cells are replicating versus non-beta cells, but then what is the functional impact of that effect on insulin content.

In the clinical trial, you can't measure beta cell proliferation, but you don't need to. What you need to show, really the proof in the pudding, is that patients have an effect that's from a novel mechanism of action and that the effect is long-lasting.

Eric: Maybe just a couple of questions related to Part 2 of COVALENT-101. This is the multi-arm dose-expansion phase of the trial. From Part 1, it seems like there was a food effect for some of the dose cohorts. In one case, that may seem to have limited exposure with 219. On the other side, may have contributed perhaps to tolerability or may have been confounded by tolerability issues.

How are you managing or further interrogating the food effect property [laughs] interaction of 111 in the expansion cohorts?

Tom: It's a great question. The food effect that we saw preclinically and in our healthy volunteer study is that if you dose 219 with food, you get a positive effect. You get an increase in exposure.

What surprised us was the 100 mg, where you saw a reduction in exposure. We think that is just a nuance of having a small N in the cohort and having a few patients who had very little exposure.

We would anticipate, if you were to continue enrolling in that cohort, that the 100 with food would actually end up with a higher exposure average. When we transitioned to 200 mg with and without food, the with-food resulted in an increase in exposure, as predicted from our healthy volunteer study and from our preclinical work. It's not a tremendous increase. It's an increase of 50-plus percent.

What we ran into from a tolerability perspective with the 200 mg with food, we think we probably

should have finished that cohort. Maybe the nuances that we saw was patient-specific.

What we're doing as we continue our development with 219 is you don't need to take 219 with food to get the exposure you need for the efficacy we want. What we want to do is basically tighten up the dosing instructions.

Right now, we have it where you just take 219 two hours after a meal. We'll try to tighten it up so it's one hour or even 30 minutes after a meal. It's just a very clean dosing instruction.

Eric: You've offered some broad eligibility criteria, the study being open to patients that are on compound treatment, standard of care. Given the fact that you might see a fair amount of variation in that population coming into trial, how are you...

Can you just talk a little bit about the ideal treatment background and also severity of disease that you're hoping to enroll in the expansion cohort in the trial, appreciating that you probably want to get some consistency across the patient population in different study arms?

Tom: That's right. The escalation phase, just as a reminder, is really an all-comer. Years since diagnosis is to 15. We don't limit the number of anti-diabetic medications up to three. Beyond three, we limit.

What I want to point you is on slide 16. If you look at the graph in the center, the beta cell replication, as you age, especially for a type 2 diabetic, your beta cell replication rate goes down. Age can be an important prediction.

It's no surprise, when I showed the case study of the 29-year-old with 200 mg, this patient only needed four weeks to have such a dramatic effect. It makes sense. They're 29.

When we look at transitioning to 8 and 12 weeks in the expansion phase, what we're looking to do is capture those who have a little bit lower proliferation rate, that didn't have the strong response that this individual had in the escalation phase.

To your point, what we're doing in the expansion phase is limiting years since diagnosis to seven years or less. Then 75 percent of patients will be on metformin alone.

We still want to understand the other combination partners of SGLT2 and GLP-1. We still want to understand the 100 mg dose effect for longer periods of time in those patients. We've really

reserved the fourth cohort in the expansion phase to study patients who are on multiple agents, who are later in their disease course, more than seven years.

Eric: I wonder whether baseline C-peptide level might be an entry criteria to some extent. You're controlling for that or keeping it within a certain range by limiting time since diagnosis within seven years. Obviously, background treatments might also create some uniformity along that dimension. Specifically on C-peptide, is that an entry criteria that you're monitoring for?

Tom: Not for type 2. Certainly for type 1. The type 1 experience will give us a lot of data for how we can guide for type 2. Going back to this chart that shows how many folks are on insulin with diabetes, the majority of these folks are type 2. We do want to understand what are those limits in C-peptide capacity in order to respond to 219.

For us, we don't have any guardrails in terms of HOMA-beta and C-peptide because we still don't know what those bands are. As we complete the expansion phase, we hope to know a lot more. We don't want to get caught up too much in what we see from a trend perspective with 4 weeks of dosing because it can be completely broadened when we transition to 12 weeks.

Eric: That's probably a good point to segue to type 1. Just stepping back, just having generated data in type 2, a broad question is the extent to which the data that you've generated today to four weeks derisks...How does that inform or provide confidence that you'll be able to see a similar effect on C-peptide and ultimately A1C? Really, C-peptide in the type 1 population.

Tom: It's a great question. It really comes from what we're seeing in improvement in beta cell functions. We can't comment on how the patient's beta cell pool has expanded or not, but we can say that their function has increased dramatically. We see that it's correlating well or highlighting that it's coming with a dramatic increase in C-peptide AUC.

That's where we get the confidence of transitioning into type 1, is seeing that our patients are getting an increase in C-peptide production with 219. Then also, if you look at, as an example, patients that continue to benefit while on treatment and show that the expansion of the HOMA-beta or the HOMA pool is leading to an increase in glucose control.

Eric: From a dosing standpoint in type 1, can you just talk about the doses that you're going to be leading with, how they compare with the type 2 experience?

Tom: For type 1, we start with two open-label cohorts of 20 patients each. They'll be receiving

100 mg and 200 mg for 12 weeks.

[pause]

Tom: Back to your point too around type 1 and how do you know based on what you're seeing with type 2, how does that give you confidence with the type 2 study, we know that in the honeymoon phase, which is approximately the first three years since diagnosis with type 1, your beta cell proliferation capacity is about tenfold that of a type 2.

If we're getting really strong, durable results in our type 2 patients, it should be easier to see with type 1, especially in that honeymoon phase. What I would also say is, typically a type 1 doesn't have a lot of insulin resistance and other metabolic issues within the islet that may limit the impact of a new set of beta cells.

Because you're starting with such a small pool, our scientific advisory board members, like Rohit, will remind us that you only need to increase the pool by a few percentage points in a type 1 to have dramatic increase in glycemic control. For a type 2, you need to increase the percentage by much more because you're trying to overcome additional metabolic problems.

Eric: Maybe just talk a little bit about the profile of the type 1 patient coming into the 112 study, in terms of are they in that honeymoon phase, having transmission through it. Maybe perhaps you want representation from both populations a little bit to see the breadth of activity.

Tom: That's right. Great question. The open-label component are two cohorts. One cohort is zero to three years, in the honeymoon. Then the second cohort is beyond, so 3 to 15 years.

We know that there are type 1 patients who still have C-peptide production, who still have islets, even though they've had type 1 diabetes for a very long time. We think that there's potential to proliferate those existing or remaining islets to restore their insulin production capacity.

Eric: Particularly in the older or longer-time-since-diagnosis population, how do you remove the...Never mind. Silly question. You can just look at C-peptide. I was going to ask you about how you control for a confounding factor with exogenous insulin. Basic question.

Maybe just on the oncology side, in the time we have left, maybe can you set the stage for what to anticipate in terms of further readouts this year? What would be compelling signals, both on the heme malignancy side but also in solid tumors, that would warrant advancing the program

forward there?

Tom: Great question. Maybe I'll start with COVALENT-101, our study in liquid tumors. We see that as we determine the recommended Phase 2 dose, the next step would be then to sort what combination therapies we want to get into.

From a competitive perspective and also to generate really exciting data is really supported by the development of BMF-500, our covalent FLT3 inhibitor. Doing those novel/novel combinations, doing the ven/aza combinations, would be the next steps.

2024 is very much centered around, let's complete the dose escalation. Let's determine the recommended Phase 2 dose and then start to plan those combination efforts. It goes back to our philosophy is you need multiple agents at one time when you're trying to handle such a heterogeneous, aggressive cancer like acute leukemia.

Typically, one agent alone cannot address it for a very long time. That's why you see all of the menin inhibitor development programs shifting to that combination effort, is to drive patient benefit.

Eric: Are there any questions from the floor? If not, we'll leave it there for time. Thanks very much, Tom.

Tom: Thank you, guys.
