Company Name: Biomea Fusion (BMEA)
Event: 6th Annual Evercore ISI HealthCONx Conference
Date: November 30, 2023

<<Analyst, Evercore ISI>>

Good morning, ladies and gentlemen. Very privileged to have the management team from Biomea Fusion at our conference. Welcome, gentlemen. Thank you so much for making time to fly down here to Sunny Miami to be with us.

But before we dive into specifics, perhaps you could give an overview for folks who may be new to the story as well as what we should be focused and excited about heading into 2024.

<<Thomas Butler, Chief Executive Officer>>

Yeah, absolutely. No, thank you so much. It's a pleasure to be here. Biomea Fusion is a biopharmaceutical company focused on the discovery and development of novel covalent inhibitors. And for those who are not familiar with covalent inhibitors, those are small molecules that look for a key amino acid inside the target, whether it be a kinase or a scaffold protein like menin. And we form a permanent covalent bond to the target that allows us to get dramatic control from a PD effect perspective, but keep the patient with very low exposure, if any at all, during the majority of the day.

And we think that efficacy to safety potential can really give you significant advantage long term, especially in the context of oncology when you have to stay on therapy on a very high exposure long term if you're a reversible inhibitor. And so the covalent inhibitor can really lead to an improved overall safety and efficacy profile. And our first asset is BMF-219. It's a covalent menin inhibitor. We have also a second molecule in the clinic, BMF-500, that is a covalent FLT3 inhibitor for acute leukemia.

And what I'd like to do first is just introduce you to our new CMO, Dr. Juan Pablo Frías. We announced his joining of the company a few months ago and it really represents our interest in, obviously the data that 219 is generating in diabetes as breakthrough potential type data. Juan?

<<Juan Pablo Frías, Chief Medical Officer>>

Yeah, no, thank you. Pleasure to be here, really appreciate it. And I'll just say a couple of words if you don't mind, but I'm a practicing endocrinologist. Over the last 15 years, I'm doing a lot of clinical research, very involved in the semaglutide, dulaglutide, tirzepatide, retatrutide programs, published a lot. But what I've seen over the span of my career, which actually started in 1989, was just an explosion of medications for Type 2 diabetes and combinational therapies. And despite this, really not being able to get most of our patients in the U.S. under good glycemic control, and at the end of the day, it's because we don't have agents that act at the core defect of Type 2 diabetes, which is dysfunctional beta cells of the pancreas that don't allow sufficient insulin secretion.

So BMF-219, actually, as we'll discuss, acts at that point in Type 2 diabetes to regenerate and proliferate beta cells, increase insulin secretion. So I think it's going to be very key therapy either on its own or combinational therapy with agents that we have today to help more patients get under good control.

<<Analyst, Evercore ISI>>

Excellent. Excellent. Still kind of high level. Why target menin in the first place? And why go to the route of a covalent inhibitor rather than a reversal inhibitor? Because, you know, sometimes covalent inhibitors could be a double edged sword in terms of a trade-off between safety and efficacy. But why covalent? And why menin?

<<Thomas Butler, Chief Executive Officer>>

Yeah, great question. And actually, we started with a reversible inhibitor program we inherited back in late 2017. And we were approached by a computational chemistry company that just came to us, myself and [indiscernible] (0:03:44) chemistry help. We were kind of minding our own business coming off of the heels of the Pharmacyclics AbbVie transaction having been totally wiped out from that experience. We set up an innovation fund to continue being involved in novel mechanism of actions that have shown initial proof-of-concept clinically and that's we would start doing our due diligence and investing in supporting that new therapy.

We got a knock on the door one day and a gentleman from Boston said, hey, we need your chemistry help. We've designed a virtual library of reversible menin inhibitors. At the time, we had no idea what menin was. We had to learn that menin has no function on its own, but it serves as a very important scaffold protein to form complexes at the epigenetic level. And as we were figuring out the chemistry for these virtually designed reversible inhibitors.

We learned that menin is involved in multiple binding partners, not just MLL. MLL is one of many, and even within MLL, there's over 100 different flavors. So you can imagine that you have over 100 different magnetic strengths that I need to break apart as a reversible inhibitor. And you are able to, "break it apart by driving exposure". And so we thought it would be very difficult to predict in the clinic. What dose or what exposure does this patient need if they have an MLLr translocation, it's very difficult to profile their fusion partner ahead of time.

And you don't want to intrapatient dose escalate every patient. That would be very difficult also to do in the commercial setting. So we thought, how can I become independent of the binding partner? How can I just focus on menin it? And we started to build very large, small molecules that could kind of wedge itself in there's a very large pocket that MLL engages in. That seemed to work okay. And then we learned during one of our crystal structure sessions that there's actually a very important cysteine in the key pocket. And we really scratched the original designs. We started from scratch designing covalent inhibitors. And the key here is that you have to look at what's the right angle to the cysteine and what's the right distance to the cysteine to get efficient bond formation.

And as soon as we started to get even just the first generation covalent inhibitors, you could see that we had the same potency independent of the fusion partner. So we knew that we were solving that problem. It just turned out that by going covalent and we were solving the problem for acute leukemia, that opened up the door to all these different oncology indications and opened up the door to diabetes.

<<Analyst, Evercore ISI>>

So that's pretty much a way to kind of become a fusion part diagnostic type of modality interesting so. Also too, just through my research, I mean I know that 219 inhibits menin, but only works on a reduced beta pool in a hyperglycemic state. Maybe, perhaps give us some color on what makes this such a "smart adaptive molecule" like, why wouldn't 219 just continue to make beta cells?

<<Thomas Butler, Chief Executive Officer>>

Yeah, it's a great question. And we have to go back to how do beta cells proliferate in the background without any therapy? And what happens in the case of prediabetes obesity, prediabetes and diabetes is that over time, the pool that you're born with stops growing. And this stops growing in your adolescent years. Once the pool is set, that's the pool that you have for the rest of your life. And beta cells have a very long half life on the order of 15 plus years. So that's why the pool is kind of set at that age.

Now, as you go through your lifestyle, you put more and more pressure on the pool. Obesity certainly accelerates the exhaustion and workload on beta cells, and the beta cell pool starts to decline over time. When you get diagnosed with Type 2, you've already lost half of your pool. When you get diagnosed with Type 1, you've lost 90%. And so we as individuals, we have the ability to grow your pool of beta cells. Obese people actually grow their pool by 20% to 50%, and it's because the blood sugar is slowly elevating over time and beta cell proliferation is glucose controlled.

And so what we've learned is with 219 and we're going to be highlighting this and we'll get to this a little bit later, but we'll be highlighting all of the key work that we did from a discovery and development in diabetes with 219 at World Congress next week. And so we'll be describing all the human eyelet work that we did, all the in vivo work that we did. And what we found out is that 219 proliferates beta cells within the eyelid, but only proliferates when there's hyperglycemia, when there's glucose trigger, which is the natural state. And we only proliferate beta cells, no other cells in the eyelid, which I think is extremely exciting.

<<Juan Pablo Frías, Chief Medical Officer>>

Yeah, I think if I could add from a clinical perspective, that becomes extremely important, because you don't want to have too many beta cells and too much insulin obviously causing hypoglycemia. So having this glucose dependency when it's used either on its own as monotherapy or in combination with agents that do not cause hypoglycemia, SGLT2 inhibitors, GLP1 receptor agonist, we don't see any hypo.

<<Analyst, Evercore ISI>>

Got it. Great. So maybe digging down more into the data you presented ADA, it was 100 milligrams with food, without food. And as you alluded to next week at WCIRDC, we could expect additional doses from this escalation phase, correct?

<<Thomas Butler, Chief Executive Officer>>

That's correct.

<<Analyst, Evercore ISI>>

Okay. Could we expect the data for these other doses that will generally be presented in the same format as it was at ADA?

<<Thomas Butler, Chief Executive Officer>>

Well, actually at World Congress, what we'll be presenting is still the 100 with and without food. But now out to week 26, what was presented at ADA was to week 12. We'll have a high level of other cohorts in a press release, but that will be a four weeks. And then at a meeting, subsequent meeting, first quarter next year, which is ATTD in Florence, there we'll present some of the 200 milligram data and potentially some other data as well in those cohorts.

<<Analyst, Evercore ISI>>

Okay, so this is the escalation part, but you've already begun the expansion part of the study? When can we expect data for that?

<<Juan Pablo Frías, Chief Medical Officer>>

We're starting to enroll that now. So we're enrolling and what this is actually eight and then 12 weeks of treatment with 40 weeks of follow up. So it'll be a full 52 weeks of follow up. But that's enrolling at this point it's not fully enrolled.

<<Analyst, Evercore ISI>>

Okay.

<<Thomas Butler, Chief Executive Officer>>

Yeah. And I would just add when we look at week 26 data, when you discontinue an antidiabetic medication, typically your weight comes back and your A1c comes back to baseline. We're enrolling patients that are uncontrolled on current standard of care. So they're taking either metformin alone or they're on an SGLT2 or a GLP-1 or all three. And 219 is going on top of these patients. And what's happening is that the pool keeps declining whether or not you start an

antidiabetic medication and it declines by 5% a year. And so what's happening is that their A1c levels are continuing to increase on a slope.

And what we're trying to see with 219 is can we get that slope to actually stop? Can we halt the progression of the disease, actually what if we see a decline in the slope? What if we can actually reverse the progression? And that's what we're trying to capture at these various dose levels in the escalation.

<<Analyst, Evercore ISI>>

Just dovetailing on what you just said. Does it become a critical time point when you reach a kind of a critical mass threshold of beta cells at which 219 doesn't work?

<<Thomas Butler, Chief Executive Officer>>

Yeah, certainly we think as the beta cells come online and produce insulin, they're going to start getting into normal glycemic control and at that point the beta cell proliferation would stop. The beta cell proliferation only occurs when you have 219 on board and you have hyperglycemia.

<<Thomas Butler, Chief Executive Officer>>

Yeah. But also to your point, that is a patient potentially too far out in the natural history of their disease where they've lost too many beta cells to have recovery withdrawal? Probably not I mean and that's the reason we're looking at eight and 12 weeks of dosing. So increased exposure and we'll have more patients. We feel in the expansion cohorts, there are further along on two, maybe three oral agents and still not achieving control. So the thinking is that we would, but maybe at the higher dose and longer exposure.

<<Analyst, Evercore ISI>>

Got it. So just we just zero in on the cohort free data from ADA. This trial enrolled a heterogeneous group of Type 2 diabetes in terms of time since diagnosis and presumably beta cell mass reserve. In fact, the baseline characteristics show that patients reign from like six months to nine years since diagnosis. So when we consider how the treatment effect persisted from week four to week 12, could that have been driven by the small subset of patients who happened to have a high beta cell reserve?

<<Thomas Butler, Chief Executive Officer>>

Yeah, I think certainly if we look at the 100 milligram, we know that we had such a great result from an efficacy perspective. And also the safety profile was very strong and supportive. And when we look at that data set and we see 1% reduction within four weeks, that means that the majority of the patients are getting in that near normal range while on treatment from a glycemic control perspective, that is a very impressive A1c reduction in that short period of time.

And certainly those patients, the majority, especially the 100 milligram without food, are in that front line, second line position where they're either on diet and exercise alone or they're on metformin. And certainly as we go to and now so we feel very good about 100 milligrams and 100 milligrams is selected for the expansion phase for those patients who are a little bit earlier in their disease.

Now, as we proceed in the escalation phase, as we go to 200 milligrams and 400 milligrams, what we're looking for is, how do we make sure that we handle those patients, as you mentioned, that have a little bit of a lower pool or they've been stressed on a GLP-1 for many years, and that's what we're trying to achieve.

<<Juan Pablo Frías, Chief Medical Officer>>

But I want to reiterate also what you say the 1% at four weeks is really big. I was a lead author on the Surpass-2 study, which compared tirzepatide to semaglutide, and during the first four weeks we had with tirzepatide, a 0.8% average. I mean, not apples and oranges, but big control study versus 10 patients. But that indicates, like you say, that patients are getting pretty much in the normal range, because the A1c lags behind about two to three months before it.

<<Analyst, Evercore ISI>>

Got it. So it's a similar question for I guess the Cohort 2. I mean how do we tease out the food effect versus beta cell reserve when we think about the fact that Cohort 2 had a significantly muted efficacy?

<<Thomas Butler, Chief Executive Officer>>

Yeah, definitely. What's nice to see is that, that kind of gives you already a sense of dose response, right. That we definitely have a food effect and that the lower dose level food resulted in a lower exposure. And patients who took the drug with food had about a third of the exposure than without food. And those patients also had about a third of the A1c reduction. So it's nice to see that more exposure, three fold more exposure gave you three fold more reduction in A1c.

<<Analyst, Evercore ISI>>

Got it. Got it. In terms of just the C-peptide dynamics during the oral glucose tolerance test, I mean, Cohort 3 data makes sense in that it increases during the treatment phase, peaks during the off treatment period and then decreases. I mean however, Cohort 2 shows an initial decrease followed by a slight increase during the off treatment period, whereas placebo begins to increase during the off treatment period. Like how do we reconcile this?

<<Thomas Butler, Chief Executive Officer>>

Yeah, I think at the end of the day, when you're looking at 10 patients worth of Datum, and obviously we're highlighting with this Cohort 3, those are 10 active patients. They can come in the door with a wide spectrum of HOMO-beta or beta cell function. And I think when you're

trying to match people who come in the door with high beta cell function versus those with low beta cell function, you're trying to find what the mean is telling you. And what I think is probably best for us to highlight and do this in future presentations is maybe make sure we set the baseline for the patient so that you're creating an apples-to-apples perspective.

But certainly for patients who are coming in with a depleted pool with low HOMO-beta, we expect 219 to show an increase in stimulated C-peptide and that to yield durability. And so I think what these charts are showing you is that once you get past the four week treatment period, then you have a variation of long-term durability and that can be a function of did you get enough drug from an exposure perspective? Did you get enough time on treatment? And for those that did, they're the ones who responded as they should.

<<Analyst, Evercore ISI>>

Got it. I could talk for another hour on diabetes, but just last question on diabetes before we kind of shift oncology, I mean, get this question all the time. Assuming this gets approved, where will 219 best fit in the whole treatment paradigm?

<<Thomas Butler, Chief Executive Officer>>

We think one.

<<Juan Pablo Frías, Chief Medical Officer>>

Yeah, I think it'll have a place throughout the paradigm. So I could see this as being a monotherapy at initial diagnosis. Certainly if you're using other medications, whether SGLT-2 inhibitors, GLP-1 receptor agonist for extra glycemic effects, for weight loss, cardiorenal protection, liver protection, these drugs, I mean, they make sense to combine as well. So I think initially we'd like to look early and in combination with maybe one two agents, but ultimately, certainly it'd be important to see even further out patients who are already on basal insulin for example. And I also think at the other extreme, potentially in the future, looking at pre-diabetes as well, particularly those patients who are very close to sort of meeting the diabetes threshold, who have a very high chance of converting to Type 2 diabetes.

<<Analyst, Evercore ISI>>

I see. Okay, a couple of questions on oncology. I mean, I know 219 is also being developed in that field on liquid and solid tumors. Like what's the level of menin dependency among the tumors that you are pursuing?

<<Thomas Butler, Chief Executive Officer>>

Yeah, this was something that we looked at early on when we first wanted to do all the key translational work with a covalent menin inhibitor. And when you look at the DEPMAP portal, DEPMAP portal leverages CRISPR to do knockout of the gene of interest for your target and in this case, it's MEN1. When you knock out MEN1 and you look at cancers that have the most

sensitivity to that knockout, actually acute leukemia ranks number three, which kind of surprised us early on.

DLBCL ranks number one in terms of menin sensitivity, and certainly from a subtype perspective, the majority is sensitive to menin disruption, which got us really excited. Number two on that list is actually multiple myeloma, which we're really excited about. And then, as I mentioned, acute leukemia ranks number three. And that really helped craft COVALENT-101 as we target several blood cancers. We also have COVALENT-102 targeting KRAS mutated, pancreatic colorectal and non-small cell lung cancer.

<<Analyst, Evercore ISI>>

Got it. Got it. For AML back in July. You top line that two out of five patients had two complete responses in the COVALENT-101 trial. One was a CR, the other was a CRI. So for the CRI, when we expect this to convert or not convert into a full complete response.

<<Thomas Butler, Chief Executive Officer>>

Yeah. I think what's interesting is, when these patients come in the door, even though they may have an MLLr, NPM1, they typically come with other mutations and as a menin inhibitor. And what the challenges overall with acute leukemia is that when you're a monotherapy, you can drive down the clones that your target address, but that means the other clones just come up over time. And that's why we have a vision for acute leukemia, where we have our covalent menin inhibitor, but also covalent 3 inhibitor.

So we could do novel-novel combination, I think, with 219. And the data that we'll share at ASH and these complete responses, sometimes the CRI comes from patients who don't have the capacity to restore their bone marrow. Even if you were to clear the cancer because they've seen multiple rounds of chemo and it's very difficult for the stem cells to recover.

<<Analyst, Evercore ISI>>

Got it. In each of the time one last question, if you could briefly touch upon BMF-500, your oral covalent FLT3 inhibitor just brings up the date in terms of what's the latest and greatest in terms of that asset.

<<Thomas Butler, Chief Executive Officer>>

Yeah, I thought it would take a little bit of time for momentum to pick up for that molecule, given that quizartinib was approved and you have gilteritinib. But that's not true. There's a tremendous momentum from the Pi from the site perspective, people are getting really excited about the utility of a covalent FLT3 inhibitor, and that's because we don't expect to have the QTc prolongation issue. We don't expect to have the neutropenia issue so that you can get bone marrow recovery and get those complete responses.

And then, lastly, we can hit those mutations that gilteritinib, quizartinib can't address. And so that study is going extremely well. And then as I mentioned, once we get to a recommended Phase 2 dose, that's when we can start doing those novel-novel combinations with 219.

<<Analyst, Evercore ISI>>

Excellent. Well, gentlemen, unfortunately, we're out of time. But again, thank you so much for taking the time to be with us, and I very look forward to keeping tabs on the story.

<<Thomas Butler, Chief Executive Officer>>

Thank you so much for having me.

<<Juan Pablo Frías, Chief Medical Officer>>

Thank you. I appreciate it.

<<Thomas Butler, Chief Executive Officer>>

Take care.