[BEGINNING OF Biomea Fusion Inc. (BMEA).mp3]

Joe: Great. Thanks so much, everybody, for joining us here, second day of Piper Sandler Annual Healthcare Conference. I'm Joe Catanzaro, one of the Piper biotech analysts. My great honor to start -- kick off this session with Biomea. Joining us is their CEO, Tom Butler. Obviously, Tom, a busy end of the year for you guys. Gonna get a bunch of data over the next few weeks to a month. A lot of things to talk about. I wanna maybe give you a couple minutes just to introduce the company, what you guys have been up to, what we have to look forward to, and then we could jump into Q&A.

Tom: Great. Happy to. Yeah, thank you very much for having us. So Biomea Fusion is a biopharmaceutical company focused on the development of small molecule covalent inhibitors. Our first molecule that we've developed or discovered and developed in-house is BMF-219. It's a covalent menin inhibitor that's in seven indications in a phase I, II study for liquid and solid tumors. So we're looking at acute leukemia, multiple myeloma, DLBCL, and CLL in the blood cancer space, as well as the solid tumor cancer space, KRAS-activated mutated pancreatic, colorectal, and non-small cell lung.

And we also have a diabetes program, which was added earlier last year that's covering type 2 diabetes, and then later this year we announced that we're expanding into type 1 diabetes. And so we're very excited about the potential of 219 in these various indications. And it stems from very novel biology of menin, which is a scaffold protein that forms multiple protein complexes and really acts like a joystick. And that's kind of the best way we describe how menin functions.

And the joystick can be stuck in the off position preventing beta cell proliferation, even though you've lost your beta cells and can't produce enough insulin. Or the joystick is stuck in

the on position in creating uncontrolled cellular growth in white blood cells. And so, all we're doing with 219 is putting the joystick back into the neutral position.

Joe: Perfect. Before we maybe jump into the interesting stuff, I'm wondering if you had any insights into today's stock move and what's driving that pretty meaningful… We've gotten a lot of questions on it, a lot of people speculating. Wonder if you have any thoughts there?

Tom: Yeah, certainly. I think people are starting to get really excited about the data releases that are happening both at World Congress in L.A. next week as well as at ASH the following week. And I think, you know, and then also the abstract acceptance at ATTD, and I think people are starting to see, and you can see in the titles that, you know, not only are we seeing good responses with 219 during the treatment period, we're starting to see glycemic control. And then we can also highlight special case studies where we see, you know, super, quote, unquote, responders.

And, you know, the World Congress was supposed to release their abstracts today, and then earlier this morning we got a notification from them that they decided not to release their abstracts and that they wouldn't be publishing ours today, but they're gonna wait until the conference. So I don't know if there was an accidental leak of information, I have no idea. But I think truly it's an appreciation for what we have in diabetes and also in acute leukemia.

And at the end of the day, if you think about 219 in diabetes, a diabetes patient has a gradual incline in their A1C over time because they lose the 5% of their pool of beta cells every year. And that pool diminishes whether or not they start an anti-diabetic medication. So, if we can show that 219 can actually take that slope to flat, which means we're now halting progression of diabetes, I think that would be an amazing achievement.

But what if we can show that we actually get a decline? And that happens while off drug, meaning we're now reversing the progression of the disease. And I think that's really what we're after, we've designed the escalation phase to see if we can achieve this. We've certainly designed the expansion phase to see if we can achieve it in a much broader patient population. But I think just that concept alone and the potential to be able to achieve that, is getting a lot of people excited.

Joe: I wanna maybe actually start with sort of high-level mechanistic questions. I think this is one that is often asked around, like, what's known around 219 and how it acts against menin relative to other menin inhibitors that people are familiar with? What is it maybe doing similarly? What is it doing differently? Where do you sort of stand with what you guys know there right now?

Tom: Yeah, high-level, you know, reversible inhibition, and keep in mind that the company started with the reversible inhibitor program that we inherited from a computational chemistry company. And we learned the biology over time that menin is engaged with multiple binding partners, MLL is just one of them. And even within MLL there's over 100 different flavors, so you can imagine 100 different magnetic interactions that have different strengths, right?

And so how much exposure do I need to disrupt which magnetic strength? That's really the puzzle that we're trying to solve with the menin inhibitor. And you can see this in cellular line data with different acute leukemias, you can see that it's a different fusion partner, takes a different level of exposure to disrupt the protein-protein interaction or the, quote, unquote, magnetic strength.

And you can see with reversible inhibitors, they focus on just one protein-protein interaction, menin-MLL. And certainly based on how much exposure they can achieve in a patient, that'll predict or dictate how many of the different flavors of MLL they can disrupt. Now, 219 doesn't create disruption of a protein-protein interaction via concentration. That's the key nuance. What we do is we drive concentration to form a covalent bond to the target, and then the target is sent out and degraded or deformed, so that it can no longer form protein-protein interaction. So, not only do we disrupt menin-MLL, we interrupt other protein partners like JunD, like MYC.

Joe: Maybe moving beyond sort of molecular mechanism, we could specifically talk about 219's mechanism within the context of diabetes and what your understanding is there. And maybe as a sort of follow-up to that, I think there is, like, a contingent of some who believe that the proposed mechanism of beta cell proliferation is biologically implausible. What's your response to that? What's the level of evidence you think that there is the opportunity to sort of repopulate, regenerate the beta cell pool?

Tom: Yeah, I mean the good news is you can measure it, right? We can measure beta cell proliferation and we can measure in human islets, so that is easy to do. I think what the challenge is and where the skepticism comes from is, how do you do that in the clinic? How can you measure beta cell mass? It's something you cannot do; it's very difficult. But what you can do is you can run all your preclinical work, understand what concentrations are required to get proliferation to go? How high of a proliferation can you achieve?

And if you can achieve that proliferation, how long do you need to be on drug to have a meaningful improvement in your beta cell, quote, unquote, mass? And I think it's well known that in pregnancy you have a dramatic increase in your beta cell mass. If you're obese, you have also a dramatic increase in your beta cell mass. Now, people have tried early on to say, can I correlate that with proliferation? And the challenge is you have to have elevated glucose because proliferation is glucose controlled; it's not controlled outside of glucose.

So, just like 219, we can't get proliferation to go under normal glucose conditions. That's why we don't expect hypoglycemia, that's why in our healthy volunteers, we have no change in their hemoglobin A1C. So, those are very important nuances. What we can say though, is you can measure HOMA-beta, you can measure stimulated C-peptide, we can say that we improved the function of the pool.

And if we just -- if we look and say, look, we've reduced their A1C, we've increased their ability to produce insulin, and now that ability continues without drug, well, whether or not we can say we regrew the pool, the pool is certainly functioning on its own, and we are happy with that statement.

Joe: Great. So, maybe now digging into some of the data, and we've seen data a couple times over this year from the 100 mg cohorts initially out to sort of 4 weeks and then we got the 12-week data in June. What do you think based on that data thus far, you've been able to definitively establish around 219 and what it can do in the context of type 2 diabetes? And then maybe also, what will we learn before the end of the year around 219 as we get some additional data points?

Tom: Yeah, and it just comes back to, you know, these papers that said, look, prolactin secretion inhibits menin function, and menin function is what's preventing these beta cells from

repopulating. And when we take a step back and we think, okay, how is type 2 described? And in the beginning, it was always about insulin resistance. And people thought that type 1 and type 2 had a different relationship. But now if you ask clinicians, and if you ask the academic world, they now agree that actually they both suffer from beta cell loss.

So, a type 2 suffers from a 50% pool of beta cell loss at diagnosis, and a type 1 suffers from 90%, right? And so in our clinical studies, we're trying to figure out how much beta cell mass gain is required to restore glycemic control, and we're enrolling all comers, so we enroll patients who are on metformin alone, they may represent more of the treatment-naive frontline patients. That's very much what the 100-milligram cohorts were comprised of, right? That had that 1% reduction.

So we feel very good about the 100 milligram dose level for that setting of type 2 diabetes. Now, as we go through our escalation, we go to 200 milligrams, whether it's QD or 100 BID, and certainly we're also doing 400 milligrams is what we're trying to make sure we can achieve is, how do we now get dramatic reduction in patients who have a little bit later disease? They've had diabetes for more than 10 years, they're on a GLP-1 and an SGLT2, and their A1C is 8.5 going to 9.

And that's really the purpose of, you know, continuing with the 200, with the 400, etc. And some of the data that we wanna highlight is with the 100 milligram, you know, how much durable control can you achieve in that patient group, which is four weeks of treatment? And then how much can you achieve at 200 milligrams, right? At week 26. And if we can understand that relationship, then we can get a better feel and calibrate how will it change then when we go from 4 weeks of dosing to 12? And how do we ensure that we get the majority of the patient population to have a durable glycemic response?

Joe: So maybe specifically around the World Congress update that's coming in a couple of weeks, just to help us sort of frame up what we should expect to see there. It sounds like we'll see longer-term follow-up for the 100 mg cohorts and potentially some data from the 200 mg cohorts?

Tom: Yeah, so World Congress will be focused on the 100-milligram cohorts. But actually, when the conference kicks off, we're doing an educational session and a breakfast at day 1 of World Congress. And there'll be the five of us, I'll kick it off and we'll be covering the discovery and the development of 219

in diabetes. So we'll be sharing new pre-clinical data and translational data of work with 219 in human islets, we'll be sharing new data from a gene expression perspective, from a proliferation perspective with 219, wanting to share right dose response, what's the proliferation rate?

How does that compare to a molecule like harmine? Harmine actually has been talked about, right, as a DYRK1A has been talked about as being able to do beta cell proliferation. What about non-beta cells in the islet? What does 219 do to them? These are all key components that crafted our development in diabetes, which we'll be sharing for the first time. So, a lot of new exciting translational data within the field. And then we'll have Rohit talk about what impacts he thinks we can have long-term in patients? And what should we be looking at from a beta-cell health perspective?

And then he'll turn it over to Juan who will highlight some of the 100 milligram case studies. And that will then transition into our poster in oral, which will highlight the 100-milligram cohorts with and without food. And then what's nice is that you already see a dose-response, right? Because we have a food effect, and with-food created a third of the exposure than without-food. And the response of the with-food group had about a third of the A1C lowering.

So it was very nice to see that AUC, which is exposure during a 24-hour period, really dictated the response from an A1C lowering for 219. And what we'll highlight in the poster in the oral presentation is now what about at week 26? They've seen drug for four weeks, we know what the response looks like, that's ADA, we've now seen week 12 follow-up, right, in San Diego. What happened now at week 26? Do patients still respond? Or is it like a GLP-1 where they lose the body weight loss in the A1C reduction right away? That's what we wanna highlight.

Joe: I guess I'm wondering as well, so you mentioned, like, the dose response that was observed and 100 mgs. I wonder if that should be the continued expectation as you move to higher doses and higher exposure. Or is it complicated a little bit by the fact of, maybe getting back to this, like, heterogeneity and, you know, those 100 mg cohorts. Or maybe enrich for a specific kind of population, and it gets more challenging as it gets a little bit more diverse?

Tom: Well, I think when we announce the 100-milligram data and you get a 1% reduction within 4 weeks, that's an incredible

achievement because that means their CGM is getting into that normal range. So if they're in normal range, the A1C has to catch up over time, and that's the 1% reduction at week 4. So, beating 1% I think is challenging because you're already getting patients in normal range with a certain period of time.

But what we're focused on from a 200-milligram, 400-milligram perspective is, as I mentioned, is trying to address the patients who have much less of a pool. They're not just at 50% or 40%; they're at 20% or 10%, or even less, and they're on GLP-1 and SGLT2 as an example. And they don't respond to current mechanisms of action, can we use 200 milligram or 400 milligram to get glycemic control back for them?

Joe: And so maybe along those lines, I guess, how do you go about figuring out… It seems like a very challenging exercise to try and figure out what's the dose, and what's the schedule, duration of treatment needed for these like, sort of, diverse pool of patients with different underlying beta-cell mass.

Tom: Yeah, I think, you know, what we have to do first is, and the reason why we went this way is do all comers first. Then you can see where patients benefit the most from either four-week or, 10-week, or 12. But at the end of the day, we think at 12-week we should handle the majority of the patient population. And, you know, it's our job to interrogate what's the right dosing scheme to cover the majority of the patients, and we'll design an induction phase to handle those patients. And then those who still need a little bit more drug, we'll go onto a maintenance phase.

But the reason why we go all comers is, as I mentioned, is you really wanna understand what's the critical concentration for those patients and then what's their critical duration. And then we can go into the expansion phase to learn more about the drug. But if you do an all-comers, you just have a greater opportunity to look at HOMA-beta influence baseline A1C influence, combination influence, right? Because this will actually dictate how we design the later-stage studies. So we need to generate this data now.

Joe: Couple more questions maybe sort of connected. Where exactly are you within the 50 mg, 400 mg cohorts? And then, you know, you mentioned the ATD abstracts that you'll have in March. What data will we see then?

Tom: Yeah, so 50 milligrams, that's done in enrollment. So we should be able to provide at least a four-week here soon. And then for the 400-milligram cohort that's still enrolling, so we won't be able to share top-line on that yet. But hopefully, by World Congress, we should be able to... Oh sorry by ATTD, we should be able to provide top-line for the 400 milligram. And as we announced in the press release, there's three clinical abstracts that were accepted. The first clinical abstract covers about 40 patients' worth of data, and it's covering our escalation experience out to week 4.

And so, that'll cover the first four cohorts, so the 100 milligram and 200 milligram. And then the additional clinical abstracts, one covers durable glycemic control with the 200-milligram cohort, and then the third clinical abstract covers case studies. And it really gives you a detailed look at patients and what do they come with at baseline? How long have they had disease for? What current anti-diabetic medication are they losing response to? And then how is 219 coming in and helping them?

Joe: Last question on the diabetes side of things. Type 1, I guess, what gives you confidence that, you know, the mechanism of increasing beta cell mass will have utility here and not be subject to, sort of, autoimmune destruction?

Tom: Yeah, it's a great question and I think, you know, the KOLs have been pounding the table for us to start type 1 as soon as possible. Because their perspective is that, this is actually an easier indication to show success versus type 2. And the reason being is even though they have a smaller pool to work with, you only need to increase the pool by a few percentage points in order to regain dramatic glycemic control.

And the reason being is you don't have all the other metabolic disorders going on with this patient, like, severe insulin resistance because they were just diagnosed. The autoimmune component is an important one, and when we looked at our animal work with 219, we saw that there was an incredible reduction in inflammation and necrosis of the islets. So 219 does have some inflamm component. We've run inflammatory models with 219 that shows a reduction in inflammation.

And then also we presented a poster at ASCO highlighting CLL. The reason why that's important is when we did gene expression analysis in B cells, it showed that the top pathway that's disrupted by 219 is type 1 diabetes, so, the B-cell, T-cell

crosstalk, so we do feel that 219 will have an ability to bring a component to try to dampen the autoimmune system. And there's also literature that shows, if you can slow down or halt the destruction of the beta cell pool, it's actually the cellular component that's getting dumped into the environment that's allowing the autoimmune system to continue the destruction.

Joe: Great. And maybe in the last five minutes we could touch on leukemia and other oncology indications. So maybe specifically in the context of acute leukemia for 219. You know, we got some data in the ASH abstract back in July. What do you think is most notable within what we've learned so far and at ASH, what should we expect to see there?

Tom: Yeah, I think what's exciting for us is once we focused on the menin-sensitive mutations, that's when we started to get our first responses. And what's nice is that we got very deep responses, right, getting complete responses. And so, in the poster, we're gonna have a later data cut, so there'll be more patients. We haven't guided to how many there will be and what mutations [?that showed there'll?actually will?] be. But we focus now on menin-sensitive mutations, so there'll be more of those, certainly.

And then, longer follow-up with existing responders or dose level-four patients. We'll also be going in a little bit of a deeper dive into those that responded to 219. What does their gene expression analysis look like, right? Some [?MLA?MLLr?] work. Does this look like what you'd expect for menin inhibitor? So I think these are very important components for the poster. And then what characteristics are different? What does 219 look like? Is it a different animal than what the reversible inhibitors have published? And I think what'll be nice to see is, what is that depth of response that you're getting even at the suboptimal exposure?

I think that's what gets us really excited. And then, long-term, you know, the vision for the company was never just to develop 219 as a monotherapy for acute leukemia. That's why we have BMF-500, a covalent FLT3 inhibitor. We think that novel-novel combination is what's gonna establish and maintain long-term competitive advantage. Because we have both agents in-house, we can hopefully one day put it together in a single tablet, and then obviously that would be one price.

Joe: How do you think -- so, you know, I presume we will see data from higher-dose levels than we've seen in diabetes.

Tom: That's right.

Joe: You guys have gone until 500; I think now it's 625, 650.

Tom: Yeah.

Joe: I guess, where are you in sort of figuring out what the move-forward dose is in leukemia? And how do you think, like, safety in oncology at these higher doses, sort of, portends for, say, the 400 mg within the context of diabetes?

Tom: I think that's what really helps us is, it keeps us really busy having all these different indications. But it actually provides a lot of learnings and understanding from a safety and efficacy perspective is because, as you mentioned, in oncology, we go to much higher-dose levels, much higher exposure, and these patients are staying on drug for much longer than four weeks, right? We have patients up to eight months or so. And I think if you have that type of scenario, you can really learn and get confidence from your drug in a non-oncology indication because you can see the safety profile that 219 is highlighting at much higher exposure.

Joe: So, maybe going back to something you said in terms of like depth of response, you know, in leukemia. When you look at the competitive menin space in leukemia, we've gotten data sets within, sort of, both biomarker populations. Where do you see the best opportunity for 219 to differentiate from some other programs that are a little bit further ahead?

Tom: Yeah, that's a great point. I mean, obviously superior efficacy trumps, but I think there's certainly an opportunity to show improved efficacy in the MLLr patient population as well as NPM1. But we still need to first get to our recommended phase 2 dose, expand into a larger end so that we can do a proper comparison. We're not there yet, but I think what we look at from a reversible inhibitor perspective, obviously we see the size exclusion mutations that pop up, right?

They pop up pretty quickly within the first two cycles. And so, we would not expect to see those same mutations with 219 because we don't drive our efficacy through size, right? We're not a large, quote, unquote, small molecule that's disrupting a protein-protein interaction; we're actually forming a covalent bond. And you can look at our patents, you can see that our chemotype is very different than Kura and Syndax. So if we can

lead to a response that's more durable because we don't generate those size exclusion mutations, that could also be a significant competitive advantage. But let's see the data once we get it.

Joe: So, last minute or so here, I think at the top you mentioned the number of other oncology indications that you guys are exploring with 219. I guess, maybe quickly, you know, is there a specific indication within that basket outside of leukemia where the biological rationale, the preclinical data are particularly compelling? And then is there -- what's the next cohort? What's the next indication we might see data from?

Tom: Yeah, I mean, when you look at the debt-map portal and you do a rank ordering of the most sensitive cancers to menin disruption or MEN1 disruption, actually acute leukemia ranks number three, which was really surprising to us when we started this effort. DLBCL ranks number 1; multiple myeloma ranks number 2, and acute leukemia ranks number 3. And that's how we really constructed our first phase 1 study, Covalent 101. So, we're really excited about what 219 could do in multiple myeloma, in DLBCL. But -- and then also we have our solid tumors. We think there's a space to be a disruptor as -- even as monotherapy. And I think, you know, third-line, fourth-line colorectal and pancreatic, that's a huge unmet need, where these tumors are menin-sensitive if they're KRAS-driven.

Joe: Perfect. With that, out of time. I wanna thank Tom for his time and thoughts, thank everybody for joining us here. Take care, and enjoy the rest of your day. Thanks.

Tom: [CROSSTALK] Thank you very much.

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