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<<Nancy Weidenbacher, Analyst, Jefferies>>

Welcome everyone. I'm Nancy Weidenbacher. I'm member of the Biotech Equity Research team at Jefferies. It's my pleasure to host a fireside chat with Thomas Butler, the CEO of Biomea Fusion. Thank you so much for joining us.

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yes. Thank you for having us, Nancy.

<<Nancy Weidenbacher, Analyst, Jefferies>>

So before we get into the Q&A, I was wondering if we could start with an overview of the company and how your background and the background of your team, helped lead to the founding of Biomea Fusion?

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yes, absolutely. Great question. So, hi everybody. I'm Tom Butler, CEO, and chairman of Biomea Fusion. I'm an organic chemist, medicinal chemist by training. I start down the industry working at Gilead Sciences first on the hepatitis C cure program, which is where I met our Head of Chemistry, Thorsten Kirschberg. And I – so I started the industry at the bench doing drug design against antiviral targets like polymerase for Hep C. And we worked on that together for gosh, six years or so making polymerase inhibitors around the clock. And we acquired as a company, Gilead acquired Pharmasset for the NS5B portion. We made the NS5A internally, which is now called ledipasvir for the eight week cure. So that was a very exciting program. And then it just turned out one of the last molecules I helped design and scale up before I left for Pharmacyclics was remdesivir.

And then fast forward into Pharmacyclics, that's where I really learned the impact of what a covalent inhibitor can do for oncology. Ibrutinib has been a very successful small molecule. When I joined we were just starting to get off into the clinical trials. We initiated 13 Phase IIIs with J&J and had six FDA approvals in 18 months. So very successful program. And at ASCO just this past weekend, they announced data of patients on ibrutinib for seven years. And that really describes what a profile of covalent inhibitor can do, which is have maximum suppression of the pathway of the target, but have minimal exposure every day that allows the patient to stay on drug for a long time. And our philosophy, the core thesis of the company is if patients can stay on drug, they can benefit from it. And that's why we started with a covalent inhibitor for menin. And try to think of us as this discovery engine, development engine. We continue to crank out novel covalent inhibitors. We just announced our second program again split three. We

think it's another target where reversible inhibition leaves a lot on the table and program three and beyond are coming.

<<Nancy Weidenbacher, Analyst, Jefferies>>

Yes, that's really exciting. Thank you so much. I think you started to mention some of the benefits a little bit, but I was curious on the benefits of irreversible inhibitors versus the reversible inhibitors in development for cancer targets and especially the benefits when it comes to menin inhibition. Why an irreversible versus reversible inhibitor?

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yes. Great question. And really the company was founded back in 2017 based on a reversible menin program. Myself and Ramses were in Palo Alto. We got a knock on the door one afternoon in the summer. And it was a company, who was developing inhibitors against menin and the target we at the time knew very little about. We knew that it was engaged in these protein, protein interactions and really these translocations, which we thought was a great opportunity to focus on a driver mutation for acute leukemia. And they came to us because of our expertise myself as a chemist, but I surround myself by great chemists, like Thorsten I mentioned at Gilead, like Jim Palmer, the inventor of ibrutinib or co-inventor of ibrutinib. And they came to us because the Achilles heel with computational based methods of drug design is that the intellectual property is wide open.

The engagement to the target is extremely novel, but the chemistry is very, very difficult. And that's because the chemistry just has never existed in time before because the scaffolds are brand new. And it took them about a year and a half to make a handful of molecules in a program you need to make 200 to 300 molecules. And they knew that it would just take a really long time to get there. And so, we just started off with a logical pragmatic approach of reconfiguring and constructing the scaffolds. But as we were designing and developing the reversibles, we knew that it took really high concentrations to keep the pathway suppression as we moved from in vitro to in vivo experiments.

And based on our experience with ibrutinib and other molecules, it's very difficult to try to maintain high concentrations over a 24 hour period because reversible inhibitors maintain their effectiveness by keeping a certain semen trough level concentration. Irreversibles have a huge advantage from that perspective, because you don't have to maintain the semen trough concentration. You just need several hours of exposure so that you can form what's called the covalent bond that's why they're called covalent inhibitors. So if you take target like menin and you take the small molecule, you basically form a permanent bond to the target. And it doesn't matter if the drug washes out from your body and still attached because the bond is so strong. If you're reversible, if the drug washes out or exposure decreases, the connection falls off, and that's really the power of the covalent inhibitor.

<<Nancy Weidenbacher, Analyst, Jefferies>>

And for BMF-219 in particular, are you disclosing the bond that you're forming and how that interaction works?

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

We don't - there's – if you look at the crystal structure, there is probably only two that you can really approach. It's one of the two. It's deep in the corner pocket. And it really forced us to kind of redesign the initial scaffolds that we inherited because what you have to do and what is – whatnots appreciated is the specificity and selectivity to the target. So you have to figure out what's the right angle to hit the target and the right distance to form the covalent bond. If the angle is not right or the distance is off, you won't get efficient bond formation.

<<Nancy Weidenbacher, Analyst, Jefferies>>

Great. So you're currently running Phase I COVALENT-101 with the irreversible menin inhibitor, BMF-219. Can you talk a little bit about the trial design, especially with the new indications looking at DLBCL and multiple myeloma?

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yes, absolutely. So COVALENT-101 has three cohorts. Cohort 1 is an acute leukemia and is broken down into two arms, a CYP arm and a non-CYP arm. The reason why we have two arms is because our small molecule is metabolized by CYP3A4 and we just don't know what impact it has if you're on a CYP inhibitor. You can do in vitro experiments and in vivo experiments before the clinic. And we did that with 219, that shows about a fourfold separation. So that's why if you look at the dose level, it's staggered by a fourfold difference.

Arm A starts at 100 milligram, arm B starts at 25 milligram, and we just have to learn is that fourfold correct in humans. It could be greater. It could be 10. It could be none. It could be zero. We would collapse the arms. We have to learn that. Cohort 2 is DLBCL, relapsed/refractory, Cohort 3 is multiple myeloma. And what's so exciting is that we continue to do key work from a translational perspective to see do we keep adding some cohorts of other liquid tumors where we think 219 can have significant effect. CLL could be another one. And what's so profound is it's the same concentrations that we're disrupting acute leukemia, the same concentrations by disrupting diffuse large B-cell, multiple myeloma and CLL.

<<Nancy Weidenbacher, Analyst, Jefferies>>

Yes, that's really interesting. So for initial data for Phase I study, are you guiding to when we might expect that or the number of patients we might see for the initial data and – or potential endpoints?

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yes, I think about half of our analysts and you are included in that have us pegged for year end for data. I think that's a good goalpost to have for now. We want to get a little bit more experience with patient numbers before we as a company formally guide. We don't want to release data that's an NF1 or in NF2, and we don't want to just release escalation data. We want to release data of patients that we think are near or at OBD and that we've expanded into enough patients that say, okay, the response rate or the data that we're providing, we think is reliable data moving forward into the expansion phase, but also beyond.

<<Nancy Weidenbacher, Analyst, Jefferies>>

Okay, great. Yes we are…

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

And I'll add just, sorry, one more thing about COVALENT-101 is we're escalating an accelerated titration, so that means it's one patient per month. And that allows us to get through those dose levels relatively quickly. That's very different than that three plus three, right, that's just requires more patients. We would move to the three plus three if we see a DLT. But if your molecule has a profile, you hope it has – then you just quickly go through the dose levels and then get to the OBD and then expand.

<<Nancy Weidenbacher, Analyst, Jefferies>>

Great. Yes, we are really looking forward to seeing the first data. And I know you're looking at BMF-219 for other oncology indications as well. And I think at ASCO recently, you reported data for CLL. So I was wondering if you could describe some of the more recent data in these other indications.

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yes, ASCO was great. That was just this past week. And what's nice is it feels like the old days. It feels like we're back. There was probably 39,000 people there out of the expected 42,000 or 43,000, which was very impressive. I was really surprised, got to see everyone that you typically see at ASCO similarly at ASH in December. And we had a nice crowd around our poster during the entire session, which is also great. It shows a very high interest and excitement. And I think what's – what the buzz is – about is because what we're showing you is 219 versus ibrutinib, bendamustine, idelalisib and venetoclax, and these very important relapsed/refractory CLL patient populations that are difficult to treat. CLL as a disease doesn't grow very aggressively. That's why they have what's called their watch and wait kind of status for patients as they get diagnosed is because the disease just doesn't take off like a rocket like acute leukemia.

So you do have time and then you kind of weave in a therapy as appropriate for the patient's disease setting or tumor burden. However, when you get to relapsed/refractory

setting, the CLL replicates acute leukemia from a perspective of cell growth. It gets very aggressive. And if you ask a physician, if you have a patient who's on the standard of care like ibrutinib or acalabrutinib, what do you do when they start relapsing? You know, what they tell you, they keep them on drug, because if you pull it, then you have no option and it goes even faster. That's how aggressive the disease becomes. And so you need to have an agent that has high levels of cell killing, high apoptosis, and has great control of the many pathways that start to take over for these patients.

And so the buzz is, look, you're even showing greater inhibition than venetoclax, which is really focused in the relapsed/refractory setting. And then from a safety profile, because we're not the BTK inhibitor, we're not a kinase inhibitor. You would expect that we would have less impact from the tox perspective, right, from the bleeding. We would have less AFIB cardiovascular effects, because we don't hit hERG as hard as these other agents do. And so that overall safety and efficacy profile looks quite exciting.

<<Nancy Weidenbacher, Analyst, Jefferies>>

And should we be expecting more data in CLL coming up soon or in other different oncology indication?

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

So the team internally will continue to produce data for CLL. But if you think about B-cell malignancies in general, we've published data at AACR with DBCL, multiple myeloma. We just gave you CLL at ASCO, but all we're doing is working through the different maturation states of the same B-cell, right? And so you could imagine maybe we just kind of continue walking that line into other maturation states of B-cell malignancies, for example, mantle cell.

<<Nancy Weidenbacher, Analyst, Jefferies>>

So switching to diabetes, you recently presented at American Diabetes Association and hosted a virtual R&D investor event. And starting with some background here, could you give us an overview of the role of menin and beta cells in diabetes?

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yeah, absolutely. And when we started this project, we saw obviously the acute leukemia potential in some of the other liquid and solid. And we saw that there was work even being done in our backyard at Stanford that looked at the role of menin in diabetes. And we kind of parked that in the corner, because we're really precision oncology drug developers by training. And so when we got through meeting with all these key investigators early on, this was two Circa 2018, we met with one of our friends, who's a medical oncologist, and as we were walking out the door, he reminded us, don't forget to look at Type 2 diabetes. And we thought, well, that's strange from a medical oncologist.

And we started looking at some of the proof-of-concept models and he was right, in the literature if you would size men one the gene responsible for producing the target menin, you see that the typical diabetes models that Eli Lilly, Novo Nordisk and the rest of the groups used to translate their drug in preparation for the clinic, these animals were not recapitulating the hyperglycemic state just by merely exercising men one. So you knew that menin was playing a central role and we had to learn over time that actually the reason why your pool of beta cells don't regrow is because of menin, menin is acting like the breaks, doesn't regrow like your liver cells.

And what happens is, even for healthy individuals, the pool that you have when you're born is the pool that you have, it doesn't recapitulate. And just over time as you age, the pool of beta cell shrinks over time. And maybe it doesn't shrink as fast as a diabetic patient, but your pool does shrink even for healthy individuals. Now, if you have Type 2 diabetes, as you progress in the disease, the pool continues to shrink to very low levels.

And really standard of care is focused on trying to leverage the existing pool, trying to squeeze more insulin out. What we're doing with menin inhibitor is basically taking the breaks off and allowing the pool of beta cells to grow to the size that you were born with. And really what's so exciting too is the beta cells have a half life of 20 plus years. So, you don't need to chronically regrow cells. You just reestablish the pool and then check back to see how durable that is.

We showed that in our preclinical models at ADA, generated a tremendous amount of excitement. We have to now make sure or verify that the growth we're seeing in animals can be recapitulated in humans. But all the data that we're generating internally suggests that yes, it can be recapitulated in humans and this would be kind of a paradigm shift for Type 2 diabetes.

<<Nancy Weidenbacher, Analyst, Jefferies>>

Yeah, I guess, with that, could you give us just a – I guess some highlights from the recent posters that you prevent – that you presented on the two different rat models?

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yeah, absolutely. So the standard abstract that was accepted, looked at two models ZDF, Zucker diabetic fatty rat, and the STZ induced diabetic model. These are two models that are varies in their standard format. They were really just two studies that we decided to run to really look at two parts of diabetes. Diabetes is multifactorial, no question, but two of the leading sources of diabetes is insulin resistance and then just low beta cells. And over time, the insulin resistance can get you into low beta cells. And the ZDF really represents the insulin resistance, and the STZ represents low pool of beta cells.

And really we didn't optimize you. These were our first two animal studies and the STZ model generated historic data. Meaning this model is designed to only work with direct injection of insulin. There is no mechanism of action. That's been shown that regrows the

pool all the way back to normal and 219 did that. That's why, when you look at the pioglitazone arm, it did it just overlapped with a vehicle. If there is no effect, because there's not enough beta cells to this effect. And that was so striking. The GLP1s is the same, there's no difference versus vehicle. And 219 eight of nine rats were normalized within two weeks of dosing.

So very, very unusual data got us quite excited. And then the late breaker abstract that was accepted focuses on four week treatment. So we took the ZDF animal model, treated the arms with four weeks of 219, oral once daily and then followed them for four weeks. And what we learned is that as we showed in the two week study that the, the effect that we're eliciting in these animals with durable they're lasting.

And so we used a key endpoint hemoglobin A1C, which is used as the key primary for most diabetes pivotal studies is the lowering of hemoglobin A1C. We used a positive control liraglutide which is a GLP-1 agonist and GLP-1 in the clinical and commercial setting does about 1.5% to 1% hemoglobin lowering, hemoglobin A1C lowering 219 to 3.5. If you look at the, the drug just approved by Eli Lilly, which is an incredible drug especially from a weight loss perspective that molecule does about 1.9% single agent. 219 to 3.5 and it looks like it's durable. So this would represent a huge shift and that's why it was accepted for late breaker. I don't think that, there are any agents out there that can have that significant low reduction within 28, 29 days of dosing.

And so it was funny when we got the, the abstract accepted for late breaker, we got a call from ADA TV and they said we'd like to do a film series on you. Can we come by your offices? We said, sure. So they brought a film crew and recorded us where they wanted to learn more about who is Biomea, what are we doing? What are we opt to? And what is this molecule 219? And so they played this, they did the two videos at one minute and a six minute. And they played these videos in the buses and the shuttles and the hotels and at the conference center which was really exciting. And it was an honor to be there. But it's just funny, how things morph because, we as I mentioned, we're a target oncology company. We didn't expect that we would be involving in diabetes and these animal models just displayed historical really game changing data. So it's, the onus is on us to pursue it and continue pursuing it aggressively.

<<Nancy Weidenbacher, Analyst, Jefferies>>

Yeah. Really exciting data. So I'm glad to get a chance to talk about it. I think you've guided for a Phase 1/2 start for type 2 diabetes in the second half of 2022. Is that on track and can you speak towards the trial design?

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yes. So we are filing an IND for Phase 1/2 and it's a typical standard format. So the Phase 1 portion is in healthy, single ascending dose. The Phase 2 is in patients with type 2 diabetes. We haven't talked about sizing and those things because those details are being ironed out, but we're setting it up so that we can get at least a proof-of-concept of,

can we get significant reduction in hemoglobin A1C with 219 and is it durable? And that this study will be designed to give us that data.

The good news is with these studies that they don't take very long to execute the SAD goes very fast and healthy. And then the MAD portion which is broken out by dose level. Think of it as very similar to COVALENT-101 where you, you have cohorts and dose escalation, but the cohorts are larger than the end of one. And that way we can understand the, the right dose response in these patients. And we look forward to find that IND in the second half of this year.

<<Nancy Weidenbacher, Analyst, Jefferies>>

Great. And giving the preclinical animal data, where do you see this therapy fitting in for type 2 diabetes and what patient population would be an ideal target for the drug?

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yeah, that's a great question. And we'll continue to publish data, we gave a portion of the data we've been generating, but there's a lot of data, a lot of exciting data to share about 219 in diabetes, so that will continue to roll out this year. And then, in terms of different animal subtypes and that brings you, that brings us to the question of where do you think this fits within the treatment landscape? Just over 50% of type 2 diabetes patients suffer from a reduction of their pool of beta cells. And that's only because it's basically a disease where if you were to graph the reduction, it just happens over time.

And as you have diabetes for a longer period of time, your pool continues to shrink. And so we'll, we think that 219 is going to work well in those patients, where the pool has already come down and is not in patients who are mainly suffering from insulin resistance. We did see an improvement in insulin resistance in the ZDF model. So there is that component for 219 but really patients who are suffering from a reduced pool of beta cells is, where we think 219 will shine. And that's greater than 50% of the patient population.

<<Nancy Weidenbacher, Analyst, Jefferies>>

Great. And I know we're running out of time. So one last question for me here, as I'm wondering if you can compare the pricing, dosing and duration of treatment of BMF-219 between the oncology indications and diabetes.

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Yeah. Great question. So based on our preclinical work, the dose level is about half of what we think the OBD is for oncology. And then from a pricing perspective, look 219 we think is not a chronic therapy for diabetes. We think it's a fixed length of time. Is that one month? Is it two months? Is it three? We have to sort that out in the clinic; we think it's on an order of one to two months where we sit today. And if you think about it from

that perspective, the pricing of oncology and diabetes is actually quite similar. Right. And so and keep in mind too that you have separate labels, you have different dose regimens. And so we don't see a huge concern from that perspective. It seems to line up actually quite nicely.

<<Nancy Weidenbacher, Analyst, Jefferies>>

Great. Well, thank you so much and thank you everyone for joining us today.

<<Thomas Butler, Founder, Chairman and Chief Executive Officer>>

Thank you, guys.