Biomea Fusion, Inc.

September 7, 2023
9:30 AM EDT

Mohit Bansal: Thank you very much for joining us today. Again, one more time, good morning. My name is Mohit Bansal, and I'm also joined by my colleague, Adam Reineke. We both are very happy to have Biomea's CEO, Mr. Tom Butler, with us. Ramses decided not to – just to leave all the difficult questions to Tom. So, it's just Tom today, but I'm very happy to have you.

Thomas Butler: Definitely. Thank you for having us, Mohit.

Mohit Bansal: Thank you. So, maybe let's just talk a little bit about your journey as a CEO so far. And there are a lot of assets you are developing in this company. So, can you talk a little bit – give us an overview for the people who are new to the story.

Thomas Butler: Of course. Thanks, Mohit.

Hi, everybody. I'm Tom Butler, CEO and Chairman of Biomea Fusion. Biomea Fusion is a company in Redwood City, California. We're a biotech company that's focused on the discovery and development of small molecule covalent inhibitors. Covalent inhibitors – again just as a quick refresher – are entities that can form a permanent bond to a target of interest. And we've learned through our experience at Gilead and Pharmacyclics that if you can do so efficiently, you can drive enormous benefit from an efficacy to safety profile perspective. Whereas the patient spends the majority of the day with no drug onboard, you only need a few hours of exposure to form the covalent connection to the target, and the target is then removed from the body via protein degradation.

We started this endeavor, this research project back in 2017 when we inherited a virtual library of reversible inhibitors against a target called menin. At the time, we knew very little about menin. We knew that if you looked in the literature, you'd find one paper that said menin is a tumor suppressor. Another paper said, no, that's wrong; menin is a tumor promoter. And a third paper said, actually, those guys are wrong; menin, if you inhibit it properly, you can cure gestational diabetes.

So, we had to learn which of these three is correct. And maybe they're all correct. It depends on the context.

And we learned, as we figured out the chemistry of this virtual library of reversible inhibitors, we learned that the best way to target menin – which is involved in over 1,000

different protein-binding interactions – the best way is to hit it covalently, not reversible, because I can just take menin out altogether. It doesn't matter if it's bound to MYC, if it's bound to MOL, if it's bound to JunD. We just take menin out, have control, and that actually opens up the door to pursue other indications outside of acute leukemia. Diabetes is an example of one of those.

And as we built the company and sorted out this chemistry with menin, we really focused on first establishing an R&D engine, which is the fusion system, the fusion platform, and every third hire was an organic chemist to help us achieve that.

And in the summer of 2020, it was an employee base of two – that was myself and Ramses – and then we quickly grew from there over the course of the rest of the year. We did our Series A. That was led by Cormorant and Andy and Bihua.

And then we quickly went public in April of 2021, with about 14 employees, leading the way with 219. But at that time, we only knew 219 in oncology; we didn't yet know the potential in diabetes. But we knew that we had this fusion system that could continue to interrogate properly what menin does as a very unique target. And then we started to build up other programs like BMF-500, which is our other clinical-stage asset, against FLT3.

Mohit Bansal: Got it. That's a great overview and a great story, actually.

So, now that you are adding new people, so maybe let's just talk about the latest appointment offer, Juan Pablo Frías. And how do you convince him?

Thomas Butler: I mean, the hiring of Juan Frías as our CMO is a huge hire for us. We had been focused over the last couple quarters, because of the data that we saw in diabetes with 219 as the first potential disease-modifying agent for the disease, we knew that we had to build up our internal expertise in diabetes. The company was very much structured in oncology, even though we had a few MDs that had diabetes experience. We really made it a mission to get diabetes experts into our company. And we built up our scientific advisory board that helped us really establish our knowledge base. And then we wanted to increase that further with full-time employees.

And for Frías, it was just right place, right time. The stars aligned in terms of Frías' ability to actually join another company, as well as the evolving data with 219. And he is one of the most excited KOLs about 219 because the existing unmet need in diabetes and because diabetes at large is only treated by targeting the symptoms. So, diabetes is not really targeted as a disease itself.

And so, it's a huge score for us, for the company. It just elevates us, and his entire network elevates us. When we were organizing the stats on his experience, he's conducted as lead PI over 250 clinical trials in diabetes, and over half of them were Phase III. So, 125 Phase III studies. He's been a part of 25 approvals in diabetes. These numbers are just staggering, right? And he has this whole network, too, that wants to come in and help us and make 219 a success.

And this hiring also represents – you guys should see that as a shift in the mindset of – it's no longer "will 219 work in diabetes?"; it's now "how big is 219 in diabetes?" And then, how do we make sure we maximize the value creation that 219 can accomplish, given the profile it affords us in this disease indication?

Mohit Bansal: So, let's just go on that. I mean, so since you talked about the current drugs are only treating symptoms here, what is the understanding of the root cause of diabetes? I mean – and then, how 219 attacks that root cause? Can you just talk a little bit about the mechanism there?

Thomas Butler: It's been really paradigm-shifting in terms of our understanding of diabetes at large. And early on, it was very bifurcated that Type 1 is a separate disease as Type 2. And what the community is starting to realize is that both Type 1 and Type 2 diabetics suffer from the same root cause, and that root cause is a depleting pool of beta cells.

When you get diagnosed with Type 1, you've lost 90% of your pool; you only have 10%, approximately, remaining. And then when you're diagnosed with Type 2, you've already lost 50% of your pool. And your pool continues to deplete about 5% a year, and that's independent of starting treatment. If you start (inaudible) and you start with (inaudible) D2, that pool is going to continue to deplete. And that's why you have millions of Americans that are insulin-dependent Type 2 diabetics, is because their pool has depleted to about 10% and now mimics a Type 1.

Mohit Bansal: Got it. And that's led to where 219 comes in, basically.

Thomas Butler: And that's where 219 comes in. That's right. And so, some of the key experiments that we ran with 219 with human islets is that 219 proliferates only beta cells within the islets. It doesn't proliferate non-beta cells, like alpha cells, delta cells. And it only proliferates beta cells under stimulation of glucose or a hyperglycemic state. That's very important. As well as that you're not proliferating beta cells unnecessarily. You're proliferating beta cells in a patient that has a depleted pool. And so, there's 219, or a menin-inhibition component covalent, and there's also glucose trigger to it. So, you need to have both pieces.

Mohit Bansal: Is there a time point where this proliferation could be more successful, like early stage of diabetes versus late stage? Is there a stage where (inaudible) are too far gone and it won't be helpful there?

Thomas Butler: Absolutely. So, what we learned from a proliferation capacity or proliferation rate that 219 can exhibit on these islets, we learned that about 12 weeks should be sufficient for the majority of the patient population. Keep in mind in the escalation phase, we're only dosing up to four weeks, and that just helps us to understand response rate and initial response to 219 during that treatment period. But in order to recapitulate the pool and have that long-term durability, we believe most patients have to go out to about 12 weeks.

And what's known also is that the maturation process of these new islets can take time, too. It can take up to 12 to 14 weeks for them to fully mature and be insulin-producing, functional beta cells.

So, the data we announced in March with a median reduction of 1% after four weeks with our first dose was an incredible response and very exciting to see. But at that first dose level that's initial exposure – that's the lowest exposure that we've explored in the escalation cohort, and those patients very much are a little bit earlier in the course of their disease and they're only on metformin, which makes sense based on where they are in their diagnosis.

And so, there's a lot of literature that shows that these patients have the highest background proliferation rate, very similarly to Type 1s in the honeymoon phase. Type 1s have a very high proliferation rate, background rate, in the honeymoon phase, which is the first three years, which we'll be targeting with 219. And it really matches what we saw in the March data.

And then, as we continue to enroll the escalation phase we really want to understand – there's more to diabetes than just the early-stage patients. There's also middle- and late-stage progressors: those that are on dual therapy, like metformin-SGLT2 or metformin and GLP-1, as well as triple combination. So, we're enrolling patients who are on metformin, on an SGLT2 and a GLP-1 and their baseline A1C is 9.5, 9.6. That's incredible, right? They've basically exhausted all the treatment options that afford in the United States. You can add a DPP-4, but that gives you a little benefit on top.

And we're going to 219 as triple or quadruple combination to see what 219 can do for these patients and try to get their pool back. And we think that those patients would certainly represent a fast path-to-market opportunity if we can get their glycemia controlled.

Mohit Bansal: Can you talk a little bit more about this clinical program? And then how would you – like, how informative would it be for a bigger pivotal-type of program there?

And then, I want to get into toxicity as well. Like, is there too much proliferation, which could be an issue at some point?

Thomas Butler: So, great questions. So, we're starting with COVALENT-111, which is Phase I/II, in Type 2 diabetes. The first stage of the study is going through escalation, which we're currently wrapping up by the end of this fourth quarter. And we're going through the different dose levels, increasing exposure. And as I mentioned, we're doing that so that we can make sure we capture even the patients who have lower background proliferation rate, those who are on dual or triple combination.

Once we have finished up the escalation portion, we'll transition to an expansion phase, where we'll dose up to 250 patients out to longer treatment periods; so, up to that 12-week time point. That way, we think that we can recapitulate the pool of beta cells for the majority of those folks.

With that data in hand, I think that creates a large body of evidence of what 219 can do in diabetes.

And then, in parallel, because of the insulin secretion increases because of the C-peptide increases we're seeing in our Type 2s, we absolutely want to get into Type 1, because we think that also is a significant unmet need. And this would be for Stage 3 patients. Again, Stage 3 is Type 1s who have just been diagnosed. And we think if we can capture them in the honeymoon phase, those patients have about a tenfold higher background proliferation rate. So, 219's ability to recapitulate the pool is really strong in that patient group. And we'll run that study in parallel so that we can generate Type 2 body of evidence and also Type 1 body of evidence.

Mohit Bansal: How are you thinking about this? This being a chronic treatment or this being an episodic – not episodic, like, a treatment (inaudible) a longer-term treatment or longer-interval treatment kind of situation?

Thomas Butler: We think it's certainly an induction phase. And then for those patients that need to see redosing, we'll have a maintenance scheme for them.

And we're really excited to see who can have that super response, who can have that long-term benefit. And we think as we get through this exercise of figuring out what's the right dose exposure, what's the right time on treatment, we think we can capture the majority of patients.

Mohit Bansal: Great. I know Adam has prepared a lot of these questions. So, I want to give him (inaudible).

Adam Reineke: Great. I just want to ask about how 219 differs from the current diabetes therapies that more address hyperglycemia and how really the mechanism is different from how you try to resolve these situations with 219.

Thomas Butler: 219 would represent a new drug class. So, the mechanism of action is completely complementary to all the other agents out there. So, SGLT2s, they work by increasing the flow rate and the glucose secretion to the urine, and then the GLP-1s work as incretins and increasing insulin secretion from the existing pool. But they both rely on an existing pool. And that's the crux, is that the pool continues to deplete while patients continue these other agents. And so, they're trying to drive down blood sugar, but they're not able to address the failing pancreas.

And that's really our approach, is let's go after that root cause, let's go after this failing pancreas. And to tag on to Mohit's question about what about over proliferation, what about toxicities, how can we manage this, is there a concern of cancer risk, what we've learned is that there's only proliferation under stimulated glucose. If patients have normal blood sugar, there is no proliferation. So, we don't need to necessarily land the plane and figure out when to pull drug, we can keep patients on and make sure that we get their pool back.

What's also important is that even if patients are under a hypoglycemic state or stimulated glucose, if we wash out 219, the proliferation also stops. So, you need to have both onboard at the same time in order to get proliferation.

And then the new cells that we're creating are glycemic-controlled, meaning they only secrete insulin under glycemic cues (ph). So, they're normal functioning beta cells, which is also very exciting to know.

And from a toxicity perspective, we're going to much higher doses, much higher exposures in oncology. So, we're going to exposure during a 24-hour period of about 3,000 AUC. In diabetes, we're going to 300-400 AUC. So, about a tenfold reduction in exposure compared to oncology.

Adam Reineke: Could you also just talk about how you can tell that 219 is taking effect? Likely, you can't really measure the islet cells directly, but measures like C-peptide and time and range on CGMs and how that kind of gives you an understanding that you're really seeing the effect of replicating those cells.

Thomas Butler: That's right. There's no direct way of measuring proliferation yet; hopefully, that technology comes over the next several years. But what we can say is that we're increasing the function of the pool. And that's an easy measurement that we can do. It's used by calculating how much insulin is required to control how much glucose lowering

in the patient, and that is called HOMA-beta. And that's a great beta cell function scoring that we can conduct. And what's great to see is when we look at AIC lowering, we look at CGM, we look at (inaudible) blood glucose, they're all matching step for step, as well as the CGM data that we're seeing.

And the best way to show that you've done something to modify the disease or the progression of the disease is how do the patients perform while off therapy. And if we're recapitulating the pool, you don't have to grow the pool continuously, because beta cells have a very long half-life – on the order of 15-plus years. So, once you set the pool, it should be very long-lasting. And so, when we look at how patients are performing while off treatment, that gives us a good sense of did we actually slow the progression of the disease, did we halt it, or maybe we actually reversed the progression of the disease. And that's what we'll be looking at as we conduct our expansion phase.

Adam Reineke: Got it. One more for me. So, as you treat different patients in the diabetes continuum – maybe early diagnosis, be it SQ patients, too, patients on insulin – are you seeing variability in effect? And what is the kind of early feedback for which patients (inaudible) the KOLs are most eager to treat with 219?

Thomas Butler: I think as we go through this escalation, as we drive higher exposure, we think that we can capture even those with lower background proliferation rates, and those who have a lower background proliferation rate are those who have had disease for 10-plus years. That's what we see in our escalation data.

And also, those who are in later disease, typically, they're not just on metformin; they're on an SGLT2, they're on a GLP-1. And so, that pool is getting really exhausted. And for those patients, you need a little bit more drug, but you also need a little bit more time on drug to get sufficient proliferation of the pool.

And so, we think it's a function of exposure, but also time on drug, to capture those both bookends: so, high background proliferation rate and low background proliferation rate.

Mohit Bansal: Got it. Super helpful. And thank you, Adam. So, maybe there's a lot of talk about GLP-1s right now in obesity/diabetes. I mean, it seems like there's a lot of interest. Obviously, the Big Pharma interest. Is it a good thing for a new class of –? I think it is a good thing, but I mean, are you seeing some kind of interest in terms of potential partnership opportunities or things like that? And what would be your –? Given that it could be a big class, what would be your go-to strategy to develop this asset?

Thomas Butler: I think it's a great thing. And I think the experts in the field, like the Novo's and Lily's in the world, they see that this is completely complementary to what they're doing, and we see it the same way, as you have this potential to address the disease. This could represent the next breakthrough in diabetes, and they see it the same way.

I think, for us, an engagement with those experts could be highly beneficial. We had a great experience at Pharmacyclics with J&J. We did a co/co (ph) where it just allowed us to plug into much more resources and then go with speed and get to the finish line with a higher probability of success and with just more attention, more spotlight on it.

So, I think certainly a program of this size could certainly benefit from that.

And I think experts in the field and the industry in pharma, they've been looking for a beta cell proliferator for a long time. This is not a new mechanism of action to them. It's

only a new mechanism action to us and to the Street because it's the first time an agent like this has been able to make it through all the preclinical experiments and now, for the first time, show clinical efficacy. And I think it's getting the broader community really excited because they see the potential.

And so, we're really excited to move forward. And I think as we generate the large body of evidence from the expansion, as we wrap up the escalation, I think what the world will appreciate is the potential. And like I said before, it's no longer "will 219 work in diabetes?," it's now "how big is this opportunity?" And we're all after the same goal, is long-term patient benefit.

Mohit Bansal: Makes sense. And in terms of potential impact on body mass, is it going to be neutral? Or is there going to be also some level of efficacy among obese patients?

Thomas Butler: Our expectation is, over time, there should be body weight benefits. And that's because as you drive down a patient's blood sugar, what will happen is that insulin will also come down because of efficiency of the pool. And as insulin comes down, body weight will come down. And that would be our expectation over time.

Mohit Bansal: Got it. Super helpful. So, last question on this topic, unless the audience have any questions, in terms of timelines and upcoming milestones, what should we expect this year, next year?

Thomas Butler: So, for the escalation summary, we're going to provide a top line summary in Q4 this year, and that'll cover our experience with all of our dosing cohorts within the escalation phase.

And then we're targeting ATTD, which is a conference in March, in Florence. And that's where we'd like to highlight the key characteristics or the exciting profile of 219.

So, we'll give you more detail around the escalation summary. We'll give you detail on continuous glucose monitoring effects, super responders, who's responding out to Week 26, what about patients who are on this dual and triple combination we add 219 on top, how are they responding. Those are some of the things that we'd like to highlight.

Mohit Bansal: So, Spring in Florence.

Thomas Butler: Spring in Florence.

Mohit Bansal: Very interesting. Awesome.

So, let's move on to oncology, because that's where you started, right? And then it became a diabetes company over time. So, let's just talk a little bit about your recent data in AML. I think you have seen two out of five patients complete responses. Could you talk a little bit about that and the therapeutic window and how can you improve on that?

Thomas Butler: Absolutely. So, we announced in a press release our experience from dose level 4. Dose level 4, again, is about half of the target exposure for 219 in this indication. And what we wanted to share and get out there is 219 is working very well in acute leukemia.

Getting these two complete responses out of five patients treated we think is really strong. One was a full complete response; meaning, they have blast count back to normal, and they have full recovery of their bone marrow, long-term patient benefit. And the

other CR is a CRI where the cancer has been removed, they're back into normal blast count, but we're waiting for some of the bone marrow components to fully restore until that's called a full complete response.

And for us, we're now moving to next dose level, which is dose level 5, which we think will be at or above our target exposure. And again, we're focusing on patients with the key subtypes; so, NPM1, MOL, and there's other key mutations like NUP98 that are menin-dependent.

And so, we hope we can share that at an upcoming medical conference. Hopefully, ASH – we're waiting for acceptance – that would be a great conference to share more details around dose level 4, and then also dose level 5.

Mohit Bansal: Got it. And what would be the dose-limiting toxicity? I mean, like, how should we think about the long-term safety of this?

Thomas Butler: Dose-limiting toxicity. So, we have dose level 5 that we're currently executing. Dose level 6 is kind of our top-end dose, which is 1,000 milligrams per day. And what we saw from a toxicity perspective or dose-limiting toxicity was appetite suppression and body weight loss. And that's what really created the kind of ceiling for us in our dose selection.

Mohit Bansal: That's a side effect of a diabetes drug.

Thomas Butler: That is a side effect of a diabetes drug. That's correct.

Mohit Bansal: It makes sense. And then, can it be combined with Vidaza? Because we have seen some – obviously, CD 47 (inaudible) example. I mean, with Gilead, there was a hiccup with the combined ability there. In AML, that's a drug we use a lot. So, how do you think about the combined ability and eventual development pathway here?

Thomas Butler: BMF-219's profile really affords a combination approach. And really, that's really the vision of the company when we organized our pipeline, is we looked for key combination partners for 219 in liquid and solid tumors. And that brings up BMF-500, which is our second clinical-stage asset, which is a covalent inhibitor against FLT3.

Our plan and long-term vision for 219 in certainly AML is that when we get to recommended Phase II dose we'll do the same thing with BMF-500. And that combination, we think, is going to be very powerful for acute leukemia. Because if you look at the coverage of the patient population with menin plus a FLT3, that would be the majority of acute leukemia.

We've already published some initial combination data from BMF-500 and 219, where we think that gave us really strong additive, if not synergistic, effects. So, we're really excited about that combination.

And then, of course, 219 can be combined with standard of care, like Vidaza, with venetoclax, (inaudible).

Mohit Bansal: That makes sense. And then, in terms of, like, let's just talk a little about the broader plans in liquid tumors as well as solid tumors. I mean, how are you envisioning it as a drug (inaudible) or as a drug in multiple cancers eventually?

Thomas Butler: So, COVALENT-111 targets four liquid tumors: acute leukemia, DLBCL, multiple myeloma, and CLL. The reason why we target those specific four liquid tumors is those are the liquid tumors that show the highest sensitivity to menin knockdown. Actually, DLBCL ranks number one as the most sensitive from a subtype perspective of menin sensitivity or menin dependency. Multiple myeloma ranks number two in terms of menin dependency. And acute leukemia actually ranks number three, and most people don't realize that AML is actually ranked number three in terms of the percentage of the disease and how dependent they are on menin.

And so, we're really excited about executing all these different liquid tumors to see what 219 can do, first, as a single agent, and then transition to combination based on the treatment landscape.

And then, for COVALENT-102, which we kicked off earlier this year, is our solid tumor trial in three indications. So, it's pan-KRAS colorectal, pancreatic, and non-small cell lung cancer. And here, again, it's really because we're taking out menin globally. And so, menin is engaged with MYC and KRAS-mutated tumors. So, we take out menin, and the cell loses its ability to continue to survive and replicate. So, we're really excited about that potential as well.

219 has great volume and distribution. So, we get great exposure in the tissue. That affords us to get into solid tumor. It also affords us to be able to get into diabetes.

Mohit Bansal: Got it. That completely makes sense.

I think so for menin, there are other companies as well, in oncology at least, in development. Can you talk a little bit about what are the benefits of covalent binding here and how it differentiates itself from the other competition?

Thomas Butler: That's a great question, Mohit. The reversible inhibition of menin is really driven through the interaction inhibition of menin in MOL, which is one of the binding partners to menin, one of many. And so, the reversible inhibitors are really focused on driving those two proteins apart, but both proteins are still remaining in the nucleus.

For 219, what we do is not focus on an interaction. We focus on actually taking menin out. It doesn't matter if MOL is engaged, it doesn't matter if it's MYC or JunD or other binding partners. We're actually driving down menin protein in the nucleus and in the cell. And that's what gives us the strength.

And when we started doing our preclinical work, we obviously had to do peptide mapping to look at the cysteine that 219 binds to. We know it only binds to one cysteine; there are six possible. So, it's very specific. What we realized is that when you transition from the typical CDx to cell-based assays like MOLM-13 and B411, you can see right away the benefit of a covalent is that it doesn't matter what the fusion partner is. And that's really the difference of MOLM-13 and B411; two different cell lines that are menin-dependent and menin-MOL-dependent.

However, if you look at the reversible inhibitors, they are much more potent in B411 versus MOLM-13, because it's a different fusion partner. So, they're really dependent on the fusion partner to drive potency. Because they're both menin-dependent, the same potency drives cell-killing for 219. It doesn't matter what fusion partner it is.

And as we transition from those cell-based assays into ex vivo patient samples, that's where you could see the strength of 219 again, is that at much lower concentrations can you drive cell-kill of these acute leukemia cells in these patient samples in a reversible inhibitor. Because the reversible inhibitor is reversible. It's competing with other proteins and engagement with other proteins. 219 forms the covalent bond, and it's over. Any protein binding of 219 from a plasma protein perspective just serves as a depot (ph). And that's a huge benefit for covalency.

Mohit Bansal: That's very helpful. Thank you very much for (inaudible).

Maybe one question. Again, so talk a little bit about the discovery platform at this point here. And then, I mean, is this something where you will pump out more INDs in coming years or so? And how should we think about it?

Thomas Butler: That's right. So, now that we have 219 firmly anchored in oncology and in diabetes, our discovery engine is focused on finding combination partners for 219 in diabetes and oncology, both liquid and solid. And so, you should expect from us over time that we'll continue to announce covalent IND candidates that will serve as great combination partners for 219 in the various diseases that we're anchored in.

Mohit Bansal: Great. My last question, my favorite question. September 2024, I hope you are here. I hope I am here and if I'm asking this question. If you look back (inaudible) – like, when you look back, what would make you really happy that just we accomplished something here?

Thomas Butler: In one year from now?

Mohit Bansal: Yes.

Thomas Butler: So, what we're really excited for – and you probably don't even have to wait a year for it – we're really excited to see what can 219 do for the broader patient population in Type 2 and then what proof of concept can we show in Type 1. If we can crack that and show that we can get Type 1 diabetics to regrow their pool and remove the need for insulin, that would be such a huge outcome, such a huge win for these patients. And we are 100% focused on trying to deliver that. And so, that would be an incredible outcome for patients and for the company if we can achieve that within the next six to 12 months.

Mohit Bansal: Knock on wood. Thank you very much, Tom. Really appreciate it.

Thomas Butler: Thank you very much.