Biomea Fusion

*Biomea Fusion presentation delivered at the 2022 HC Wainwright Bioconnect Conference*

**Mike King:** Everyone and thank you for joining the HC Wainwright Bio Connect 2022 conference. My name is Mike King and I'm a managing director and senior biotechnology sector analyst here at HC Wainwright. While we are virtual again this year, we're confident we're going to be able to provide value to you with over 550% ING companies at this conference.

For those of you that don't know us, HC Wainwright is a full service investment bank dedicated to providing corporate finance, strategic advisory and related services to public and private companies across multiple sectors and regions. We have a total of 23 publishing senior analyst and over 630 companies covered across all sectors. You can find more information at our website whichishcwco.com For more information from a logistics standpoint, please make sure to reference your Bioconnect virtual conference online portal that provides your individual links to your meetings and all presentations. Also please join us for corporate presentations and panels that will be available live in streaming from January 10th through the 13th, with that having productive and enjoyable day, and I now like to introduce our next presenting company, which is Biomea Fusion. Presenting on behalf of Biomea is the CEO and Co-founder, Tom Butler. Tom, Welcome to the Bio Connect 2022 conference. Appreciate you joining us.

**Thomas Butler:** Yeah, thank you very much. Mike, thanks for having us.

**Mike King:** Absolutely, wouldn't think of having Bio Connect 2022 without you guys. So I know you Tom, I know your colleague Ramses very well. How about we go back to the Pharmacyclics days, but Biomea was one of quite a number of IPOs in the biotech sector last year, so maybe it would be worth starting just with a quick description of the company, its history, how you guys started it, etc. And orient us to that and then we'll go from there.

**Thomas Butler:** Yeah, absolutely thank you Mike. The company started back in 2017 through a reverse inquiry myself and Ramses received coming off the heels of the AbbVie / Pharmacyclics transaction. We had set up an innovation fund in Palo Alto, a small office on Emerson St in downtown and we were focused on looking at novel mechanisms of action, looking at companies who had initial proof of concept with their, with their phase one and were about to build out their pipeline and their clinical development strategy. And we got a knock on our door one summer afternoon and in 2017 and it was a company that was focused on computational chemistry based out of Boston that had this menin program. They started with a reversible inhibitor program and had designed really novel chemical structures and chemical scaffolds. That got me really excited as a chemist. At the time, we knew very little about menin. We just knew that the literature had described it both as a tumor activator and a tumor suppressor. So we knew that it wasn't really well understood all the way, and so we knew that we had a little bit of work to do, and we inherited a program that had a lot of virtually designed molecules. But synthetically maybe only a handful [of actual synthesized molecules], and we really set out to be pragmatic about targeting menin, and we had always admired folks going after targets that were very patient centric that you would really understand the genetics behind the tumor and that you could design a molecule behind those genetics. I came from Gilead in the industry and then I was lucky enough to join a smart team at Pharmacyclics and Ibrutinib was a phenomenal drug. We had six labels in 18 months, but one thing that we'd always admired was that patient centric modality of really understanding how to be very precise in the clinic and really be able to be predictive of who's gonna, who's gonna benefit the most from your drug? And that's really the hallmark of this type of effort going after mutations called translocations and others. It just turned out as we explored menin further, we learned that it's not just translocations that menin can disrupt. There's a lot of liquid and solid tumors at large where menin is this this key node on the transcriptional level that's controlling growth and survival of tumor cells. And then we took it another step further. It also appears that menin acts like the brakes on beta cells very much like GLP. One acts like the gas and they actually colocalize together in the pancreas, which is pretty interesting. Coregulate, and so we knew that there was a lot of work to be done in terms of understanding menin and then what's the right way to properly design against the target. And through a computational means, we learn that going after menin with a covalent hitter is a very novel way of controlling the pathway in a very consistent way to be efficient and control multiple tumor types and disease types.

**Mike King:** Great. Well, I appreciate that that that over you I think the answer to my next question is probably hints of it in in in your opening statements there. But I'm just curious, you know, as folks don't know you, know you and I had interacted a number of times while you were at Point Sur. And I just wondered what was it about menin in particular that made you guys want to do this again? The company saying there's you know most people come out of industry and if they start a fund they are kind of happy with their lifestyle and their ability to kind of pick and choose the things that they do. So what was it about this program in particular that made you guys eager to kind of do it again, so to speak?

**Thomas Butler:** Yeah, and we were drug developers by training. That's that's our, that's our bread and butter. That's our core skill set is to do this type of work. I started on the industry as a medicinal chemist, organic chemist working at Gilead at the bench. I started working on HIV, designing protease inhibitors and then was fortunate enough to work on the Hep-C Cure program. And that's where I met Thorsten, our head of chemistry. And you know what made us do it is just that that potential to do something different and be able to have high impact. For us, it's all about impact and we want to put a molecule forth into the clinic but also know that whatever we're doing in the clinic has high commercial, has high commercial potential success and menin had that written all over it. We knew that because it wasn't well understood we had the time as a small company to understand menin. If there were too many participants in menin, it would be very difficult as a young small company to try to catch up and it was just fortuitous that we found meant in when we did and we found that. The potential of a covalent inhibiter when we did and it was really what the literature was telling us. One of the first things we did was kind of reach out to our network and we reached out to a KOL that really had a big impact on the ibrutinib clinical development. And he told us as we were describing the menin program, he said, look, I think this. I think this target is great. I think you guys are on the right track and it should be a wonderful target for leukemia. You better develop this in diabetes.

**Mike King:** Wow, this is new. Medical oncologist is pretty interesting, right? So without exaggerating, but I guess it's fair to say that you felt there was another opportunity to kind of recapitulate the experience that you had at PCYC?

**Thomas Butler:** That's exactly right.

**Mike King:** OK? So yeah, Speaking of menin, you know there you do have some competitors in the space. The signs have been around for for decades, but only recently has the industry started to catch up. But why do you think this is the case? Is menin hard to drug or is there some other reason men is very difficult to drug?

**Thomas Butler:** The pocket that we all target is relatively featureless in the broad sense and comparatively to a kinase. It is. It is quite shallow and so you know with those type of properties as a target you typically have to build a very large molecule. A lot of real estate, right? 'cause you're engaging with non covalent interactions. And you can't. You can't build a reversible inhibitor that's 300 or 400 molecular weight. You have to go much bigger because of its relatively featureless attributes, and I think you don't really understand the potential of a target until you get a great molecule to study it, and there just weren't great molecules until a recent day that you could actually properly study menin. And I think the book on menin is just we're in the first chapter.

**Mike King:** Well, if there's this featureless, this featureless aspect of the target sounds a bit like K Ras, and it sounds like you took some of the learnings, maybe from Karas discovery to apply here. Can you maybe talk a little bit about that?

**Thomas Butler:** Yeah, that's right. And you know when we first started building and designing our small molecule you can do certain things even if you think about just from a physical property perspective. You can build propellers to try to wedge yourself into this dynamic protein. That's what the that's what they care as developers. They just build these these kind of propellers and and we did the same for menin to try to create a reversible molecule. That was two that was a little bit more sticky that had a longer K off but then as we explored the PK/PD properties of reversible inhibition, we knew that you know this isn't going to work well. It's going to vary. It's going to limit the potential of your molecule and it's going to be difficult to study in the clinical setting. It'll be virtually impossible in the commercial setting and so we wanted to build, again, a molecule that just demonstrated strength from a pathway control perspective but also consistency across multiple tumor types. And through the advent of this system, that sits deep in the pocket you are afforded that capability and really, that's how we get this deep targeted activation but also really strong selectivity.

**Mike King:** Specificity of BMF 219, right? So we can take this in kind of two directions. The first direction would be irreversible inhibitor to menin. Talk about what made you confident that you need an irreversible inhibitor, and maybe we can talk more about this after that about you sort of philosophically, that biomea is focused on irreversible inhibitors, but to back up a second. You know, menin is expressed widely. You know how confident were you that you could drug the target without inducing talks and were there are some experiments that you needed to do. To understand the biology better, like knocking it out with CRISPR or some other methodology to make sure that you know you aren't going to do any harm by irreversibly binding the target.

**Thomas Butler:** Yeah, we did all the initial work that that that you guys on the other side would do. And in understanding the target. What happens when you have a knockout scenario very similar to when you study BTK there? Where does exist this knockout scenario? How do you study this? The good news is that a covalent inhibitor never recreates. Knockout scenario in high brightness didn't do it with BTK and we don't believe BMF 219 does it with MEN1, but you do show strong pathway control but the protein is there and is available. And so you never completely recreate the knockout scenario. But menin is ubiquitously expressed. However, its strength or the way it's used is quite focused, and whether it's in the pancreas or another target organs, one can quickly understand where menin is. With strength and when you start to apply it into these menin driven tumors, really these these tumors are addicted to menin and it's complex. And whether it's MLL that's part of the complex or another protein like MYC really menin is the core scaffold protein. That's kind of keeping it all together on the on the chromatin level, right?

**Mike King:** Let's go a little deeper on that because I get so important for the validation of the target to understand the biology mentioned in a deeper fashion. And that is, I mean again, in the same similar fact. I mean not same similar to BTK where we had human knockout validation. We have sort of the same thing with men. And can you elaborate on that?

**Thomas Butler:** Yeah you do. In and when you when you knockout men in all the way and they've studied this in in animals and humans when you have complete knockout what happens is over the course of many years humans develop. Benign tumors in the majority setting and in the very few they form malignant tumors in very small percentages. After 20 plus year experience of having continuous menin knockout in animals in mice and rats. When you do a MEN1 knockout, you see formation of these tumors after one year. But again one year in a row or in a mouse is like 25 years plus in a human. So again the phenotype that is seen doesn't have any negative effects and doesn't happen for many years down the road. That's very important. And when it does happen, they're benign, resectable tumors.

**Mike King:** But it does. It does manifest in a pathology, so we know that's right, there's that there's your genetic validation there. That's right, there is genetic validation absolutely. And then at least you. You know your boundaries, right? And you can, you can tailor make your molecule to make sure that you're operating within those boundaries, right, right, OK, well let's go a little further into current plans. I know your IND is active. You had an announcement this morning about your your development strategy. Why don't you take an opportunity here to kind of. Summarize the release that came out this morning and tell us about the plans for 219.

**Thomas Butler:** Yeah and so for us. It's all. We understand that the benefit of speed, of going in parallel. And so what we announced this morning is that we are going in parallel up to 7 tumor types this year. We will be enrolling up to 7 tumor types this year in 2022, and what that allows us to do is to properly explore BMF 219 in parallel or in as closer parallel as possible. We will also be exploring in type 2 diabetes patients this year. Again, the preclinical work that we've done both on the safety side first and then also complemented with the efficacy side is just a molecule that that is unparalleled for diabetes. We're looking for an oral long-acting medicine that we want to study this in Type 2, but certainly type 1. Certainly, the door is still open. We have to explore it, but. To be able to have a molecule that has a long lasting effect on patient after a short term duration of treatment, I think would be a game changer for diabetes. So we're extremely excited about this potential and we'll be announcing presenting data later this year on our preclinical findings.

**Mike King:** OK, and talk about the two. The you know in oncology side talk about the the liquid in the solid tumors. You've chosen and maybe a little rationale why you've chosen the ones you've chosen.

**Thomas Butler:** Yeah, the reason why we chose it again is to take a step back and even why we decided to go after this program was because we admired this patient centric approach. We really wanted to pick tumor types where we knew the subtyping ahead of time. We knew meaning what patient would have the highest probability of success with amended inhibitor that shows this type of effect on the pathway which BMF 219 does, and that's how we put together our clinical development plan in DLBCL in multiple myeloma. And then, in KRAS activated tumors, you gotta make sure the drug gets there in sufficient concentration, you gotta make sure that you have your therapeutic window, and you gotta make sure that you have a deep understanding of the biology and the rationale, which has been wonderful for 219 and for our clinical development. We're very excited to be able to explore this broadly because of what we think menin can do for these patients and in need, right?

**Mike King:** Maybe a little digging down a little further, you know you talk about, so you got the DLBCL double, triple hit lymphoma, double expresser lymphoma and multiple myeloma and at least initially and then also in KRAS driven cancers. Are you looking for sort of biomarker? Driven strategies or will you employ them once you've got some idea about PK/PD safety in these in these different tumor types?

**Thomas Butler:** Yeah, that's right. So you know at the end of the day we know the, we know the subtyping. We believe we have a strong rationale for being specific with particular subtypes within DLBCL and MM as well as leukemia. It's very, very synonymous with going after MLL rearrangement, or NPM1 for DLBCL. It's a double hit, triple hit and double expressor. These are all tumor types or subtypes of DLBCL that have strong MYC control, and we've seen that if you have MYC as a as a major driver, then BMF-219 has a very strong impact on your tumor, and so that would be somewhat self selecting.

**Mike King:** The genetic profile or tumor types.

**Thomas Butler:** That's right, and we'll you know we'll do full paneling as well so that we understand what else is going on with that particular tumor type. But we want to be smart about it and be patient centric up front right.

**Mike King:** And then I think you had said in may be misquoting, but I thought that there may be some data available on some of these studies in the first half. Or maybe I'm wrong on that front.

**Thomas Butler:** Yeah, so during Q4, we published some of our DLBCL work and will continue to publish multiple myeloma and KRAS activated tumor preclinical data. You'll get that work as well that that supports the rationale and which was so profound is that you know at the at the same concentrations that were disrupting acute leukemia, we're disrupting these other more types. And that's what gets us so excited. So as we go through the dose escalation in acute leukemia, we will understand the proper exposure to control tumor growth and control the cancer in that patient setting. We'll be able to then translate that into the other tumor types as well as we're enrolling them right?

**Mike King:** OK, terrific, maybe we can switch gears a little bit to diabetes. You know you had some preclinical data out last week that appears to validate the biologic hypothesis. Maybe talk a little bit about that for us at 1st, and we'll pick up from there.

**Thomas Butler:** Yeah, so that there's a growing body of evidence that supports the use of a menin inhibitor in diabetes and the premise is that you know, as I mentioned before, that meant it was acting like the brakes. And so your beta cells, which are consistently exposed to a hypoglycemic state in in diabetes, they get exhausted and they just can't pump out enough insulin. Now you can try to use GLP-1 and other agents that try to squeeze more insulin out of them, but at the end of the day when you continuously exhaust your beta cells. It's just aggressing type of situation and so the reason why you don't have a rapid turnover of your beta cells is because you have this gatekeeper menin that's preventing turnover and all we're doing is taking the brakes off of this gatekeeper and allowing the beta cell to turn over and reestablish a pool of healthy beta cells. And there are there's several pieces of literature that suggest this can be done. We've been doing our own preclinical work that suggests it is being done and if you think about that fundamentally you don't have to continuously grow a pool of beta cells. You just have to regrow it completely because diabetes doesn't happen overnight. Type 2 diabetes doesn't happen over a weeks time. It happens over many years. So if I give you now a pool of fresh beta cells, we're kind of resetting the clock on your disease, right?

**Mike King:** And the thing you can, I think obviously remains to be determined, but. It would seem that beta cell can regulate itself normally, so you wouldn't have to be too concerned about you, know Hypo or hyper glycemia?

**Thomas Butler:** That's exactly right. And that's the beauty of menin. And as a gatekeeper is that it. It doesn't. It doesn't tell the body to now create a hypoglycemic state, you just get to normalize glucose levels, right?

**Mike King:** You know, I gotta ask, you know the obvious question which is you know. To develop 219 for both diabetes and oncology, you know you eventually run into the issue of, you know, giving a cancer drug to treat diabetes. You know pricing differentials, thing, you know things like that. Do you contemplate at some point? Perhaps after you prove concept with 219 that related molecule or a new molecule could come through and be the one that carries forward for for diabetes? Or what kind of decisions do you making there on that yeah.

**Thomas Butler:** It's a great point and just take a step back you know and consider the oncology drug profile. If you look at if you look at most oncology drugs, even if they could do it, they can't go into non oncology settings because their safety profile is not clean enough. They would they would never pass and oncology studies. 219 can and that's how special BMF 219 is. So imagine if you have an oncology drug that can pass not oncology toxicity studies. Wow, that's pretty special. And think about what impact it can have in oncology patients. Then if you have a drug that that has that type of profile, so flip it the other way. It's got to be a tremendous molecule first of all, and it can maybe provide tremendous benefit for oncology patients on the other end to be able to pass those hurdles and get into non oncology. Again, well, the reason why we would do it is because there's potential for a breakthrough and to have finite treatment for diabetes and to turn the treatment paradigm on its head is an opportunity that we'd love to take, and that's why.

**Mike King:** You know at the end of the day, from a pricing perspective, from a patient targeting. And how do you manage through that at the end of the day, you know, breakthrough medicine takes care of all those things. And yeah, I understand. But there are pragmatic considerations. You know there, obviously diabetes, much more expensive, much more elaborate, long term studies, different dynamics in the marketplace, I mean. Seems like you could partner that program off with a separate molecule or family of molecules.

**Thomas Butler:** Well again, keep in mind that you know the reason why the sizing of clinical trials and diabetes and the time is usually predicated that you're giving this drug to people chronically for the rest of their lives. That's not what we're doing, right? So we'd be doing finite treatment for short period of time. And obviously we need to learn more about what those guidance trials would look like. With the sizing and timing like, but we're doing we're doing something that's never been done before.

**Mike King:** Right. It would be interesting to see a small company bring a diabetes drug all the way to market on its own. I think that would be. I don't even know if. Maybe Elan did it, but that's about all I can think of at the moment. But anyway, unfortunately we're out of time. It's a fascinating story, folks. I urge you to take another look at Biomea. I know there were flood of names in the marketplace last year. This one is certainly worth your consideration, especially given the experience and track record of the team. So let me thank Biomea. Thank you, Tom, for taking the time and effort to preparing your talk and hopefully the next conference we do here will be where COVID is endemic. Rather than pandemic and we can do it in person rather than virtually, but in the meantime we're grateful for your flexibility and your presence online this year. So thanks again for myself as well as the HC Wainwright team and enjoy the rest of your day.