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KOL Call Discussing The Role of Prescription Digital Therapeutics in Type 2 Diabetes

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PRESENTATION

Rahul Rakhit

Good afternoon everyone. Thank you for joining us today. I'm Rahul Rakhit with LifeSci Capital, and today we'll be taking a deeper look at the topline readout for Better Therapeutics's lead asset, BT001, which is a novel prescription digital therapeutic that's being developed for the treatment of type 2 diabetes.

Joining me today in the discussion is Dr. Mark Berman, Chief Medical Officer of Better Therapeutics, and Dr. Marc Bonaca, a cardiologist and vascular medicine specialist, who serves as the executive director of CPC Clinical Research and CPC Community Health out in Colorado.

Before we dive into our discussion, I'd like to remind everyone in the audience that you can submit any questions you may have for Dr. Berman or Dr. Bonaca with the Q&A function at the bottom of your screen. We'll periodically pause to take some of the questions as they flow in, and if we don't have the time to address all the questions we'll be sure to follow up with you after the call.

With that, we'd love to jump into it, first with Dr. Berman. Maybe you can tell us a little bit about the design of the study, and ultimately what were you primarily aiming to evaluate for the time to date period?

Mark Berman, M.D.

Happily, Rahul, and first, thanks so much for having us here, it's an honor to be with you both. I'm very excited to share more about this study and our work.

So, to your question about study design, this is a pivotal trial for this novel therapeutic that we call BT001. The principal purpose of the study was to assess both the efficacy and the safety of BT001 when used as a novel form of treatment for patients with type 2 diabetes, so to assess that we wanted to use the gold standard in clinical design, so we used a multi-site randomized clinical trial, which really allows us to isolate the effect of the intervention in this study population.

We had two study arms, so we had a control group and an intervention group; the control group received standard of care treatment for type 2 diabetes along with a sham or a control version of the BT001 app, and the intervention group got standard of care as well as two 90-day treatment periods of use of BT001.

The goal is that we wanted a large sample, we wanted to have enough power to detect what's viewed as a clinically meaningful difference in A1c change between the two groups, so 0.4% A1c. We wanted to

make sure we had a nationally representative patient population, so patients who specifically had type 2 diabetes and a slight use of pharmacotherapy or other treatments were not able to achieve the level of blood sugar control that's recommended.

Finally, in terms of outcomes, two principal outcomes that really kind of drive determination of success for the trial. The one is 90-day change in hemoglobin A1c, and specifically the difference between the two groups in terms of A1c change. Then safety; this is both an efficacy trial and a safety trial, so we're looking at the occurrence, the severity, and the relatedness of adverse events that are experienced in both of the arms at 90 days, and then again at 180 days.

Rahul Rakhit

Got it. You did mention that you're getting (inaudible) a pretty significant change, 0.4% A1c. Kind of hoping you could expand on that a little bit; where does that number come from, ultimately, what does it mean, and just from a clinical perspective, maybe to help us, I guess, add a little bit more color to that.

Mark Berman, M.D.

Yes, happily, and happy to get Dr. Bonaca's perspective on it around, as well.

So, a 0.4 A1c difference between groups is regarded as a clinically meaningful difference. It's an endpoint that's recognized by the FDA as well as other major associations that oversee guidelines for patients with type 2 diabetes. It's regarded as not only a big effect size but also one that's clinically meaningful.

Generally what we know about A1c is that it's a measure of average blood sugar control, and it's long established that, as you make improvements of A1c, you not only get control of the disease but that control of blood sugar correlates with improvements in things that we really care about: mortality and morbidity. That's a continuous effect, meaning that, for every few points of A1c reduction, you're going to get in a population improved mortality and morbidity reductions in those populations.

So, to kind of put that in perspective, if we look at some of the old kind of gold standard evidence around A1c reduction, a 0.4% reduction in a population would correspond to about an 8% reduction in mortality and about a 15% reduction in microvascular complications, things like blindness and kidney failure and peripheral neuropathy.

Rahul Rakhit

Got it. Dr. Bonaca, would love to hear your input as well on I guess how clinically meaningful is a 0.4% A1c change, especially when you're treating patients and you're on the ground, I guess, in the real world environment.

Marc P. Bonaca, M.D.

Yes. No, it's a great question. I think Dr. Berman discussed that very nicely. I guess I'll just add that we have to remember that that "clinically meaningful" description really was developed in the era of drugs to lower blood sugar, and that drugs that lower blood sugar have their sort of maximal effect early and tend to wane over time. So, looking at a snapshot as well, that's what we got from this drug, and its sort of best case scenario early, we know that all of the effects tend to sort of attenuate as patients progress. Diabetes is a progressive disease, and they get beta cell fatigued or obesity worsens and other things. So it was really developed in that paradigm.

I guess I would just caution that A1c is a static marker. If you have a therapy, if you add an intervention that progressively improves people's control over time, so ideally weight loss should even eventually lead to reversal of diabetes, right, and the 0.4% is only clinically meaningful for that snapshot but may actually grow over time. So, I think that what we're thinking about here, as a therapeutic from lifestyle, is one that we're putting in the context of drugs, where drugs tend to have their initial benefit wane over time but lifestyle intervention should have an initial benefit and then grow over time. So, I would just say that that may underestimate, that 0.4, the benefits of something that actually helps people reverse the underlying drivers of diabetes.

Rahul Rakhit

Got it. Really appreciate that color. Actually want to kind of dive into that in a little bit, but before we get there, there's one more thing I want to touch on and get both of your perspectives on, and that is clinical trial design, and in particular that's the population that was enrolled in this study. I think you said you wanted it, Dr. Berman, you wanted it to be nationally representative, a diverse population. Maybe you can expand on what that means, and I guess even more particularly, how did the patients that were enrolled in this study kind of compare to the broader population that might end up using this in the real world setting? Dr. Bonaca, would love to hear your perspective on it as well.

Mark Berman, M.D.

Thanks Rahul. I think it's really important because when you think about the results from any one trial, you want to understand, is this trial representative of the patients who will ultimately use the treatment in the real world? So, that's why it was critically important for us, and it'll be important for the FDA, to look at the trial and say well does this contain representative patients?

So, we specifically target a very broad and diverse set of patient populations, we located our recruitment in six states spread across the country in order to target that diverse set of patient populations, and it's reflected in just the basic demographics that we saw. So, in this group of 670 participants, we had 40% of the population that were non-White, we had 40% had no college degree; the vast majority of these patients were of low-income and middle-income households. It was a sick population. The baseline A1c was 8.1%, so above the level of control, and these folks had long-standing diabetes, on average about 11 years since their diagnosis.

There were also other indications that diabetes was not the only thing that they are struggling with. On average, patients had about—not only had obesity but also had three other comorbidities on top of that, and their calculated cardiovascular risk was 15%, which, to put that in perspective, is about, you know, that's a chance of having a heart attack or a stroke or other cardiovascular event within 10 years, and that's about three times what you might expect for a healthy population that was similar in age for—similarly matched in terms of other characteristics.

So, taken together, the baseline characteristics of this population align with the American population who has diabetes across the country. If anything, one could say there is some slight over-representation of minority groups and low-income groups, which for us is very exciting because those are principally some of the populations who have the greatest need.

So, this is a diverse population that had a lot of unmet needs and so really the types of patients that we hope to see our therapeutic in use in in the future.

Rahul Rakhit

Got it. Got it. Dr. Bonaca, given that many of the patients that, if you're using that databased tab logs (phon) vascular complications, many of whom I assume have kind of advanced diabetes, would you say that the typical patient profile that you have kind of aligns with some of the patients that were enrolled in this study?

Marc P. Bonaca, M.D.

Yes. No, it's an excellent point. I see a lot of patients in clinic, many of whom have diabetes as a comorbidity, and I do think this population really represents a lot of the patients that we see. You always wonder, when you look at trials, is this the kind of patient I'm seeing that's sitting across from me, and really was, and I think what was very impressive to me, and this is why large well-conducted trials are so important, it's that they were able to utilize the invention, right? I mean, this is one where you might say, this was all sort of younger healthier people, maybe it wouldn't apply to people who are from diverse backgrounds or have a lot of comorbidities or other things. Lo and behold, it's a positive study, it's really important for me as a clinician to see that this is a representative population; as Dr. Berman said, I think it is actually more representative than any of the trials we do in the cardiovascular diabetes space.

Rahul Rakhit

Got it. Yes, appreciate that. Dr. Bonaca, just to kind of continue with you. So, jumping into the results, after 90 days, we saw that net reduction in A1c of 0.4%; on the other side we also had no device-related AEs. Can you help us, you know, can you tell us a little bit about the clinical significance of these outcomes, and I guess how favorably do you view that value prop, kind of based on the safety and efficacy profile?

Marc P. Bonaca, M.D.

Yes, I mean to put it into context, if I could achieve a lowering of A1c in my patient population at 90 days through counseling, then I would probably declare myself as like one of the most successful physicians out there, I mean it would be incredible. I mean it is just so hard to achieve cardiometabolic or glycemic control through counseling. It's just really difficult. I think it was quite ambitious to look for a change at 90 days, that's pretty early for lifestyle; it takes time. So I think it's a dramatic benefit.

I mean to me it's two things. One, it's gold standard evidence, it's a true randomized trial, it's the level of evidence that I look for, for all the therapies I'd prescribe; but I think to show a difference there is really important. As a clinician, the second thing I always ask is, what's the safety of the intervention? Because ultimately you have to talk to your patients about the risk/benefit. I mean, they're the ones that have to take the pills, they're the ones that have to suffer the side effects. To see the safety is extremely reassuring. It makes it a simple discussion in the clinic, right, where I can say well this is an intervention that could be prescribed or could be utilized, there's not a lot of downside to it, right?

The other thing I'll say is, what intrigues me is, and we'll probably get to this later, is what's going to happen over time, because I would expect that early adoption of these effects, with glycemic control it's a 90-day average, right, so the A1c is sort of probably a lagging indictor. This should grow over time, right, with patients that are responding to it and utilizing it.

So, as a clinician, this is really exciting. For me it takes the burden of trying to achieve lifestyle modification potentially out of my 15 minutes with the patient, and there's an intervention that I could say has true statistically significant efficacy and an excellent safety profile.

Rahul Rakhit

Got it. When you say that, and trying to get them to do lifestyle modifications having those conversations with them, are you speaking specifically around some of the patients with earlier-onset diabetes who you're just seeing for the first time, or are you talking about with all of your patients across the board, just having this continuing dialogue with them and having this being utilized with everyone?

Marc P. Bonaca, M.D.

Yes, because what the Better Therapeutic intervention does is different than lifestyle counseling. Right? I mean, it's clearly a different intervention, and Dr. Berman can speak to that. What I do is traditional lifestyle intervention, which is I talk to people about the ADA recommendations for diet, or the AHA recommendations for diet, and I talk about smoking cessation and exercise, and I point people to websites for nutrition, and I often will refer them to a nutritionist. I just have to say it's not a very effective way at achieving better cardiometabolic control. It just doesn't work for the majority of patients. Now, there are studies that have shown, if you can find the right patient and they're highly motivated and they can actually make those changes, they can lose weight and lose A1c. But on a population level, it's very hard to achieve and I'd say rarely occurs; in fact most people get worse over time. That's one thing Dr. Berman could also talk about is what happened in the control group here: were their A1c stable or did they go up?

But I think what this therapeutic does is different. It's not just lifestyle counseling, because we know that's really hard. I'll let the people that sort of developed it talk about it, but to me it's a different approach to reversing the drivers of diabetes.

Rahul Rakhit

Got it. Really appreciate that color. I guess you kind of touched on it where, yes, Dr. Berman, would love to kind of shift to the results and what you guys saw, I mean in the control arm and the treatment arm, but also, I think a lot of question that was on people's minds is, in prior studies you guys saw a little bit more of an effect, or a little bit more of a change in A1c. Was kind of hoping you could walk us through some of the key differences between those studies that might have accounted for these differences, and also help expand on the difference you saw between the control arm and the treatment arm in this pivotal study.

Mark Berman, M.D.

Happy to, Rahul, and thanks Dr. Bonaca, I really appreciated that summary of that conversation with patients in terms of the risk/benefit profile, because that is principally what we're interested in.

What's a nice segue there is that, when we talk about the results in this population, it also gives us another view on this, is that providers are going to be thinking about these results in terms of that one-on-one conversation. Is there something that is definitively effective and reasonably safe that I can offer my patients? People who oversee health systems, the physicians who oversee health systems, and payers are also going to be thinking about things in terms of a population control. So that's where our results can be translated on both sides.

So, to give you an example, we saw 0.4% reduction in A1c difference between the two groups, we've talked about why that's clinically meaningful. But it's important to know that the proportions of participants in each population, the control group and the intervention group, that reached that threshold were very meaningfully different. So, we saw almost half of the participants in the BT001 group reach that level of clinically meaningful significance, versus about a quarter in the control group.

So, from a population point of view, that's a meaningful difference in terms of the proportion of the population that is getting a benefit. So, about twice as many participants in the intervention group were able to get their A1c level down below 7, versus the control group.

Those changes were very statistically significant, so the difference between those who reached 0.04 threshold in BT001 versus control had a *p* value of less than 0.00001. So highly statistically significant and meaningful from a population size.

Then I think the other thing that can be lost when you just look at those raw numbers, we're just talking about averages here, but it's important to know that what we're really trying to do there is identify, is there a group of participants that are responders? Right? So, and yes there are. There's clearly more responders in the intervention group than the control group, and what happens in those responders? So in that group of participants who were able to meet that threshold of 0.4% A1c reduction, is that the extent of the reduction that they saw, or not? The answer to that is no, on average in that group, the mean A1c reduction was 1.1% in that group of responders. So, that's a sizable additional benefit that we see in the responder group.

To come back to your question about different studies, I mean one of the reasons why we're so committed to doing research is that you can't prove anything in one singular study, you need evidence that generates over time. This is not our first study, but all of our studies have consistently shown benefit.

So, the first study that you're referencing is our pilot study that we did. The goal of that was simply to establish, is there an efficacy signal here? Which it definitively did. But it's just entirely different study. Number one, it wasn't a randomized controlled study; number two, it did not take place during the pandemic, which has arguably made it more difficult for many participants to achieve glycemic control; and number three, did not take place in the dead of winter, and we know that there's a seasonality effect to A1c where A1c naturally gets a little bit worse over winter, which was the main point we were measuring an A1c reduction in.

Rahul Rakhit

Got it. Yes, that's helpful, it adds a little bit more color to what we saw. You know the point that you made there, I think it was 43% of patients kind of crossed that 0.4% A1c threshold, I know you said the mean was about 1.1 there, but maybe could you expand on were there any similarities in the baseline characteristics for these patients that saw that kind of reduction, or was it seen across the board? Like maybe help us understand if this worked really well with a certain type of patient, or you kind of saw that effect across the wide range of patients that you guys enrolled?

Mark Berman, M.D.

Yes. No, that's a wonderful question. So we started to dig into what are some of the baseline characteristics for example that may predict response, for example. What we know thus far is that there are three relatively clear signals. One is that patients who had a higher baseline A1c did better, so those in the 8% to 9% or the 9% to 10% baseline range, they, I mean, tend to treat and also saw a reduction of 0.4% to 0.5%. When you look in the protocol population, that difference increased to a 0.5% to a 0.8% reduction in A1c. We also saw participants in the South, in Florida and Georgia, their reductions were about 0.7% to 0.8% on average. Interestingly we actually saw a better effect in patients who are lower-income versus middle-income.

So, when you take that together, our interpretation of that is it suggests that the patients who are coming in a little bit more poorly controlled, who have a little bit higher need for behavioral therapy, kind of are at

worst odds if you will, are the patients who seem to be getting the biggest response. So we're encouraged by that.

I guess the last thing I'd say, it's also interesting, we know that, as Dr. Bonaca's nicely describing, this is a novel mechanism of action, it's a therapy that's intended to change behaviors and deliver behavioral therapy, and we know that there's a lot of kind of preconceived ideas about who's going to benefit and who's not going to benefit. So, we're seeing some interesting things on that front too. For example a lot of people might intuitively think that only your younger digital natives are going to do well with a therapy that's delivered digitally. In fact, we find it's just the opposite. Participants who are 60 years and above, clearly not digital natives, are the folks who are getting the best A1c reductions.

Rahul Rakhit

Got it. Okay, got it. Appreciate that.

Dr. Bonaca, I guess, given everything you've heard, data that you've seen, maybe just to kind of take a step back, talk to us ultimately about what you see about this clinical utility of BT001, and where in the existing treatment paradigm do you see this kind of fitting in, or do you think you'd start using this with your patients?

Marc P. Bonaca, M.D.

Yes. I think this is incredibly exciting. It fills a big gap in clinical practice. I'll just make a couple comments about the A1c delta. I guess, as a clinician, I'm not so wed to the absolute change, because I think, obviously the people who start higher can go lower, but there's a normal range, right? You can't go below normal. So, the closer someone is to normal, the lower the absolute delta, but boy, as a clinician, if somebody's got a hemoglobin A1c of 7 and they can get to 6.8 rather than getting worse, which is the typical progression, that is incredibly clinically meaningful to me, and to the patient, right, because you're not having that conversation in six months or a year of "oh, we got to add another drug now" or "now we got to start insulin," right? So we have to be a little careful, or at least I'll say as a clinician, I don't really care so much what the absolute delta is, because we're modifying the course of disease.

The other thing I'll say about the delta for these initial data is I think we have to be cautious because not everyone may respond at the same rate. It may take people 120 days or 180 days to really sort of get their delta, and so we're looking at a very early time point.

So then to take that forward to the question you asked me is what does this do for clinical practice, well the foundation has always been to treat the drivers of diabetes. Yet our toolkit has consisted only of band-aids. We want to lower the blood sugar through some pharmacologic mechanism so that we can make these surrogate markers look better with the hopes, as Dr. Berman said, that we can prevent microvascular disease down the line and so on. We actually know that some of these drugs are harmful. We've learned from studies that lowering A1c really intensively with drugs sometimes can have adverse events. So, it's really complicated, in the clinical domain, to care for these patients, because you're trying to get the biomarker low, but the tools are all sort of ones to just control the sugar.

Now, despite the long-standing recommendations of "lifestyle intervention", we just haven't had a way to effectively do that. So, as a clinician, to me this is a different paradigm. Now we're talking about a therapeutic that would enable patients, and as Dr. Berman says not necessarily the digital-savvy, the younger patient, it's actually the opposite, right, i.e. the people in the greatest need, we have an intervention that takes a lot of burden off of the clinician and the clinical space, and a lot of utilization of things like time for education, other things, that haven't been that successful, and where we can actually hope we can modify the course of disease.

So, I think of this as a foundational therapy. Right? First thing that a patient with diabetes says is, "I don't want to take insulin." Right? No one wants to take insulin. They don't want to progress and they don't want to have drugs. So despite the fact I might say, "Well you shouldn't have a doughnut," or whatever, like, we all know, myself included, it's hard to do that stuff. So, as a foundational therapy, the first thing we should be trying to do is prevent people from progressing to need more drugs, to getting more obese and having those complications.

So, as a clinician this is something I would consider very early on, I'd want to talk about with patients. As Dr. Berman said, there may be some people who do better or worse, we'll learn more from the data, and that will elucidate how we should translate it. But this is something I would reach for early, and broadly.

Rahul Rakhit

Got it. So, not to forage (phon) around, just kind of clarify or get some clarification on this: you don't see this as being something that is necessarily an alternative to drugs or something that can be used instead of treatments; you're saying this is something that's complementary and even maybe just earlier in line as a first line treatment prior to using drugs.

Marc P. Bonaca, M.D.

Yes, no, it's complementary for sure. There are certain diabetes drugs that have really great benefits that we've learned from the patients you get anyways. Right? I mean there are classes like SGLT2 inhibitors and GLP1 agonists. I certainly wouldn't say, "Don't give good drugs because they—you're getting this." This is how to treat a whole patient, right? But part of that would be, if I can prevent you from needing additional drugs, and there are some of these drugs, the older drugs, the secretagogues, where they may not be so good for patients, although they lower blood sugar, if I can prevent them from needing those or progressing to insulin, that's important, and I think this is part of a strategy for cardiometabolic care, one, of using the right drugs but I think even more importantly, what is driving the development of diabetes? What underlies it? It's not a blood sugar problem. It's a metabolic problem. It's a problem that has to do with obesity and all of the complex areas we go with that, of the—they call it the Ominous Octet, right? But this is a disease modifier, so you would want to use these synergistically with drugs and standard treatment.

Rahul Rakhit

Got it. No, really appreciate that color. I think that's just to the next thing I wanted to talk about is engagement. Obviously you saw these great results, and when Better Therapeutics put out the top line data they showed, I guess, kind of three buckets of engagement. In the highly engaged group we saw A1c reduction of 0.5%, in the moderate engaged group we saw A1c reduction of 0.3%. Look, once again, I know we're talking mostly about averages like you alluded to, Dr. Berman, so just to kick it off, would love to hear, just give a little bit more color on that, outside of just the averages, in this high responder group, moderate engagement group, low engagement group, I guess, what broader range of A1c change did you see? Was there a lot of variance, or did the patients kind of hug closely to that mean?

Mark Berman, M.D.

I think the most important thing when sharing that data is to understand why we're doing that analysis. When we're breaking out participants based on their level of engagement, the question is why are we doing that. What we're principally trying to do is to understand whether the dose of what is the mechanism of action, the behavioral therapy and what we call the nutritional cognitive behavioral therapy that we have delivered in this digital therapy, does the dose matter? I mean, remember, what's different

about this therapy versus say a drug is that this isn't a "one size fits all" dose. This is a therapy that allows participants to have a unique dose of CBT for them, and so the question is, does the dose matter? I mean, do you get a benefit if participants don't use it at all? Do you get more of a benefit if the participants use it more?

So we're looking to see, is there a dose response here? I think the data shows very clearly that, if a participant does not use the lessons, the CBT that's in the app, then their benefit is small; if they use a middle dose, the benefit is moderate; and if they use the higher dose, they get a higher benefit. So that trend, that what we'd call kind of a dose response, is what that data is really showing.

I think, as you noted in another conversation, like those middle and high engagers account for about three quarters of the patient population, so a sizable chunk of the patient population has self-selected, if you will, to have that type of dose, but it's very powerful information for us, it allows us to communicate to patients and providers, a little bit more clearly, what is the dose that is required, so for example the top tier dose was 10 lessons, so about 80% of the lessons that were delivered over the 13-week period. By no stretch an onerous ask of participants, but also more than just picking up the app for one day.

So, that information will be very helpful. The most important take-home, again, is that this establishes a dose response. There's something to using this mechanism of action that is associated with true clinical benefit.

Rahul Rakhit

Got it. I mean look, when we've seen a lot of digital therapeutics in other areas as well as in metabolic space, you tend to see engagement kind of wane over time. So, given that you've seen a greater improvement in A1c with a higher dose of nutritional CBT, should we expect to see kind of a similar drop-off if we do see engagement wane over time, particularly as we start to look out to 180 day outcome or as we think in the real world setting, as you look at patients in a one-year, two-year, or longer time frame, I guess how should we think about that?

Mark Berman, M.D.

It's a right question to ask, and I think you should think about it in a couple ways. One is, what is different about this form of digital therapy versus a consumer health apps for example? The mechanism of action here is different. This is a form of behavioral therapy, this is not a diet app or a tracking app. Those type of health consumer apps, it's very clear from the evidence that there is steep drop-off in terms of use over the course of even just a month. It's also clear that the benefits that you get with those consumer apps only last when the participants are using it. So, as soon as they stop using their health tracker or their diet app, they revert back to their prior behaviors, their weight goes up, their blood sugar goes up.

This is distinct from that, because we are delivering a form of behavioral therapy, a variant of cognitive behavioral therapy, and cognitive behavioral therapy is what is described by medical providers as a time-limited therapy, meaning that it's an effective therapy that is not intended to be used for life. This is not the equivalent of sitting on a couch for the rest of your life doing psychoanalysis. This is a focused and intense period of examining the thoughts and the ideas that drive human behavior, and learning how to fundamentally make changes in the way we think, the way the brain is organized to process information, so that you can progressively act in healthier ways.

So, with all CBTs, engagement is not expected to go on forever. Most CBTs typically are run for about 8 weeks to up to about 20 weeks. There's good evidence that that limited dose of intensive therapy will have effects that will sustain or even grow over many years to come.

So, when we think about engagement, we're of course interested in how people use the digital therapy on a daily basis and to what degree, but what really matters is, have they engaged in the underlying mechanism of action, the underlying therapy, and was that enough to effect both a clear benefit without additional harm.

So, the engagement that we saw with this on average, about eight lessons being done in that 90 weeks, with very strong retention at the end of that 90-day period, for us was very encouraging. It means that the vast majority of participants should be expected to get what would be a clinically meaningful dose of the behavioral therapy as a part of use of the app.

Rahul Rakhit

Got it. Appreciate that.

Dr. Bonaca, from your perspective, hearing that, knowing that they're kind of focusing the therapy in that 90- to 180-day window, I guess, how does that resonate with you? Do you think patients would be very receptive to that? Do you think it'll be enough to kind of drive these long-term changes? Maybe just give us your perspective.

Marc P. Bonaca, M.D.

I mean, I think it's very exciting that the notion of a legacy effect here, that you're enabling people to rethink how they interact with food and how that interacts with their health, I do believe that the benefits for those that are responders should amplify over time, because even though they're not interacting with the app the lessons, the change of therapy, the sort of impacts of that have been delivered and have been received.

So I think it's very exciting to think of a legacy effect here, and I think that's one of the questions my patients would ask me, is, "Well, do I have to do this forever?" They ask that for every drug. When I prescribe them drugs, they always say, "Do I have to take this forever?" No one wants to know that, and so I think the notion of a time-limited intervention, it's very well established for CBT, that can deliver long-lasting benefits, is extremely appealing, and we hope to observe that in the forthcoming data.

I'll just also comment on the dose response that Dr. Berman talked about, because I think that's also important: are you going to get the legacy effect unless you sort of engage with all of the lessons. Generally in trials we underestimate true engagement, because people don't know whether the thing works or not, right? There is an effect when you see a patient in the clinic and you say there's actually data. I have a lot of patients come in and they say, "Well I'm using this calorie tracker, or this nutritional thing, does it work?" I say I just don't know. If it works for you and it makes you happy, whatever, go ahead and do it, but I really can't say from a medical perspective it works or not. I think it's very powerful to say, this was shown in the gold standard of evidence to actually work and to be safe. That would mean to me I would expect in clinical practice that the proportion of patients who actually engage would be much greater in the real world, because you can talk about that trials, it's always uncertain and you have to be balanced around the equipoise (phon).

So, I think, as a clinician, most patients would love the fact that this is a time-limited engagement; I think if they know that it works, and that the benefits would be long-lasting, they're much more likely to engage than what was observed in the trial. I do think that it would have the potential to have long-lasting benefit.

Rahul Rakhit

Absolutely, got it.

I want to cognizant of your guys' time obviously, and the audience's time, so I think that this allows for a great segue into kind of setting the expectations for this next readout, about therapeutics, right? We're looking at this 180-day data expected in Q2; would love to just kind of level set expectations here, maybe starting with Dr. Berman, what do you think is a reasonable expectation for the change in A1c from 90 days to 180 days, what do you consider a home run? Just, I guess, underlying that, I guess, what are some of the nuances in the treatment that change from 90 days to 180 days that we should be keeping in mind as well?

Mark Berman, M.D.

That's important. So, I think a couple things. One is an ongoing trial, right, so we're in the midst of that, we have not yet seen any day 180 data, of course we're very excited to get our hands on it shortly. But thinking about how we designed this trial, the day 180 objective of this trial is to demonstrate a statistically significant difference between the A1cs of the two groups. The design objective is not to get some arbitrary margin, but just to show that there is a difference that persists.

The nuance that's really important to understand is that this is designed to be as close to real world as possible, with one notable exception: what I might call the prescription effect that Dr. Bonaca really nicely articulated, whereby you're getting a therapy from a trusted provider who can speak to evidence. We specifically left that out of the study, because it would potentially make it hard to interpret, was the effects coming from that therapeutic relationship or was it coming from the device itself?

But the other important nuance is that, at day 90, all these participants are receiving standard of care. The standard of care calls for regular and routine evaluation of blood sugar control, and for participants who are not well controlled to have their blood sugar—offered to have additional medications or additional therapies to improve their blood sugar. So, that means, at the day 90 point, when those physicians are looking at A1c results, they are free, as in the real world, to advise the patient to take additional medications.

To put that in context, about 90% of patients in the standard of care group are not at that point of control at day 90. So, that means a large number of participants potentially could be offered additional medications on top, irrespective of kind of what arm they are.

So, this is part of the interactions that we'll see, and we'll have to wait and see how that plays out on the population level.

But I think what's important to stress is that, in any case, however that plays out, the objective of the study is to determine, is there a true efficacy signal, and is that efficacy signal confounded by poor safety? What's the balance of efficacy and safety? So, kind of any way the data flows, our expectation is that we'll see that clear benefit versus safety signal established and kind of reinforced by that day 180 data as well.

Rahul Rakhit

Got it. Appreciate that. I know a long time that you guys were also running real world evidence study, which Dr. Bonaca, I think, you're a part of as well. Just kind of hoping to get your take on that. Tell us a little bit about what that study is, what you guys are hoping to learn from that study, and also, I guess to the extent that you can provide any insight into what you've seen in terms of patient receptivity and feedback to BT001.

Marc P. Bonaca, M.D.

Yes, no. Thank you. So yes, I mean, I'm a clinician here at University of Colorado, I don't work for Better Therapeutics, but for full disclosure I'm an investigator in one of the ongoing real world evidence trials. We started this trial before we knew the results of the pivotal study, which have been incredibly exciting.

As Dr. Berman said, when I talk to patients about the study, I'm very careful not to have that prescription effect. I don't want to—we want this to be a well controlled experiment. It is a controlled experiment, just like the pivotal study, and so I don't want to influence people's behavior just by my discussion. I am very careful about saying that you can be in this study and you'll get the app or a sham app, and that's it.

That being said, I've talked to a lot of patients now around sort of the concept of cognitive behavioral therapy as applied to nutrition, and the ability to use an app, and it's been very well received over all, and I think it's interesting, I guess I hadn't thought as a clinician about the barriers to change. When people come in the office, people don't understand their nutritionist, and maybe they're not doing so well with their diet or whatever. There's sort of a, even if you're supportive, a feeling of shame, right, or a feeling of like "well I'm not doing what I'm supposed to," you have to come into the office, you talk about it, "well your A1c's going up," and there's something private about doing this through an app, that they're under control of this in how they interact. The people I've spoken to really like the notion of them being empowered to take control of this, rather than them showing up somewhere to be told what to do.

So, it's been a really interesting revelation for me, and may actually modify a little bit of how I deliver care. So, I think that's been a very interesting observation.

From the real world data perspective, clinicians, I mean, clinicians want to know how it's going to apply to their patients. I think the pivotal study was very representative. But there are other populations and other groups, and having more data is always helpful. I'll say, as an investigator, I do a lot of clinical trials; what Better Therapeutics is doing is quite unique. I mean, delivering a standard of evidence that I've never seen in the digital area, and that even not so many drugs do, by doing multiple trials, different populations, slightly different designs, to really test the robustness of the findings, so that clinicians really understand and can communicate with their patients in terms of shared decision-making about whether it was right for them.

Rahul Rakhit

Understood, and appreciate that color.

I guess, kind of pushing on that and going a little bit further, I guess, if, given the differences in study design or some of the nuances between these two studies, I guess, ultimately, what are your expectations or how do you think the safety and efficacy outcomes might differ between what we see in a pivotal study and what we see in a real world study? What questions might ultimately answer about how this gets used, if BT001 gets approved and ultimately starts being utilized by a broader population?

Marc P. Bonaca, M.D.

Well, I think there are many downstream questions that remain to be answered. Pivotal trial results are exciting. Do they underestimate the true benefit in the real world? Maybe. Then what are all the downstream other issues? So, as Dr. Berman said, for people who aren't getting the app and they're getting treated with the standard of care, they probably will have an augmentation of their medical therapies; well some of those medical therapies lead to problems, like low blood sugar. Are we preventing emergency room visits for low blood sugar? Are we reducing the need for more drugs? Are we doing other things? I think those all are lessons that we need to learn from these other real world evidence

trials; and also broader populations. How does this work in the elderly? I've had a really great reception with calling people that I wouldn't necessarily, and this is my own deficiency, have expected to embrace a digital therapeutic. But, I don't see an upward limit of age, to be honest with this, in the discussions I've had. But I think all of those were lessons that we need to learn, and there's really going to be quite robust data set with all of the ongoing trials, to provide a unique glimpse at how to do this.

Rahul Rakhit

Got it. If I can sneak one more in, and obviously want to hear both of your perspectives on this. You kind of both have talked about how this is a fundamental change and honestly might lead to reversals in the bio-metabolic syndrome through a lot of these modifications. Is there a potential to see actual reductions in medication use, out to 180 days or even a longer time point, and if there is a change in medication use, could that ultimately have an effect on the delta that you see in A1c, if we're really taking that with a grain of salt when we look at it at 180 days over through the real world study out to a year or two years. Maybe if both of you could kind of touch on the potential for medication change and ultimately what kind of nuance that might have on what we see as the primary outcome.

Mark Berman, M.D.

This is another great question overall. I'll take a stab at it and pass it on to Dr. Bonaca.

So, is there a possibility for medication reduction? Absolutely yes. I think Dr. Bonaca expressed it really nicely in terms of what we might call medication avoidance. So, remember the clinical decision-making when a Dr. is faced with a patient who has type 2 diabetes that isn't well controlled, is "what do I do? I need to add a therapy, I'm only going to add one therapy at a time. So, should I add this digital form of therapy or should I put the patient on insulin," for example.

So, in that way there's a potential to avoid medications. Then, we also know from our prior experience that the patients who really robustly respond to behavioral therapy see A1c reductions that allow them to reduce their current medications, actually get off some of their medications. So, there is a definitive potential to reduce medication usage in that way too. The extent of it, that's one of the reasons why we're doing these real world evidence studies, is to be able to characterize how robust are those medication changes, when do they take place? We know that there will be some physician education, for example, involved, to really—a lot of doctors will put a patient on a medication and then it's just for life, they don't really think of the possibility that they could actually take a patient off the medication. So, we know that there'll be some education involved, but we'll look at the data to see how often that reduction will take place.

Then, to your other question about kind of how does that impact A1c reduction, well, what we'll be looking at, I think, are principally two things. One is population control: like how, by adding this therapy into the mix, have we been able to achieve better population control, as a result of that addition, or not. Then we'll be looking at the totality of evidence. Because you really need to integrate all the therapies that are used for patients with type 2 diabetes, and say what's the total cost? What are the total side effects? What's the total A1c reduction? What's the reduction in healthcare utilization or adverse events like heart attacks and emergency room visits, and where does that whole picture net out; as opposed to just one myopic variable of looking at A1c and A1c alone.

So, that's what's truly exciting about the work that Dr. Bonaca and the other investigators are doing, that longer view, that bigger picture view that includes healthcare utilization and cost and other outcomes, is really the part of the whole data picture that we want to look to see the true role for BT001 in the real world.

Rahul Rakhit

Appreciate it. Dr. Bonaca, I mean, anything to add?

Marc P. Bonaca, M.D.

No, I think Dr. Berman said it perfectly. It's going to be a huge experience and a robust experience. But I think the efficacy and safety now at 90 days have been established, that's great. Now it's all learning about the broader impacts of lowering that variable.

In terms of the drugs, you'd asked about that; I think we have to recognize that, in any trial where you don't blind the treating doctors to A1c, they're going to treat the groups disproportionately because the A1cs are different and they are forced to act based on A1c, and so that means any A1c delta that's observed underestimates the true effect. Right? Because there's an artifact there of people getting more medications, one arm or the other, and I think future analyses longer term will get to that. Are people taking fewer drugs, and not just number but what types? Because some have really good profiles, and some don't, and a lot that we used in diabetes don't. So I think it'll be important to learn that.

But, I think it's overall just an incredibly exciting result for establishing efficacy and safety, and then there's just a lot more to learn.

Rahul Rakhit

Got it. Yes, no. Appreciate that.

So, if I can squeeze one more out of you guys, both Dr. Berman and Dr. Bonaca, thank you so much, but if you each had to pick one or two things that is more important for the audience to walk away from this discussion knowing, what this data said with these broader studies, what's coming up, what do you think they would be? Dr. Berman, maybe we should start with you.

Mark Berman, M.D.

Sure, Rahul. Well, I think first, this is tremendously exciting. We are demonstrating for the first time a novel mechanism of action in nutritional CBT in a digital form. I think in this pivotal study we're clearly establishing that it is both efficacious and safe. So, that clear signal of efficacy, that clear absence of signal for safety, when you net that together, the take-home for us is that it gives us a little confidence that we'll have a positive interaction with the FDA when we submit our *de novo* application.

Rahul Rakhit

Got it. Dr. Bonaca, can you bring us home?

Marc P. Bonaca, M.D.

I think I agree with everything Dr. Berman said, and I guess I would just say, as a medical business community as a group, we have to rethink the paradigm of treating diabetes. I think that that's the eye-opener for me when I look at the data that, you know, the idea that we're going to give insulin, lowers A1c a certain amount, and that's going to wane over time, and then you're going to add the next thing, this is just a different mechanism, it's a different paradigm, and we can't get locked into the way we sort of measure other therapeutics here. We have to understand the mechanism, and what we're doing with patients. So, I've thought a lot about this. But it's not just another tool in the toolkit. It's just a totally

different toolkit that we're dealing with here, and I find that so exciting. I mean, I think it's really paradigm-changing in terms of how we consider enabling people treat their own diabetes.

Rahul Rakhit

Absolutely. I totally agree and totally think it's exciting and looking forward to see the 180 day data, really looking forward to see the results from the real world study. But in the meantime, would like to thank you both so much for the time, and thank you to everyone in the audience for joining us today. I think that kind of wraps up the day, so, really appreciate it. Everyone enjoy the weekend. Thank you.

Mark Berman, M.D.

Thanks everyone. Really appreciate it.