

Preliminary Results of the BeAT-HF Post-Market Randomized Clinical Trial

February 21, 2023

Opening Remarks by Nadim Yared

Good morning. Thank you for joining us today for this important update. I am excited to share with you some additional context to the press release that we issued earlier this morning where we shared the preliminary topline results to the post market phase of our BeAT-HF trial. As we stated in the press release, we have secured a spot at the Transcatheter Heart Failure Therapy Conference or “THT” in Boston on March 21st at 10:45 am Eastern Time for a member of the Executive Steering Committee of the trial to present the full data and we will hold an investor’s conference call later that day. For now, I will be limited to speaking only about the preliminary results that we shared in our press release. I will not be able to share with you the magnitude or statistical significance of any trends beyond what is described in our press release.

Slide Title - Forward-looking statements

Before we go further, I need to state that the remarks today will contain forward-looking statements, including statements about expected product developments, regulatory matters and business impacts. The statements are based on plans and expectations as of today, which may change over time. In addition, actual results could differ materially due to a number of risks and uncertainties, including those identified in the press release issued prior to this call and in the company's SEC filings.

Slide Title - BeAT-HF Study design

To help you better understand the preliminary data from the post market phase of the trial, I think it will be helpful to start by reminding you about the study design. The BeAT-HF Trial began enrollment in 2016 with a total of 408 patients being enrolled into the first phase of the trial. An intended use population of 264 patients was identified and was the basis for the 6-month data on safety and symptomatic improvements that led to FDA approval in 2019. Let’s go to the next slide to review some of the key data points that led to that approval.

Slide Title - Barostim was approved based on previous positive data

Starting with improvements in exercise capacity as measured in a standard 6-minute hall walk test. You can see that those patients receiving Barostim plus guideline directed medical therapy, or GDMT, that are represented in the dark blue had a 60-meter improvement in their 6 minute hall walk distance when compared to the control group, in the light blue, who remained on GDMT alone. There are two very important data points to help understand the magnitude of that improvement. The first is what has been established as being clinically meaningful is 25 meters as you can see in the dashed lines running through the bar graphs. The results in this measure were more than twice what is considered clinically meaningful. The second is data from several of the landmark CRT trials from the early 2000s. As you can see, the differences in the patients with CRT and GDMT vs. those who were treated with GDMT alone was more in the order of 30 to 40 meters. The results in patients with Barostim were about twice that.

For the sake of time, I will only briefly touch on the other two measures. You can see a reduction in the Quality-of-Life measurement as measured by the Minnesota Living with Heart Failure Questionnaire showed an improvement in the Barostim treated patients of 14 points compared to the control group -- remember in this assessment, negative scores are better. As you can see, this is more than 2X greater than the 5-point improvement that has been established as clinically meaningful.

And the third graph shows that 34% more patients who received Barostim on top of GDMT improved their NYHA Classification as compared to the control group.

Before we leave this slide, I would like to remind you of how incredibly important these impressive data have been to us. Along with the safety profile and other confirmatory endpoints, this is the data that led to FDA approval without the need to go to panel and the rapid increases in adoption of the therapy that we have been reporting over the last 2 years.

Slide Title - BeAT-HF Study design (repeated)

So now let's move on to the post-market phase of the trial. Again here is the basic study design I shared with you earlier.

As you can see, an additional 59 patients were enrolled into the trial that when combined with the original 264 patients in the intended use population increased the number of patients to 323. You can see on the bottom of the slide some of the endpoints, but let's examine them more closely on the next slide.

Slide Title - BeAT-HF post market randomized clinical trial

Starting on the left side of the slide with the primary endpoint that was a composite endpoint of cardiovascular mortality and heart failure morbidity. Cardiovascular mortality was comprised of patients who died or received an LVAD or heart transplant. These are terminal censoring events, they can occur only once per patient, and no further data is collected if they occur. Heart failure morbidity is a combination of heart failure hospitalizations and ER visits that required an IV diuretic. HF Morbidity events can occur multiple times in a single patient during the trial, and the total count is used in the calculation of this component. The composite endpoint was the rate of total cardiovascular mortality and heart failure morbidity events, analyzed using a negative binomial method.

As you know from our press release, this primary endpoint was not met. There wasn't a statistical difference between the two groups. Are we disappointed in that? Of course, we are. It would have been great to have demonstrated a statistically significant difference in this endpoint.

However, I am excited about what we observed on the right side of the slide. This portion of the slide describes some clinically meaningful prespecified analyses. In previous investor meetings, we have described the importance of the totality of the evidence to FDA. A pragmatic review of the totality of the data goes beyond the primary endpoint analysis. Let's take a closer look at these analyses to show you why I am excited by what we have reported.

Slide Title - What is Win Ratio analysis?

Let's start with the why: "why a Win Ratio analysis". If I could draw your attention to the gray box at the top of the screen it will highlight two major limitations when powering a trial for a mortality and morbidity endpoint. The first limitation of traditional methods of analyzing event endpoints is that it only uses information from patients who had an event, and that may represent only a fraction of all the patients that were enrolled in a trial. The second is the lack of a "hierarchical" aspect that treat all events in a similar fashion. Death and a heart failure hospitalization may be equal in what it means to the number of events in a trial, but they are not equal to what they mean to a patient and to their physician. The hierarchical composite analysis using a Win Ratio method captures the hierarchical experience of all the patients.

Let's take a look now at how they are measured. Starting from the far left you can see that every patient in the Barostim arm is compared to every patient in the control arm. Each pair of patients is then analyzed through the hierarchy of "events" to see who had the better outcome. For instance, in a pair being analyzed

if both were still alive, but the patient in the control group received an LVAD and the patient in the Barostim group did not, the Barostim patient would be the winner in that pairing. Approximately 25,000 possible pairs were analyzed, and the results will be described as a ratio of the total wins for the Barostim arm divided by the total wins for the control arm. If the result is greater than 1, it means the patients in the Barostim arm were more likely to have a better outcome than the patients in the control arm. As we communicated, this hierarchical Win Ratio favored Barostim.

While this analysis may be new to many of you, the computational power available these days is making it a very popular method of gaining a better understanding of the results of cardiovascular trials. We look forward to sharing these results with you at THT!

Slide Title - What is Clinical Stability?

The clinical stability analysis is another standardized way of assessing patient outcomes in clinical trials. It simply assesses each patient and assigns them to one of three outcomes. They either improved, stayed the same, or worsened. You can see on the screen the specific criteria for each of those assessments as prespecified in our trial. Again, we communicated that this analysis favored patients with Barostim.

Slide Title - What is terminal endpoint analysis?

In the BeAT -HF trial, the terminal endpoint analysis is a composite endpoint using a Cox proportional hazard model that looked at all causes of death, LVAD implantation, and heart transplantation. The description of this is often stated as "LVAD and heart transplant free survival" similar to our description in today's press release. We stated in the preliminary topline results that this very important measure favored Barostim. Mortality is considered a hard outcome in clinical trials, and is an important measure to patients and their physicians. We look forward to having the full data set presented.

Slide Title - Key take aways

So let me summarize the key take aways and next steps before opening the line for questions. Barostim is currently FDA-approved for the improvement of heart failure symptoms based on the pre-market phase data at 6 months. We have demonstrated a solid adoption rate in the USA based on the 6-month symptomatic data.

While the post market phase of the BeAT-HF Trial did not meet its primary endpoint assessing the cardiovascular mortality and heart failure morbidity, the safety profile and improvements in heart failure symptoms we showed in the pre-market phase of the trial have now been shown to be durable out to 12 months, and where pre-specified and assessed, to 24 months. This is incredibly important as I believe many physicians want to see that this benefit is durable.

And now we believe that Barostim may provide additional clinically meaningful benefits, as assessed using prespecified analyses such as the Win Ratio, the clinical stability and the terminal endpoint analyses.

Slide Title – Next steps

We believe that the new data, when presented, will be compelling to our customers and strengthen the case for Barostim. We look forward to having the full data set presented at THT on March 21st as a featured presentation, so that physicians can learn more about the results of this phase of the study and evaluate clinical benefits of Barostim for their patients.

The executive steering committee is planning to submit a manuscript with the results to be published in a peer-reviewed journal. And we plan to compile the full clinical report and submit it to FDA to seek an expansion of our labeling.

Slide Title – Questions?

Now, I would like to open the line for questions, operator.

Operator

Our first question comes from the line of Robbie Marcus with JPMorgan.

Robbie Marcus

JPMorgan Chase & Co, Research Division

Great. Nadim, maybe to start, you said your plan is to submit the trial findings to the FDA for PMA supplement. But at the same time, you're not talking about statistical significance. So is it fair to assume that when you talk about trends favoring Barostim, they must reach statistical significance to get them included in the label?

Nadim Yared

Robbie, a fantastic question, and thank you again for joining us today. I know it's been a busy morning for you. Listen, yes, FDA usually requires statistical significance. Usually, a statistical significance is meant to be a p-value of 0.05. That said, I've seen in some situations where FDA would say publicly, not to throw the baby with the bath water – maybe with I've heard them say that expression exactly. But in our case, I cannot comment at this stage, unfortunately, on the magnitude of the effects or the statistical significance of any single point.

Robbie Marcus

JPMorgan Chase & Co, Research Division

Got it. Okay. And as you think about the commercial rollout here, obviously, the trial not hitting the endpoint is going to be a headline negative to doctors, and we'll have to wait to see the benefit of the individual line items in the trial. But what's your expectation for how this might impact, positive or negative, the commercial rollout of Barostim, if at all?

Nadim Yared

Yes, Robbie. So first, the guidance that we articulated back in January when we announced the results, end of January is still – I'm sorry, is the guidance that we've published. There is no new guidance. That said, I personally believe this data is net-net positive and here is why. Number one, the long-term symptomatic benefit, long-term safety confirms what we've seen previously, not only to 12 months, but also when assessed and prespecified to 24 months. Second, in heart failure, for many, many decades, therapies that improved symptoms end up having a negative effect on mortality and negative effect on morbidity, meaning patients who took those drugs back in the days to improve their symptoms, end up dying faster.

Here with the terminal analysis – terminal endpoint analysis, we're showing that the data favors Barostim . So I think beyond the negative headline, as you mentioned, when people start looking into the data and when we will have an opportunity to share that data with them, both at the feature presentation at THT and later on in the manuscript and depending on the labeling that the FDA will provide us, I believe that the net-net will be positive to CVRx.

Operator

Our next question comes from the line of Matt O'Brien with Piper Sandler.

Matt O'Brien

Hi this is Sam on for Matt. Could you speak to the rate of heart failure hospitalizations a bit? We were thinking that more favorable LVAD implantation and heart transplant would also mean better heart failure hospitalization, but your thoughts on that would be great.

Jared Oasheim

This is Jared Oasheim, CFO here. Nadim's line got disconnected again. So I'm going to go ahead and take this one. At this point, we can't speak to any additional data that wasn't already included in the press release. So for the heart failure hospitalization information, all of that's going to have to wait until we get to the THT conference, and we can give more full information on the data.

Matt O'Brien

Okay. Great. I guess one more from us about the FDA label. Previously, you had spoken to potentially asking for removing the CRT ineligible in the label, and is there any change to that plan currently?

Jared Oasheim

So what we talked about in the press release is Nadim filing for the expansion of the FDA label. At this point, we can't go any further as to what that could potentially be because there will obviously be some discussion with FDA over the next few months. Once we have more information on that, we'll be able to share it publicly.

Operator

Our next question comes from the line of Margaret Kaczor with William Blair.

Margaret Kaczor

William Blair & Company L.L.C., Research Division

Hopefully, we'll get Nadim on at some point, but if not, happy to talk to you, Jared. In terms of kind of the thoughts of the time line events -- of events from here and the discussion between you and the FDA right now, how quickly do you think you can kind of turn around, submit this data and go from there? And then from a thought process of decision points, catalysts and so on, anything there would be helpful.

Jared Oasheim

So the report -- it's already 220 pages. I think we talked about this before. We actually got the data release that even with state data, all of the tables alone result in 220 pages of data. So it's going to take us some time to pull together all of the final information and analysis related to that report before we can submit to FDA. But just based on history, maybe that takes a month or 2. And then with the FDA, the expectation is that we would see a response around a 6-month marker, so around 180 days after the submission. And so -- all in, we're talking 7 or 8 months before we would get to the end conclusion with FDA, just saying that's an estimate.

Margaret Kaczor

William Blair & Company L.L.C., Research Division

Okay. No, that's helpful. And then I guess it's probably a little bit early, but is this data enough for you guys to change any of your commercial plans or outlook? And if yes, if not when would you expect to make that decision?

Jared Oasheim

Yes. And this is another topic we talked about before the data was released, right? We have this first part where we have top line information going out. We will have more data that's going to be available at THT and so we'll be able to share more information there and see reactions from physicians. But as Nadim said,

we gave guidance earlier in January, and there is no update to that today, but we are excited to continue investing in the business, seeing the significant growth we've seen historically.

Operator

Our next question comes from the line of William Plovanic with Canaccord.

William Plovanic
Canaccord Genuity Corp., Research Division
Great. Can you hear me okay?

Jared Oasheim
We can hear you, Bill.

William Plovanic
Canaccord Genuity Corp., Research Division

Good. Yes. Tough when its coming in and out there, Nadim. Can -- just on Entresto and the new HF drugs, how could they have impacted the differences between the arms for the M&M data? Just any thoughts on that would be helpful. That's all I have.

Nadim Yared

That's a fantastic question. You know the problem that this trial is phased, is the duration of 7 years. We designed in 2015, and we're showing the data in 2023. Over 7 years, 2 new drugs were approved Entresto and SGLG2 so if all of the drugs are adopted the same way between the arms, then the impact should be neutralized if there is a differential involved in the introduction of the medication in each arm involved with these could have impacted results.

Operator

Our next question comes from the line of Frank Takkinen with Lake Street.

Frank Takkinen
Lake Street Capital Markets, LLC, Research Division

I wanted to start with the reimbursement topic a little bit. Could you just touch on any expected positive or negative changes to reimbursement from this data?

Jared Oasheim

Sorry again about the issues with Nadim's mic. I'm not sure what's going on there. Just to reiterate on the question from Bill on Entresto and SGLG2 we know that those drugs were released throughout the trial. And if there is an uptake -- a higher uptake in one arm over the other, it could have an impact on the results that we see in the trial. We can't give any additional information on that topic as far as what we observed until we get to THT. Frank, for your question on the impact of reimbursement, this is something we've been very clear on over the last year in communicating to all of the investment community is that this readout of the trial has no impact on the reimbursement that we have today.

So we have the transitional pass-through, the add-on payment for outpatient procedure. That stays, right. There is nothing that was dependent upon the readout of this trial for our reimbursement. And so the additional data that we have that will be released further at THT will allow us to have additional conversations with physicians and with payers. But we expect no negative impact on reimbursement from the readout of this trial.

Frank Takkinen

Lake Street Capital Markets, LLC, Research Division

Okay. That's helpful. And then maybe one more for me. In the concept of kind of pull-forward demand from physicians, just curious if anecdotally you were hearing anything from physicians adopting the Barostim technology under the premise that it would meet the M&M data endpoint so that they can start kind of offering the technology in front of that change? Any sense to that concept on a pull-forward demand scenario under the idea that mortality and morbidity would be positive? Or is that not something that was occurring in real time in the market?

Jared Oasheim

Thanks for the question, Frank. Yes, that is not something that we've heard about from our customers to date. At this point, all of the reasons that they're using the device over the last 2 years and the ramp that we've seen is based purely on the symptomatic data that we had as a readout from 6 months. Nadim mentioned this earlier that -- we now have 12 and 24 months symptomatic data that was positive and the additional analyses that favored Barostim. And so we will see the reaction from physicians after the full data set is presented at THT. But historically, none of it was dependent upon an assumption that we would see a positive readout from morbidity and mortality.

Operator

Our next question comes from the line of Alex Nowak with Craig-Hallum.

Alex Nowak

Craig-Hallum Capital Group LLC, Research Division

I just want to confirm the secondary endpoints, those are statistic significant or was it that you just don't know what the current state since the analysis is underway.

Jared Oasheim

Nadim mentioned this earlier, maybe his line was breaking up a little bit, but at this point, we're not able to talk about statistical significance as that data has been embargoed for the THT presentation. So the only thing that we can say at this point is that they favored Barostim and that's in line with what we had communicated in the press release.

Alex Nowak

Craig-Hallum Capital Group LLC, Research Division

Okay. Understood. And then what are the secondary endpoints were ran and assessed, and generally what was their outcomes in addition to the ones we talked about this morning?

Jared Oasheim

Yes. Any additional analyses are going to be discussed at THT. Like I mentioned before, the jumbled data before we had the actual information in that clinical reports was 220 pages. So there are a lot of analyses that were run and more data will come out over time. But at this point, the only thing we can mention is the information that's in the press release.

Alex Nowak

Craig-Hallum Capital Group LLC, Research Division

Okay. That makes sense. And then just clarification. What will be the actual FDA label that you'll submit for? And then I have a follow-up question as what comps do you look to out there that you're using to assess the kind of guide the process. You're kind of in a special situation here. You showed a symptom

improvement. You got approval. You're missing the primary, but you also have very favorable secondary endpoints. So is there anyone out there you can use as a comp here?

Jared Oasheim

Yes. So on the first piece, what will FDA allow us to claim for a label. We mentioned that earlier. We're not going to go into details on what that would look like and negotiated here publicly. We'll have conversations with FDA as we get to the submission phase and see what the label could look like in the future. As far as comps go, I think we have seen some other trials that have missed the primary endpoints. The CardioMEMS as an example, where they then went to FDA with secondary and prespecified analyses, and we're able to get an FDA approval. So these situations do exist in the past. And for us, it's about submitting the totality of the evidence to FDA to then get their response as far as what the label could look like in the future.

Operator

Our next question comes from the line of Robbie Marcus with JPMorgan, a follow-up.

Robbie Marcus

JPMorgan Chase & Co, Research Division

Just a quick follow-up for me. Jared, I believe you did an analysis adjusting for the impact of COVID on the trial. Anything you could comment on that outcome?

Jared Oasheim

Robbie, thanks for the question on that one. That is another one of the analyses that are going to have to wait until we get to THT before we can go into it any further. But we're excited to share the full set of data with everybody at THT.

Operator

I'm showing no more questions in the queue. I'd like to turn the call back over to management for closing remarks.

Jared Oasheim

All right. Thank you, operator, and thanks again, everyone, for joining us today on our update call. We appreciate your ongoing support and look forward to providing more information on the full trial results at THT on March 21. Have a great day.

Operator

Ladies and gentlemen, this concludes today's conference call. Thank you for your participation. You may now disconnect.