FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE (CRDAC) MEETING

Virtual Meeting

Tuesday, December 13, 2022

9:00 a.m. to 4:43 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Rhea Bhatt, MS

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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Csaba P. Kovesdy, MD, FASN

The Fred Hatch Professor of Medicine

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Donald W. Seldin Distinguished Chair in

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. LEWIS: Good morning, and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email and phone number are currently displayed.

My name is Julia Lewis, and I will be chairing this meeting. I will now call the December 13, 2020 [sic - 2022) Cardiovascular and Renal Drugs Advisory Committee meeting to order. Rhea Bhatt is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

MS. BHATT: Good morning. My name is Rhea Bhatt, and I'm the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

First, we'll begin with the CRDAC members,

starting with Dr. Bairey Merz.

DR. BAIREY MERZ: Welcome. Noel Bairey Merz, Cedars-Sinai, Smidt Heart Institute, Los Angeles.

MS. BHATT: Thank you.

Next, we have Dr. Kovesdy.

DR. KOVESDY: Good morning. Csaba Kovesdy, a nephrologist at the University of Tennessee Health Science Center and the Memphis VA Medical Center.

MS. BHATT: Thank you, Dr. Kovesdy.

Next, we have Dr. Lewis.

DR. LEWIS: Julia Lewis, nephrologist, Vanderbilt, chairperson.

MS. BHATT: Thank you.

Next, Dr. Moliterno?

DR. MOLITERNO: Hi. Dr. David Moliterno. I'm a cardiologist and professor of medicine at the University of Kentucky.

MS. BHATT: Thank you, Dr. Moliterno.

Dr. O'Connor?

DR. O'CONNOR: Good morning. Christopher

O'Connor. I'm a heart failure cardiologist, and I'm president of the Inova Heart and Vascular Institute in Northern Virginia.

MS. BHATT: Thank you.

Next, Dr. Rossert.

DR. ROSSERT: Good morning. Jerome Rossert. I'm a nephrologist working at AstraZeneca, and I'm the industry representative.

MS. BHATT: Thank you.

And Dr. Thadhani?

DR. THADHANI: Good morning. Ravi Thadhani, chief academic officer at Mass General Brigham and nephrologist. Thank you.

MS. BHATT: Thank you, Dr. Thadhani.

Next, we'll move on to temporary voting members. First we have Dr. Blaha.

DR. BLAHA: Hi. Michael Blaha. I'm professor of medicine, cardiology, and epidemiology at the Johns Hopkins Ciccarone Center for the prevention of cardiovascular disease.

MS. BHATT: Thank you, Dr. Blaha.

Ms. Dunn?

MS. DUNN: Debra Dunn. I'm a heart failure patient, and I'm a patient advocate.

MS. BHATT: Thank you.

Dr. Gillen?

DR. GILLEN: Yes. Daniel Gillen. I'm professor and chair of statistics at University of California, at Irvine.

MS. BHATT: Thank you.

Next, we have Dr. Nissen?

DR. NISSEN: Hi. Steve Nissen. I am the chief academic officer of the Heart and Vascular Institute at the Cleveland Clinic.

MS. BHATT: Thank you, Dr. Nissen.

And Dr. Wang?

DR. T. WANG: Hi. Thomas Wang. I'm the chair of medicine at UT Southwestern Medical Center.

MS. BHATT: Thank you, Dr. Wang.

Next, we'll move on to FDA participants.

Dr. Joffe?

DR. JOFFE: Hi. Good morning. I'm Hylton Joffe, the director of the Office of Cardiology,

Hematology, Endocrinology and Nephrology in CDER at the FDA.

MS. BHATT: Thank you, Dr. Joffe.

Dr. Stockbridge?

DR. STOCKBRIDGE: Good morning. I'm Norman Stockbridge. I'm the director of Division of Cardiology and Nephrology in FDA, CDER.

MS. BHATT: Thank you.

Dr. McDowell?

DR. McDOWELL: Hi. Good morning. I'm Tzu McDowell, clinical reviewer from the Division of Cardiology and Nephrology, CDER, FDA.

MS. BHATT: Thank you.

Dr. Koh?

DR. KOH: Hi. William Koh, stats, Office of Biostats, Division of Biometrics II.

MS. BHATT: Thank you, Dr. Koh.

And Dr. Wang?

DR. L. WANG: Hi. This is Li Wang, the clinical pharmacology reviewer from the Office of Clinical Pharmacology, FDA.

MS. BHATT: Thank you, Dr. Wang.

That concludes panel and FDA introductions.

Dr. Lewis?

DR. LEWIS: Thank you, Rhea.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues. Individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the

media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Rhea Bhatt will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

MS. BHATT: The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is deemed that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting;

expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of new drug application 216401, for omecamtiv mecarbil tablets, submitted by Cytokinetics. The proposed indication is to reduce the risk of cardiovascular death and heart failure events in patients with symptomatic chronic heart failure with reduced ejection fraction. The committee will discuss whether the phase 3 trial establishes substantial evidence of effectiveness of omecamtiv mecarbil and whether the benefits of omecamtiv mecarbil outweigh the risks when used according to the applicant's proposed dosing regimen. This is a particular matters meeting during which specific matters related to Cytokinetics NDA will be discussed.

Based on the agenda for today's meeting and all financial interest reported by the committee members and temporary voting numbers, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we

encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Jerome Rossert is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Rossert's role at this meeting is to represent industry in general and not any particular company. Dr. Rossert is employed by AstraZeneca.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at

issue. Thank you.

Back to you, Dr. Lewis.

DR. LEWIS: We will proceed with FDA introductory remarks from Dr. Norman Stockbridge.

FDA Opening Remarks - Norman Stockbridge

DR. STOCKBRIDGE: Good morning. I want to thank each of you for the work you've put in preparing for today's meeting, as well as the time that you are spending today. Despite the range of product classes that have been approved for the treatment of heart failure, there remains an unmet need.

Evidence of need can be seen in GALACTIC-HF, where there were 2300 heart failure patients hospitalized; 1600 cardiovascular deaths; and 2100 deaths from any cause that occurred among the 8200 patients enrolled. Today, we will explore with you how omecamtiv mecarbil potentially addresses those needs.

As you know, the division laid out certain expectations about the evidence needed to support approval. The sponsor proposed a primary endpoint

of death plus hospitalization, and the division asserted that one study at p less than 0.05 would suffice if both components contributed to the findings. In the case that the claim was only on hospitalizations, the division proposed that the single studies supporting approval would need a p less than 0.01. The committee will need to opine on whether that advice was reasonable.

Although mortality was not the primary endpoint, GALACTIC-HF was designed to support a mortality claim. It was an event-driven study powered at 90 percent to show a 20 percent effect on cardiovascular mortality, and as it was planned, it enrolled until the required 1600 or so cardiovascular deaths were observed.

GALACTIC-HF rejected the null hypothesis for its primary combined morbidity/mortality endpoint, and it ruled out an effect on mortality in either direction of about 8 or 9 percent relative risk. Objectively, the study did not satisfy the division's specifications for a claim based on hospitalization alone.

Superficially, the case for approval here is similar to that supporting vericiguat for chronic heart failure on the basis of the VICTORIA trial. VICTORIA showed a 10 percent relative risk reduction in cardiovascular death plus heart failure hospitalization with p equals 0.02. However, in VICTORIA, there was a 7 percent risk reduction in cardiovascular death, almost as large as the effect on cardiovascular death excluded in GALACTIC-HF.

There was a more than theoretical concern about the consequences of high exposure to omecamtiv mecarbil. The sponsor implemented a program to ensure subjects remained within certain exposure limits. This plan seems to have worked to eliminate excursions in exposure that can be clearly related to adverse cardiovascular effects.

On the other hand, heart failure hospitalization is an important risk factor for death, but reduction in hospitalizations did not translate into mortality reduction in GALACTIC-HF. The committee should opine on whether it is

reassured by the neutral effect on mortality or troubled by the lack of expected benefit. I look forward to hearing your discussion on these matters, and I appreciate your service today.

DR. LEWIS: Thank you, Dr. Stockbridge.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the

committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Cytokinetics' presentation.

Cytokinetics?

Applicant Presentation - Rachel Melman

MS. MELMAN: Good morning. My name is Rachel Melman, senior director of Regulatory Affairs, and on behalf of Cytokinetics, I thank the advisory committee members and the FDA for the opportunity to present our data supporting the efficacy and safety of omecamtiv mecarbil for the treatment of heart failure with reduced ejection fraction. Most importantly, we thank the patients suffering from this serious disease, who have participated in our clinical trials, especially during the pandemic.

Despite advances in guideline-directed medical therapy, patients with heart failure with

reduced ejection fraction, or HFrEF, remain at high risk for adverse outcomes such as hospitalization and emergency department visits. Omecamtiv mecarbil was designed and developed to address this unmet clinical need by directly targeting the contractile apparatus of cardiac muscle, the central mechanism of dysfunction in HFrEF. Today, we will present the results from the GALACTIC-HF trial, which showed improved outcomes for patients with HFrEF.

When we analyzed the data, we saw that the treatment effect is increased for patients with higher risk factors for adverse outcomes, in particular in patients with lower ejection fraction. Importantly, safety and patients on omecamtiv mecarbil was similar to that seen in patients on placebo.

When we analyzed with the positive data from GALACTIC-HF and our goal of directing treatment to the patients who will benefit the most, we submitted our NDA with the proposed indication statement that omecamtiv mecarbil is a cardiac

myosin activator indicated to reduce the risk of cardiovascular death and heart failure events in patients with symptomatic chronic heart failure with reduced ejection fraction. Benefits are increasingly evident the lower the left ventricular ejection fraction. Our goal for omecamtiv mecarbil is to deliver a safe and effective medicine to the patients who will derive the greatest benefit.

We recommend that the labeled indication reflects the patient population in which the benefit was observed to be highest, specifically in patients with lower ejection fraction who despite guideline-directed medical therapy continue to have persistent or worsening chronic heart failure.

The development of omecamtiv mecarbil has been extensive, including approximately 10,000 patients with heart failure. It initially entered the clinic in 2005. Initial clinical trials continued through 2015, when we completed the phase 2 trial, COSMIC-HF. During this time, we had multiple engagements with FDA to discuss the progress of the program and to inform future

development.

COSMIC-HF served as the basis for the end of phase 2 interactions with FDA, and we again collaborated with FDA to design and agree on the program for the phase 3 trial, GALACTIC-HF, which was initiated in 2017 and completed in 2020. The data from GALACTIC-HF served as the basis for the presubmission meetings with FDA and supported the NDA submission in late 2021, bringing us to today's advisory committee meeting.

In the GALACTIC-HF trial, we saw a beneficial effect of omecamtiv mecarbil on the primary composite endpoint, and that effect was increased and greater in those patients who are at increased risk for heart failure events. The safety profile was consistent with that of the placebo group, and importantly there were no imbalances in major adverse cardiovascular events or death, whether due to cardiovascular or all-cause reasons. Today, we will present substantial evidence of effectiveness that supports the use of omecamtiv mecarbil in HFrEF patients who

are at increased risk.

In its 2019 guidance, FDA describes multiple criteria that can be used to fulfill the statutory requirement for substantial evidence of effectiveness. We intend to show how the omecamtiv mecarbil clinical program fulfills these criteria using one adequate and well-controlled clinical trial plus confirmatory evidence.

Today we will focus on presenting data from GALACTIC-HF, an adequate and well-controlled clinical trial, and data from COSMIC-HF, another adequate and well-controlled clinical trial which provides strong mechanistic support for the effects seen in GALACTIC-HF. The mechanistic data from COSMIC-HF provide the confirmatory evidence for substantial evidence of effectiveness.

Here is an outline of our presentation. Dr. Michael Felker, professor of medicine at Duke University and chair of the clinical events committee in GALACTIC-HF, will describe the residual risk that remains for patients with HFrEF. Dr. Fady Malik will present the clinical efficacy

data, and Dr. Stuart Kupfer will review the safety and dosing data from GALACTIC-HF.

Dr. Scott Solomon, professor of medicine at Harvard Medical School, will provide clinical context and review the benefit-risk profile of omecamtiv mecarbil in HFrEF. Drs. Felker and Solomon are both recognized experts in the field of heart failure and clinical trials and were members of the executive committee for GALACTIC-HF.

Additionally, Dr. Brian Claggett from the Brigham and Women's Hospital played a key role in analyzing the data from GALACTIC-HF and is attending as an expert in biostatistics. We also have several Cytokinetics employees here to address your questions. We look forward to the discussion today and thank you for your participation.

Now, I will turn the presentation over to Dr. Felker.

Applicant Presentation - Michael Felker

DR. FELKER: Good morning. I'm Michael Felker, professor of medicine at Duke University. I'm a consultant to Cytokinetics, as well as to

many other companies in the heart failure space. I served on the executive committee and chaired the clinical events committee for the GALACTIC-HF study. In addition to being a clinical trialist, I'm a practicing heart failure cardiologist and see patients across the spectrum of heart failure, from ambulatory heart failure patients, to those with cardiogenic shock, heart transplant, or LVAD. Today, I'm going to discuss unmet needs in heart failure patients with reduced ejection fraction or HFrEF.

As I think everyone is aware, HFrEF remains a major unsolved public health issue. Despite the substantial improvements we've made in recent decades with guideline-directed medical therapy, or GDMT, the risk of adverse outcomes in patients with HFrEF remains high, especially in higher risk groups.

High-risk patients with HFrEF have both higher absolute risk and are less likely to tolerate currently available GDMT, which further increases their risk. This results in a clear

unmet need for therapy that is both effective and well-tolerated in these higher risk patients.

The prevalence of heart failure continues to increase due to several epidemiologic trends, including the aging in a population, the increased prevalence of obesity and diabetes; and also due to some of our successes in acute cardiovascular care, patients are more likely to survive acute cardiovascular events like myocardial infarction, and go on to live with chronic heart failure. These trends result in an increasing burden on our healthcare system from heart failure.

Patients with chronic heart failure have daily limitations on their functional capacity and quality of life, but they are also risk for recurrent heart failure events. There are now over 1 million heart failure hospitalizations per year in the United States, and many patients, especially higher risk patients, experience frequent and recurrent rehospitalization. Heart failure hospitalizations are the key morbidity of heart failure, with profound implications for patients,

their families, the healthcare system, and the overall cost of medical care. Reducing this burden of heart failure hospitalizations, especially in the highest risk patients, is a key therapeutic goal.

There are currently four classes of drugs that are clearly established to improve cardiovascular mortality and reduce heart failure hospitalizations in patients with HFrEF. All of them have a class I indication in the relevant guideline, including beta blockers; angiotensin receptor neprilysin inhibitor or ARNi; mineralocorticoid receptor antagonist; and SGLT2 inhibitors.

Collectively, these drugs form the foundation of what's termed guideline-directed medical therapy in heart failure and represent a significant success story in our ability to treat heart failure patients. One critical point, however, is that even patients treated with our very best foundational therapy with these four agents continue to have a high, and I would argue

unacceptably high, risk of cardiovascular events.

These are data from the treatment arm of two recent SGLT2 inhibitor trials and heart failure with reduced ejection fraction, DAPA-HF and EMPEROR-Reduced. I chose to show these data because this is about as good as it gets for background therapy in HFrEF in the clinical trial. You can see the use of background GDMT in the table for each study, and of course because these are data from the treatment arms, all the patients shown here are treated with SGLT2 inhibitors.

While there are some differences in the risk profile of the populations between these two trials, you can see that for all these relevant outcomes -- whether the primary outcome, which was the composite of cardiovascular death on heart failure events; or for CV death; heart failure hospitalizations; or all-cause death -- there continues to be very high residual risk even despite the best therapy.

Now, in isolation, these numbers may lack some context. Shown here in blue are the rates of

cardiovascular death for the two trials from the previous slide, DAPA-HF and EMPEROR-REDUCED, as well as for GALACTIC-HF. The orange bars provide a comparison to CV death rates and other common chronic cardiovascular conditions, either primary prevention or secondary prevention of cardiovascular disease with statins; or PCSK9 inhibitors; treatment post myocardial infarction in the PARADISE-MI trial; or treatment of chronic hypertension in SPRINT. Even though we've had a lot of successes in improving cardiovascular outcomes in our patients with HFrEF, it's clear that the residual risk is still extremely high when we compare it to other types of cardiovascular disease.

Here's a similar concept for contextualizing what we mean when we say high risk in patients with heart failure compared to other common cardiovascular problems like atherosclerotic cardiovascular disease. This comparison clearly demonstrates there is no such thing as a low-risk heart failure patient; there are only various

gradations of high risk.

Now, the data I've shown are from broad populations of HFrEF patients, but of course all patients have different risk profiles. We have very well-established markers that identify HFrEF patients who are particularly higher risk. While there are a large number of these markers, here are five that come up repeatedly: lower ejection fraction; lower systolic blood pressure; higher natriuretic peptides such as NT-proBNP; recent heart fair hospitalization; or more severe symptoms expressed as NYHA class.

Among these risk markers, ejection fraction is a key measure that we use to risk stratify patients with heart failure. As one of many examples, these data show the relationship between ejection fraction and risk in patients from the combined database of six large randomized-controlled trials in heart failure. If you focus on the group with EF less than or equal to 35 percent on the left of this curve, which was the group we enrolled in GALACTIC-HF, you see a very

strong relationship between lower ejection fraction and higher risk. The curves been sharply upward at an ejection fraction of approximately 30 percent.

Now let's examine some of these high-risk features in heart failure in an optimally treated HFrEF population, which we looked at earlier. Shown here again are data from the treatment arm of DAPA-HF stratified by quartiles of some of these high-risk markers: lower ejection fraction, lower systolic blood pressure, higher natriuretic peptide. They all show about a doubling or greater of event rates between the lowest and highest risk quartile. These data clearly demonstrate that even on optimal GDMT, the highest risk patients still have extremely high risk of adverse outcomes.

Shown here are not clinical trial data but real-world data, this time from Duke University Health System where I work. This looks at the risk of recent hospitalization, in this case defined as a hospitalization within the last year, again showing that those patients with a prior heart failure hospitalization within the last year are

extremely high risk. Notably, if you look at the Y-axis, you see the risk rates we're talking about are much higher, more than triple what we've seen in the clinical trials, pointing out that in the real world, often a patient's risk is much higher than what we see in the optimal situations that we often find randomized clinical trials. These risk factors, which we'll talk more about over the course of the day, both individually and collectively, can help us identify higher risk patients with heart failure.

So why does that matter? It matters because perhaps counter-intuitively, the data are very clear that the highest risk patients tend to be treated the least aggressively. This is real-world data from Ontario Canada looking at patients who were hospitalized for heart failure with reduced ejection fraction stratified by their actual risk. The blue bars are the lowest risk patients, the orange bars are the middle risk patients, and the highest risk patients are in red.

What we can see is that both hospital

discharge and during chronic follow-up, the lowest risk patients were treated the most aggressively and the highest risk patients the least aggressively. The reasons for this are complex, but generally relate to intolerance and the challenges of treating the high-risk patients for the therapies we have available now. This is particularly due to the overlapping intolerance as shown on the right side of the slide, such as renal dysfunction, azotemia, hypotension, et cetera. Again, I think this is a critical message. In clinical practice, the highest risk patients are treated the least aggressively primarily due to challenges with intolerance of current GDMT.

We know that higher risk patients have a lot of residual risk and they have the most to gain from effective therapies. Because their absolute risk is high, every bit of relative risk reduction they can get makes a big difference in terms of events actually prevented. Unfortunately, the patients in the highest risk groups are less likely to tolerate guideline-directed medical therapy, and

the reason is they tend to be older, have more comorbidities such as chronic kidney disease. They tend to have lower blood pressure and also to have more orthostatic symptoms at a given blood pressure. These are all things we see regularly in clinical practice taking care of HFrEF patients. They present big challenges in providing the best possible treatment.

The significant challenge with our current therapies and in getting heart failure patients on the best treatment relates to overlapping intolerances. All of the current heart failure therapies listed here contribute to varying degrees of some of these intolerances. In clinical practice, a significant challenge -- maybe our biggest challenge -- in managing patients with HFrEF is optimizing therapy in the face of these intolerances.

We've talked a lot about the challenges of intolerance for GDMT, especially in high-risk patients. Here are some data from the LIFE study, a clinical trial of the ARNi sacubitril/valsartan

in patients with more severe heart failure. Patient population on LIFE was focused on the high-risk patients we've been discussing with a mean ejection fraction of 20 percent.

The LIFE trial had a run-in period to ensure patients could tolerate sacubitril/valsartan before being enrolled in this study. As you can see, 18 percent of patients could not tolerate the run-in period at the lowest dose. Reasons for intolerance are listed here, including many of the reasons we've discussed already, including hypotension, renal dysfunction, and hyperkalemia.

Another 19 percent of patients who made it through the run-in discontinued study drug during the 24-week trial. Thus, cumulatively, 37 percent of these high-risk HFrEF patients could not tolerate sacubitril/valsartan for 24 weeks. These data demonstrate some of the challenges at initiating or optimizing GDMT in high-risk patients with HFrEF.

In conclusion, I think it's clear that despite the very significant advances we've had in

guideline-directed medical therapy, there is substantial residual risk in our patients with HFrEF. We can clearly identify higher risk patient subgroups using readily available clinical markers such as ejection fraction. These high-risk groups of patients are also less likely to tolerate currently available guideline-directed medical therapy, further enhancing their risk.

I believe there's a clear unmet need for therapies that improve outcomes in these patients and do not have overlapping intolerances with currently available therapies for heart failure. I thank you for your attention, and now I'll turn our presentation over to Dr. Malik.

Applicant Presentation - Fady Malik

DR. MALIK: Thank you, Dr. Felker.

Good morning. I'm Fady Malik, executive vice president of Research and Development at Cytokinetics. As a physician, scientist, and a cardiologist, I've led the development of omecamtiv mecarbil since initiating its discovery program over 20 years ago. Thousands of people have

contributed to what I'm about to describe, including many talented people at Cytokinetics, our collaborators, and most importantly, patients and investigative sites around the world. I would like to recognize our contributions because without their efforts, we would not be here today. I'd also like to extend my thanks to the committee for their commitment to this advisory meeting.

My presentation today, I'm going to review four topics: first, the mechanism of action of omecamtiv mecarbil; second, the phase 1 and phase 2 clinical development program; third, the main efficacy results from the pivotal trial GALACTIC-HF; and finally, I'll review important subgroup analyses of the same trial.

We're here today, following the pursuit of the therapeutic hypothesis that improving cardiac function in a manner that's safe and well tolerated will improve clinical outcomes in patients with heart failure and reduced ejection fraction. Existing inotropes -- or more specifically, calcitropes -- work indirectly on the sarcomere,

the contractile element of the cardiac myocyte, by increasing the extent of calcium release. However calcitropes also increase heart rate, they decrease blood pressure, they increase oxygen demand, and they provoke arrhythmias, and historically have been shown to worsen clinical outcomes in patients with heart failure.

We hypothesize that avoiding the increase in calcium by directly targeting the sarcomere itself, and in particular the motor protein myosin that's responsible for generating contractile force that circumvent these limitations and ultimately improve clinical outcomes.

Following an extensive drug discovery effort focused on the cardiac sarcomere, the selective small molecule cardiac myosin activator, omecamtiv mecarbil, was synthesized and selected for development. Omecamtiv Mecarbil binds directly to the mechanicochemical domain of myosin, stabilizing it in the state, ready to bind to the actin filament and undergo a force producing power stroke. Shortening of the sarcomere and the

subsequent contraction of muscle is like a tug of war, where the rope is the actin filament and myosin is the hand pulling on the rope. As you can see here on the right, omecamtiv mecarbil results in more hands on the rope, increasing the contractile force of each heartbeat.

Preclinical studies showed that by fundamentally increasing the underlying contractility of cardiac muscle, omecamtiv mecarbil increased cardiac performance, and unlike calcitropes, this happened in the absence of changes in myocyte calcium. Uniquely, omecamtiv mecarbil increased the duration of systole, and given the effects on cardiac function were consistent with a therapeutic hypothesis, omecamtiv mecarbil advanced in the clinical development, and I'd like to briefly review the early clinical development of omecamtiv mecarbil.

The studies listed on this slide were critical to understanding the exposure-response relationship and the safety of omecamtiv mecarbil, first in healthy participants, and then in patients

with acute and chronic heart failure. In particular, I'd like to highlight two trials of several hundred patients.

First the ATOMIC-HF trial established the safety and tolerability of omecamtiv mecarbil in patients with acute heart failure. Second, COSMIC-HF, which is an oral formulation, established the safety and tolerability of omecamtiv mecarbil in ambulatory chronic heart failure outpatients, as well as piloting the doses that were employed in phase 3. Altogether, these trials contributed to the design of GALACTIC-HF, the pivotal phase 3 trial that enrolled patients from both the inpatient and outpatient settings.

In the phase 1 and early phase 2 studies, intravenous infusions of omecamtiv mecarbil up to 72 hours were used to explore its exposure-response relationship. As we can see here, there's a strong relationship between increasing plasma concentrations of omecamtiv mecarbil, plotted on the X-axis, and increases in the systolic ejection time, plotted on the Y-axis. This systolic

ejection time is the time the heart spends contracting and ejecting blood during each cardiac cycle, and historically was one of the earliest measures of cardiac function, where more severe left ventricular dysfunction was associated with a shortening of the systolic ejection time.

There's a strong relationship between the exposure and the increase in systolic ejection time, covering a range from 0 up to approximately 1200 nanograms per mL with similar and healthy participants and in patients with heart failure; shown on the right, the increase in ejection time correlated with increases in ejection fraction, fractional shortening, and stroke volume.

Here's an example of a representative patient who received a 24-hour infusion of omecamtiv mecarbil. The left ventricle is at the top of the image and the left atrium is at the bottom. Compared to the baseline images on the left, we can see on the right the contractility of the left ventricle and the left atrium are improved. Both chambers have gotten smaller in

size, the left atrium markedly so; changes that were indicative of reduced pressures in the heart. Additionally, the mitral valve now opens widely, which is an indication of more forceful atrial contraction and an increase in blood flow from left atrium to left ventricle.

This table shows some of the quantitative metrics. The stroke volume doubled in this patient, and the ejection fraction increased by 5 percent. Heart rate declined as a consequence of the improvement in the patient's cardiac function. These improvements in cardiac function are in the context of an increase in the systolic ejection time into the normal range from what had been a very short ejection time at baseline, reflective of the patient's poor cardiac function. The concentration of omecamtiv mecarbil at the end of the infusion was 378 nanograms per mL.

I would like to review with you the last trial in the phase 2 program, COSMIC-HF. This clinical trial randomized outpatients with symptomatic chronic heart failure and reduced

ejection fraction less than or equal to 40 percent into three groups: a placebo group; a group receiving a fixed dose of 25 milligrams twice a day; a group receiving 25 milligrams twice a day to start, but then titrated to 50 milligrams twice a day if the plasma concentration of omecamtiv mecarbil at 2 weeks was below 200 nanograms per mL.

This PK-guided dosing was intended to maximize exposure of omecamtiv mecarbil and minimize the potential risk of excessive exposure, as we were gaining more experience with dosing. Echocardiograms were obtained at baseline and following 20 weeks of treatment.

The next slides show the echocardiographic data from the PK-guided titration group compared to placebo. As we observed in earlier studies, there was an increase in the systolic ejection time, as well as increases in fractional shortening and ejection fraction, increases that were durable for 20 weeks.

The improvements in cardiac function produced an increase in stroke volume that was

accompanied by a decrease in heart rate, likely due to withdrawal of sympathetic tone, as there's no direct effect of omecamtiv mecarbil on heart rate. These changes did not substantially increase cardiac output, the product of stroke volume and heart rate, which is not surprising since these patients had normal cardiac outputs at baseline.

Here are the important effects of omecamtiv mecarbil on cardiac structure. This is a decrease in end systolic and end diastolic volumes. These changes in cardiac structure were accompanied by decreases in NT-proBNP, a peptide released from the ventricular myocytes that reflects cardiac wall stress and filling pressures.

Overall, the data from COSMIC-HF are not just hemodynamic data but indicative of improved cardiac structure consistent with beneficial reverse remodeling, and improvements in biomarkers such as heart rate and NT-proBNP, which historically are predictive of improved clinical outcomes in heart failure therapies. Together with the observed safety profile, these mechanistic data

from COSMIC-HF provided the rationale for moving forward into a large clinical outcomes trial.

Next, I'll review the design and results of the pivotal phase 3 trial, GALACTIC-HF. It was a multicenter, randomized, double-blind, placebo-controlled, event-driven trial. Importantly, the trial was designed to provide data across a spectrum of heart failure, so patients were randomized both from the hospital setting and the outpatient setting. After randomization, patients were started on 25 milligrams twice daily, and their final dose, either 25, 37.5, or 50 milligrams, was implemented based on the plasma concentration of omecamtiv mecarbil after 2 weeks of administration.

The first patient was enrolled in January of 2017 and the last patient was enrolled in July of 2019, and the results were reported publicly in November of 2020. Over 8,000 patients were enrolled in 35 countries around the world, making this trial the second largest heart failure trial ever conducted. Notably, this trial also enrolled

more patients in North America and more black patients than other recent contemporary heart failure trials.

The primary composite endpoint was the time to cardiovascular death or first heart failure event, which ever occurred first; the secondary endpoints being time to CV death; the change in the Kansas City Cardiomyopathy Questionnaire from baseline to week 24; the time to first heart failure hospitalization; and the time to all-cause death.

Shown here are some of the important baseline demographics of the patients enrolled. The average age was 66 years old. Twenty-one percent enrolled were women. Importantly, 25 percent of these patients, over 2000, came from the hospital setting. For those randomized outside the hospital, the median time from their last heart failure event was only 3 months.

The entry criteria required an ejection fraction of less than or equal to 35 percent, the mean ejection fraction was 27 percent, and the

median ejection fraction was 28 percent. Almost half of the patients were NYHA class III or IV. The average systolic blood pressure at baseline was 116 millimeters of mercury, meaningfully lower than contemporary large clinical trials in heart failure with reduced ejection fraction and reflective of the broad entry criteria that allowed inclusion of patients with blood pressures as low as 85 millimeters of mercury. The NT-proBNP was approximately 2000 picograms per mL and cardiac troponin I was modestly elevated at baselines commonly observed in heart failure patients.

These are very well treated patients with high utilization, renin-angiotensin system blockers, beta blockers, mineralocorticoid receptor antagonists, and some of the highest utilization of devices in an international phase 3 trial at the time. SGLT2 inhibitors were not yet labeled for heart failure when this trial was conducted. Importantly, all these characteristics were well balanced between the treatment group and the placebo group.

Over 11,000 patients were screened; 8,256 patients were randomized at 944 sites; and 24 patients were excluded from one site due to major GCP violations. Follow-up was excellent. Very few patients had unknown vital status at the end of the trial, and only one patient was lost to follow-up for vital status. The overall median study exposure was 21.8 months.

The experienced group at the Duke Clinical Research Institute chaired by Dr. Michael Felker served as the clinical events committee or CEC. All deaths, heart failure events, and major cardiac ischemic events, as well as strokes, were adjudicated by the CEC using standardized definitions and according to prespecified criteria.

As we can see here, the primary outcome of time to first heart failure event or cardiovascular death was reduced 8 percent by omecamtiv mecarbil, with a p-value of 0.025 and an absolute risk reduction of 2.1 per 100 patient-years. The curves diverge early and generally remain separated for up to 3 years.

This slide shows the components of the primary outcome, which were time to first heart failure event and cardiovascular death, and demonstrates that the primary outcome was driven by the reduction in first heart failure events. There was no improvement in cardiovascular death, but conversely, and importantly, given the history of drugs that increase cardiac function, there's also no risk of cardiovascular death.

Heart failure increased risk of cardiovascular death. Heart failure events, including hospitalizations, are clinically meaningful and frequently life-changing, resulting in loss of strength, mobility, and independence that can lead to severe or irreversible morbidity. Reducing their frequency is an important objective of heart failure treatment.

Admittedly, the effect size observed here was modest for a drug in heart failure, but it is in keeping with that of other drugs approved in cardiovascular medicine. We asked if the primary analysis was robust by performing several

prespecified and ad hoc sensitivity analyses. These included adjusting for all significant prespecified subgroup covariates, confining the analysis to participants on treatment or to those in the therapeutic range of plasma concentrations. We also analyzed investigator reported heart failure events as opposed to only adjudicated heart failure events.

All these analyses were consistent with the primary analysis intended to improve a statistical robustness supportive of the conclusion that GALACTIC-HF met its prespecified primary endpoint. Further supportive of the primary result, the effect in the prespecified subgroups showed general consistency with the point estimates favoring omecamtiv mecarbil.

However, there were two subgroups that stood out from the rest: baseline ejection fraction and baseline presence or absence of atrial fibrillation or flutter. In these two prespecified subgroups, even after adjusting for multiple testing using a Bonferroni correction, the treatment effect was

substantial enough to remain statistically significant and not likely be a chance finding in those with left ventricular ejection fraction at or below the median, which was 28 percent -- I'll call them the low EF subgroup going forward -- and those who did not have atrial fibrillation or flutter at baseline.

As Dr. Felker showed us, baseline ejection fraction is a strong risk modifier in heart failure, and not surprisingly, given cardiac dysfunction as the underlying pathophysiologic defect that omecamtiv mecarbil targets, we found that those with lower ejection fraction had a significantly larger treatment benefit in this trial; in fact, double that of the overall population.

We did a further analysis to see if there was any evidence of treatment effect modification across any of the prespecified subgroups using a global test for heterogeneity inclusive of all the prespecified subgroup variables. The global test was highly statistically significant with a p-value

of 0.008, and once again, both ejection fraction and atrial fibrillation independently emerged as the most significant treatment effect modifiers. I'll elaborate on the effect of baseline ejection fraction in modifying the treatment effect in a moment. Dr. Kupfer will discuss the treatment interaction with atrial fibrillation in his presentation on safety.

Notably, these are very large subgroups. Nearly 4,500 patients were in the low ejection fraction subgroup. This slide shows that for patients on placebo, the risk of the primary composite endpoint goes up substantially with lower baseline ejection fraction nearly doubling in magnitude as ejection fraction decreases.

Now, the green line shows the risk for patients who were treated with omecamtiv mecarbil. The difference between these two lines is the absolute treatment effect, indicating a larger treatment effect from omecamtiv mecarbil as baseline ejection fraction decreases. The relative treatment effect is shown on the right and, again,

we see a similar finding of increasing magnitude of the treatment effect for omecamtiv mecarbil as baseline ejection fraction decreases.

Shown here is the cumulative incidence over time of the primary composite endpoint for patients in the low ejection fraction subgroup. The curves diverge early, and continue to diverge out to 3 years. The absolute risk reduction is now 5.1 for 100 patient-years, more than double that of the overall population.

This slide shows the components of the primary outcome, which is, again, driven by the reduction in first heart failure events. As before, there was not a statistically significant improvement in cardiovascular death, although the point estimate is now less than 1.

This forest plot shows the prespecified subgroups restricted to the patients in the low ejection fraction subgroup. There's a strong consistency across the board with the point estimates favoring omecamtiv mecarbil, including the subgroup that had atrial fibrillation or

flutter at baseline.

Now, moving on to other evidence that ties the mechanistic data in COSMIC-HF to our findings in GALACTIC-HF, it was impractical to obtain echocardiograms in 8,000 patients, but the effects on heart rate and NT-proBNP in GALACTIC-HF are shown here. Both are biomarkers thought to be reflective of clinical benefit, as decreases in heart rate generally correlate with improved outcomes in heart failure, while decreases in NT-proBNP are generally correlated with reductions in heart failure hospitalizations.

The reduction in NT-proBNP and heart rate in GALACTIC-HF was similar and extend to that observed in COSMIC-HF, and larger in the lower ejection fraction subgroup, providing evidence that the pharmacodynamic findings translated across the two trials.

There appeared to be another clinical correlate in GALACTIC-HF related to improvements in left atrial and left ventricular size and function observed in COSMIC-HF. In GALACTIC-HF, we found

that the incidence of stroke, a prospectively adjudicated safety endpoint, was meaningfully decreased with omecamtiv mecarbil compared to placebo. Most of the strokes were ischemic in origin, leading us to examine the incidence of new atrial fibrillation, which is also reduced by omecamtiv mecarbil compared to placebo.

It's reasonable to conclude the improvements in left atrial size reduced the risk of new atrial fibrillation, while the improvements in atrial and ventricular function reduced the risk of intracardiac thrombus formation, both effects contributing to the occurrence of fewer strokes.

Now changing gears, I'd like to address the question of how can one maximize benefit-risk once omecamtiv mecarbil is approved. Cytokinetics has proposed that one should focus on patients who stand to benefit the most and provide physicians with clear guidance on how to identify those patients. The simplest way to do so, and the one supported by the evidence, is to focus on patients in the lower ejection fraction subgroup, as was

proposed in the initial submission in November of 2021 and discussed at our mid-cycle meeting in May of 2022.

As shown on the left, usually the indicated population is larger than the trial population, which requires extrapolation beyond what was specifically demonstrated in the clinical trial. This approach potentially dilutes the demonstrated treatment effect post-approval by extrapolating the populations where effectiveness was not directly demonstrated. Our proposed approach, shown on the right, instead focuses the patient population where the greatest effectiveness was demonstrated, and this concentrates the treatment effect post-approval.

In summary, this program started with a therapeutic hypothesis that improving cardiac function would improve clinical outcomes. Having developed an innovative mechanism of action to test this hypothesis, we first demonstrated that omecamtiv mecarbil improved cardiac function with positive effects on cardiac structure and

biomarkers predictive of a therapeutic benefit. We then moved on to test its effects on clinical outcomes in GALACTIC-HF, which met its prospectively defined primary composite endpoint, a result that was robust to several additional sensitivity analyses.

While the benefit was confined to reducing the risk of heart failure events, it should not be minimized given the burden it places on patients in our healthcare system. We found that the treatment effect is greater in patients in the lower ejection fraction subgroup, which is not only biologically plausible, but in fact expected given the mechanism of action of omecamtiv mecarbil. In fact, the patients with the greatest clinical risk appear to reap the greatest benefits from omecamtiv mecarbil, and thus we propose to focus on these patients.

The FDA provides guidance that the evidentiary standard for approval can be met with one adequate and well-controlled clinical investigation, supported by data that provides strong mechanistic support as confirmatory

evidence. We believe the overall program and results we presented today meet this standard. Altogether, the consistency and totality of the evidence for effectiveness is compelling, and for these reasons we believe that omecamtiv mecarbil should be approved and has a place in the treatment of heart failure, particularly in those with the greatest clinical need and the most difficult to treat.

I thank you for your attention, and now I'll give way to our next speaker, Dr. Kupfer.

Applicant Presentation - Stuart Kupfer

DR. KUPFER: Thank you, Dr. Malik, and good morning. I'm Stuart Kupfer, senior vice president and chief medical officer at Cytokinetics. In the next few minutes, I will summarize the safety profile of omecamtiv mecarbil, focusing on GALACTIC-HF. I'll first review overall adverse events and events of special interest, next, I'll review vital signs and clinical safety labs, and finally I'll profile clinical outcomes in patients with atrial fibrillation.

Starting with a high-level summary, we observed that the safety and tolerability profiles of omecamtiv mecarbil and placebo were similar in GALACTIC-HF. Incidences of total and more severe adverse events were similar between treatments in both the overall population, shown in the left panel, and the LVEF less than or equal to 28 percent subgroup in the right panel, which I'll refer to as low EF subgroup. Furthermore, incidences of serious adverse events, adverse events leading to study drug discontinuation, and deaths, were similar between treatment groups.

Moving on to events of special interest, there were no clinically meaningful differences in incidences of ventricular arrhythmias between omecamtiv mecarbil and placebo, either by standard measure query analyses or by ventricular arrhythmias requiring treatment. In addition, there was no evidence for a cardiac ischemic effect of omecamtiv mecarbil in that there were no clinically meaningful differences compared to placebo for adjudicated myocardial infarction or

other major cardiac ischemic events. We also observed a decrease incidence of adjudicated stroke possibly related to improved cardiac contractility.

Turning to vital signs, there was no evidence that omecamtiv mecarbil had any adverse effects on blood pressure or heart rate in either the overall population or the low EF cohort. And as expected, based on the mechanism of action of omecamtiv mecarbil, there were no meaningful differences from placebo in changes in creatinine or potassium. There were small increases in troponin, which have been observed throughout the development program; however, there were no adverse consequences associated with is finding, including no increases in major cardiac ischemic events, as I previously mentioned.

In addition to the LVEF interaction that Dr. Malik noted earlier, subgroup analyses of the overall population indicated a significant treatment interaction by atrial fibrillation status at baseline. In contrast to patients without atrial fibrillation, shown here in the second row,

who experienced risk reduction for the primary composite endpoint with omecamtiv mecarbil, those patients with atrial fibrillation, in the third row, did not experience treatment benefit.

Given the observation that patients with lower ejection fraction experienced greater treatment benefit, we evaluated clinical outcomes in patients with atrial fibrillation by ejection fraction subgroups. As seen in the first two highlighted rows, patients in the low EF subgroup tended to benefit from treatment regardless of atrial fibrillation status at baseline. In contrast, a subgroup of patients with atrial fibrillation and high ejection fraction, in the last row, experienced increased risk.

A similar profile was observed for cardiovascular death. While increased risk was observed in patients with atrial fibrillation, shown in the third row, the risk appeared to be concentrated in the high EF subgroup in the last row. In contrast, those patients with low EF, in the first two highlighted rows, had a trend of

treatment benefit or a neutral outcome in those without or with atrial fibrillation, respectively. Likewise, a similar profile was observed for time to first heart failure event , with risk concentrated in those patients with atrial fibrillation and high EF and trends of benefit in those with low EF.

These results further informed our proposal to indicate omecamtiv mecarbil in patients with lower ejection fraction, including those with atrial fibrillation who appear to benefit from treatment.

We conducted a systematic assessment of potential causes of the interaction by atrial fibrillation status in treatment with omecamtiv mecarbil. There was no increased incidence of cardiac ischemic events or ventricular arrhythmias in patients with atrial fibrillation. While there was an increase in adjudicated deaths due to heart failure, there was not an increase in sudden death or death due to myocardial infarction. Furthermore, related patient populations were not

at increased risk, including those patients with a history of atrial fibrillation or those with new onset atrial fibrillation.

We also investigated concomitant medications with greater baseline use in patients with atrial fibrillation and observed that the increased risk of heart failure outcomes with omecamtiv mecarbil in the atrial fibrillation subgroup was concentrated in those patients also receiving digoxin at baseline. In contrast, patients without atrial fibrillation who were treated with digoxin experienced treatment benefit. To the best of our current knowledge, a biologically plausible explanation for a potential digoxin interaction is not apparent.

In summary, and based on the results of GALACTIC-HF, the incidences of adverse events overall and events of special interest, such as ventricular arrhythmias or cardiac ischemia, were similar between omecamtiv mecarbil and placebo in the total study population and the low EF subgroup. There were no adverse effects on blood pressure or

heart rate, or laboratory measures related to renal function or potassium homeostasis. Atrial fibrillation was a treatment effect modifier with increased heart failure outcomes observed in patients with atrial fibrillation and higher ejection fraction, possibly related to concomitant digoxin.

In this next section, I'll present a rationale for the proposed simplified PK-guided dose titration strategy, which is very similar to the PK-guided dose titration employed in the GALACTIC-HF trial. First, I'll discuss how we determined the therapeutic concentration range of omecamtiv mecarbil; second, I'll review the outcomes of PK-guided dosing in GALACTIC-HF; and finally, I'll review our current proposal for simplified PK-guided dose titration and the validated assay that will support it.

As Dr. Malik described, the duration of systole is increased with omecamtiv mecarbil treatment in association with improved cardiac function. Based on PK/PD assessments of systolic

ejection time and other parameters, such as ejection fraction and left ventricular diameters, it was predicted that the therapeutic concentration range for omecamtiv mecarbil was 200 to 750 nanograms per mL, as illustrated in the green shaded area of this graph.

Furthermore, based on dose ranging studies and early clinical development in healthy subjects and heart failure patients, there appeared to be a threshold of concentration exceeding 1200 nanograms per mL that was associated with increased risk of cardiac ischemia. This was likely due to shortening of diastole and decreased coronary artery perfusion associated with excessively prolonged systolic ejection time.

Nearly all of the 16 participants with concentrations greater than 1200 nanograms per mL received intravenous omecamtiv and six developed signs and symptoms of cardiac ischemia. However, these events were self-limiting in that all symptoms resolved after discontinuation, and none of these participants demonstrated evidence of

irreversible cardiac dysfunction.

Therefore, our early clinical data identified a potential therapeutic concentration range of 200 to 750 nanograms per mL, as well as a dose-limiting concentration threshold of 1200 nanograms per mL, which indicated a sufficient therapeutic window to optimize the benefit-risk profile of omecamtiv mecarbil. However, given the size of GALACTIC-HF and the limited experience with dosing in phase 2, we decided to proceed with a conservative strategy for dose titration in GALACTIC-HF and employ PK-guided dosing.

For PK-guided dose titration in GALACTIC-HF, patients were initiated at a dose of 25 milligrams BID, and then on the basis of plasma concentration measurements at weeks 2 and 6, the dose could have been increased at weeks 4 and 8 to 37.5, or 50 milligrams BID, or down-titrated if necessary, to achieve the target concentration range of 300 to 750 nanograms per mL and to avoid excessive exposures.

Concentration response analyses from

GALACTIC-HF indicated that appropriate dose titration and achievement of the therapeutic concentration range increased treatment benefit. Within 200 to 750 nanograms per mL, omecamtiv mecarbil decreased risk of the primary composite endpoint compared to placebo. Similar transit benefit were observed for cardiovascular death within concentrations of 200 to 750 nanograms per mL. These results further validated the predicted therapeutic concentration range and reinforced the importance of appropriately dosing patients to achieve this target.

We also evaluated outcomes in the small subgroup of 61 patients with a maximum plasma concentration that exceeded 750 nanograms per mL in GALACTIC-HF and did not observe increased risk of the primary composite endpoint or cardiovascular death with omecamtiv mecarbil compared with placebo. Likewise, no increased risk was observed for safety outcomes in patients with concentrations exceeding 750 nanograms per mL, including cardiac ischemic events and ventricular arrhythmias.

PK-guided dose titration was successful in that the majority of patients achieved the therapeutic concentration range of 200 to 750 nanograms per mL while avoiding excessive plasma concentrations. However, due to the complexity and potential treatment barriers associated with PK-guided dosing, we proposed scheduled dose titration without PK guidance in the NDA, starting at 25 milligrams BID and titrating to 37.5 milligrams, and then to 50 milligrams BID, which was predicted to result in a favorable benefit-risk profile based on PK modeling and simulations. However, after further discussion with the FDA, we decided to proceed with PK-guided dose titration to further optimize the benefit-risk profile.

We are currently proposing a simplified step-wise, PK-guided dose titration very similar to that employed in GALACTIC-HF. We propose a starting dose at 25 milligrams BID with options to increase to 37.5 or 50 milligrams BID to achieve a target concentration range of 300 to 750 nanograms

per mL; and after 2 weeks of treatment at a given dose, plasma concentrations should be assessed and the dose adjusted so that patients are in the target range. Modeling and simulations indicate that the distribution profile of omecamtiv mecarbil concentrations with the proposed PK-guided dose titration is nearly identical to that of GALACTIC-HF.

PK-guided dose titration in GALACTIC-HF was supported by immunoassay validated with a liquid chromatography with tandem mass spectrometry assay, or LC-MS/MS, which is considered the gold standard for measuring the concentration of small molecules. In support of PK-guided dose titration at the time of approval, we are proposing to make available an LC-MS/MS assay which is now validated and will be run in a single central commercial laboratory to maximize quality control and further ensure patient safety. Assay development was compliant with guidances for analysis of therapeutic drugs, and the full validation report has been submitted to FDA.

The assay is fit for purpose and passed all relevant validation specifications, including selectivity, precision, accuracy, and reproducibility. In addition, measurements of plasma concentrations of omecamtiv mecarbil with the validated assay were very highly correlated with those of the immunoassay, further strengthening support of PK-guided dose titration.

Our interactions with FDA about the use of an assay have also led to a discussion about its potential classification as a companion diagnostic. According to the agency's guidance, a companion diagnostic is defined as a device that is essential for the safe and effective use of a drug and requires contemporaneous FDA review and approval of both the assay and the relevant drug.

While we think that the assay is important for dose titration, we do not believe that it qualifies as a companion diagnostic as the guidance has been applied in practice. Therapeutic drug monitoring assays, such as the assay we are proposing for omecamtiv mecarbil, are rarely

classified as companion diagnostics. Nearly all companion diagnostics have been developed in association with oncology products and are markers of gene variation or expression that identified patients most likely to benefit from a drug prior to initiation of treatment.

This is a list of therapeutic drug monitoring assays deployed at three large clinical laboratories from 2015 to the present. Importantly, none of these assays are classified as companion diagnostics. If a companion diagnostic is required, availability of omecamtiv mecarbil would be delayed by at least one year while the assay undergoes FDA review. The omecamtiv mecarbil assay is fit for purpose, has been rigorously validated, and will be ready to deploy at the time of approval to support PK-guided dosing.

In conclusion, the results of GALACTIC-HF indicate that with PK-guided dosing, a large proportion of patients can achieve the therapeutic concentration range of omecamtiv mecarbil while minimizing exposure to excessive concentrations.

The proposed PK-guided dose titration algorithm will optimize the benefit-risk profile of omecamtiv mecarbil. A fit-for-purpose LC-MS/MS assay has been validated to support PK-guided dosing and will be available in a single central commercial lab to ensure quality control and patient safety.

Now, I will turn the presentation over to Dr. Solomon, who will discuss the benefit-risk profile of omecamtiv mecarbil.

Applicant Presentation - Scott Solomon

DR. SOLOMON: Thank you, Dr. Kupfer.

My name is Scott Solomon, and I'm a professor of medicine at Harvard Medical School and Brigham and Women's Hospital. I'm a cardiologist and a clinical trialist, and I was a member of the executive committee of GALACTIC-HF.

For the next few minutes, I'd like to summarize and put into some clinical perspective some of the data that you've just heard presented. First, I think it's important to remember that omecamtiv mecarbil is the first heart failure drug specifically designed to target the primary

pathophysiologic abnormality in heart failure with reduced ejection fraction, notably myocardial contractile dysfunction. Every other drug that we've used in heart failure has been developed for another purpose or was discovered accidentally to show benefit in patients with heart failure.

For this reason, as you've heard today, the development program with omecamtiv mecarbil has been as comprehensive as we've ever seen in the heart failure field; and as you've heard from Dr. Malik, the robust phase 2 program that culminated in the COSMIC trial demonstrated that this drug behaves exactly as expected, improving measures of cardiac function and structure, including resulting in reverse ventricular remodeling.

You've also heard that GALACTIC, a very large, well-conducted outcomes trial, in fact, the second largest outcomes heart failure trial ever conducted, met its primary endpoint. Admittedly, the overall treatment effect was modest, but in the patients who have the abnormality that omecamtiv

mecarbil was designed to address, and indeed in whom this therapy is most needed -- specifically, patients with the lowest ejection fraction, patients who were most intolerant to being on vasodilators, patients with the lowest blood pressure -- the benefit appeared to be the greatest.

Finally, GALACTIC demonstrated that omecamtiv mecarbil was safe, particularly in the patients in whom this drug is likely to be used, with none of the issues that have plagued inotropic agents in the past such as proarrhythmia, no risk of increased ischemia, no increased risk of renal dysfunction, hyperkalemia, or hypotension.

While we were very fortunate going into GALACTIC to have such robust data from a phase 2 program that provides strong mechanistic support for the benefits of omecamtiv mecarbil, if we believe that the underlying pathophysiologic problem in heart failure with reduced ejection fraction is reduced myocardial contractile function leading to progressive ventricular dilatation and

remodeling, with subsequent increase in filling pressures, then we'd expect to see that improving cardiac contractile function should affect these downstream manifestations of the heart failure syndrome.

Indeed, this is exactly what we see in COSMIC, with omecamtiv mecarbil improving fractional shortening and stroke volume, leading to meaningful reductions in both left ventricular end systolic and end diastolic volumes; in other words, reverse remodeling, which has been shown in numerous studies to relate to improvement in outcomes, and then ultimately reduction in NT-proBNP, a marker of cardiac wall stress and an indirect measure of elevated filling pressures.

So let's take a closer look at the GALACTIC trial itself. As you've seen, we observed a significant, yet modest, 8 percent reduction in the primary endpoint, a composite of cardiovascular death or heart failure event, in the overall population, but in the patients with an LVEF at or below a median of 28 percent prespecified cutpoint,

a group of over 4400 patients, the treatment effect is far greater, with clear evidence of statistical heterogeneity even after multivariable adjustment for all other covariates and interaction terms.

As you all know, LVEF, especially when measured by echocardiography, is not a particularly precise measure, so I think we would all agree there's nothing magical about an LVEF cutoff of 28 percent. So instead, when we look at LVEF as a continuous measure in GALACTIC, it is evident, no matter how we model this, that the treatment effect is truly greatest in those patients with lowest ejection fraction, with a continuous improvement in benefit as LVEF declines.

So at this point, we need to ask ourselves, do we believe this finding, that the benefit in GALACTIC is truly greatest in the lowest EF patients? Is there really evidence of effect modification with real heterogeneity, or are we seeing the results of a random subgroup finding?

Well, as you all know, the primary reason we explore the results of subgroups in clinical trials

is not to look for differences but to demonstrate consistency, but occasionally we do see substantial evidence of heterogeneity that makes us believe that some patients may truly respond differently to a therapy than others. When we make this claim, however, we do it with an abundance of caution. We need to ensure that a number of criteria are met, and these have been very nicely laid out by Janet Wittes in a 2009 review in Circulation.

First, we required that the subgroup be prespecified. In GALACTIC, we did prespecify that the ejection fraction above, or at, or below the median would be assessed for efficacy. Second, we want the subgroup to be large relative to the trial as a whole, and in GALACTIC, our prespecified subgroup was cut at the median, and indeed there are 4,456 patients at or below the median.

Now, this is far more patients than were in the SOLVE trial, the RALES trial, the MERIT-HF trial, or even the EMPEROR-Reduced trial, trials that have formed the basis for our use of ACE inhibitors, MRAs, beta blockers, and SGLT2

inhibitors in heart failure.

Third, we want to see clear evidence of statistical heterogeneity, and as you've seen, in GALACTIC there was a highly significant interaction in univariate analyses that stood up to Bonferroni correction, that stood up to multivariable analysis, incorporating all prespecified subgroups and interaction terms.

Fourth, we want to see evidence of internal consistency, and in GALACTIC, as you've seen, we have greater benefit not just at or below the median, but the effect does appear related linearly when assessed continuously, with a greater treatment effect as LVEF declines.

And finally, we want evidence that the finding is biologically plausible. Well, as you've heard from Dr. Malik, omecamtiv mecarbil is a drug that works by improving cardiac contractile function, so it's not difficult to expect that we might see greater benefit in those patients who have the underlying defect that we believe this drug is helping, those patients whose cardiac

function is most reduced. For these reasons, we believe that this finding of greater benefit in lower EF patients is real, is robust, and is clinically important.

We shouldn't be surprised that ejection fraction is an effect modifier. We've seen this before. There's been ample precedent with other therapies in heart failure in which treatment effect was modified by ejection fraction, and as you can see in this slide, we've seen this same pattern with ARBs, with MRAs, with digitalis, and with sacubitril/valsartan; and indeed this finding played an important role in the expanded approval for sacubitril/valsartan.

I think we'd all agree that our patients with heart failure and severely reduced ejection fraction tend to be our higher risk patients, as Dr. Felker pointed out. They are also the most difficult to treat. Importantly, in the lower LVEF subgroup in GALACTIC, we've seen no diminution of the treatment effect in those with other markers of increased risk, including recent heart failure

hospitalization, reduced systolic blood pressure, elevated New York Heart Association class, or elevation in natriuretic peptide levels.

Indeed, the absolute risk reductions are impressive in these patients with lower ejection fraction, and any one additional risk factor, as shown here, and consistent with the benefit on the primary composite endpoint, the point estimates for cardiovascular death have also moved leftwards in these patients at higher risk, favoring omecamtiv mecarbil.

We know that many patients with severe reduction in EF are least tolerant of the medications we typically use in heart failure, particularly the neurohormonal modulators such as ACE inhibitors, ARBs, and ARNi's. Here are post hoc data from GALACTIC demonstrating that the benefit of omecamtiv mecarbil in patients who were in fact intolerant to neurohormonal modulators, who couldn't be on neurohormonal modulator at baseline, was substantial. Those patients not only tolerated omecamtiv mecarbil but also appeared to benefit

from the addition of omecamtiv mecarbil. And similarly, in the patients with lowest blood pressure, another group of patients very difficult to treat, there's a robust and meaningful treatment or response.

In a recent publication, Dr. Felker described the effects of omecamtiv mecarbil in patients with severe heart failure defined as those with an LVEF at or under 30 percent, New York Heart Association class III and IV, and having had a hospitalization for heart failure within the past 6 months, a very, very high risk. In these patients, we observed a 20 percent reduction in the primary composite endpoint and a numerically lower number of cardiovascular deaths in those patients randomized to omecamtiv mecarbil.

To put these data in perspective, here's a comparison of the findings observed in a number of contemporary trials of heart failure with reduced ejection fraction, and as you can see, while the overall absolute risk reduction in GALACTIC is modest in those patients with an LVEF less than or

equal to 28 percent, the absolute risk reduction is at least as good as in most of the contemporary trials in heart failure, including those on which class I guideline recommendations have been based.

The more advanced heart failure becomes, the more difficult it is to treat. The use of many therapies, as you've heard from Dr. Felker, including ACE inhibitors, ARBs, beta blockers, MRAs, ARNi's, and even SGLT2 inhibitors, are limited in our sickest patients because of low blood pressure, low GFR, or elevation of potassium. This is a concept we refer to as a spending function in heart failure.

As you've seen, omecamtiv mecarbil can improve outcomes in the sickest patients without much of the spending that our other therapies require, without lowering blood pressure, without adversely affecting GFR, and without raising potassium. We expect that this will be especially important in patients where some or all of these problems represent real limitations to achieving full guideline-directed medical therapy and in whom

their options are limited.

Finally, we recognize that the overall benefit of omecamtiv mecarbil appears to be less in patients who are in atrial fibrillation, or flutter, at baseline. The reasons for this finding are unclear, although we've observed similar attenuation of benefit of other heart failure therapies, including beta blockers in patients in atrial fibrillation.

In addition, as you've heard, the attenuation of benefit is most apparent in patients in atrial fibrillation and higher ejection fraction and in those in atrial fibrillation receiving digoxin. In those patients in the lower LVEF group, there is minimal attenuation of benefit in patients with atrial fibrillation, and in additional analyses, those patients with infinite atrial fibrillation during the course of the trial did not appear to be at greater risk for adverse outcomes. Nevertheless, we clearly need to better understand whether atrial fibrillation modifies the effectiveness of omecamtiv mecarbil and under what

conditions. And as you've heard, the sponsor agrees that any labeling for omecamtiv mecarbil should reflect this uncertainty.

In summary, omecamtiv mecarbil is a drug with a mechanism of action central to the pathophysiology of HFrEF and was the product of an extensive and robust development program culminating in GALACTIC-HF. GALACTIC was an overall positive outcomes trial in which the greatest benefit was seen in those patients with the worst cardiac function, with the highest event rates, and this is where we believe the greatest impact will be in practice.

Perhaps because of its unique mechanism of action, omecamtiv mecarbil was well tolerated and efficacious in patients in whom other therapies, particularly neurohormonal modulators, are most challenging to use. The overall safety profile of omecamtiv mecarbil was excellent, although we recognize that patients with atrial fibrillation may benefit less.

In conclusion, omecamtiv mecarbil represents

an important and compelling addition to the therapeutic armamentarium in our patients with heart failure with reduced ejection fraction, particularly those who are most difficult to treat, most intolerant to other medications, and most in need of new options. Thank you for your attention, and I'll turn it back over to Dr. Malik.

Applicant Presentation - Fady Malik

DR. MALIK: Thank you, Dr. Solomon.

I'd like to just briefly summarize our key points today. Omecamtiv mecarbil was an innovative mechanism of action specifically developed for heart failure, and in phase 1 and phase 2 clinical trials, including COSMIC-HF, we demonstrated that it improved cardiac function, structure, and biomarkers in a manner consistent with a therapeutic benefit for patients with heart failure and reduced ejection fraction. We would not have moved on to conduct GALACTIC-HF otherwise. In GALACTIC-HF, the safety and efficacy of omecamtiv mecarbil were assessed in many thousands of patients, and it met its prespecified primary

endpoint with a treatment effect that was larger in those with lower ejection fraction, the population omecamtiv mecarbil was developed to address.

Taken together, the two trials on this slide meet one of the definitions for substantial evidence of effectiveness, as shown in the bottom of the slide. Importantly, please consider the consistency and totality of the evidence of benefit we've presented today, particularly given that the evidence is strongest in patients that are the hardest to treat and at higher risk for heart failure related events.

Our goal is to deliver a safe and effective medicine specifically to the patients who will derive the greatest benefit and with the lowest risk. We anticipated that the clinical benefit of omecamtiv mecarbil would be modified by the degree of cardiac dysfunction, and GALACTIC-HF taught us how so.

As I described earlier, at the time of the NDA submission, we did not seek an indication for all symptomatic patients with heart failure and

reduced ejection fraction. We instead proposed to focus on patients with lower ejection fraction. Thus, we recommended the label clearly reflect these patients who derive the greatest benefit in the simplest manner possible with appropriate warning language regarding its risk. This approach should maximize the benefit to patients who despite guideline-directed medical therapy continue to have persistent or worsening chronic heart failure.

As you heard Dr. Kupfer describe, we are planning to implement a PK-guided dosing strategy using an LC-MS/MS assay with the advantages shown on the left of this slide. This assay was used throughout the omecamtiv mecarbil program, including all the phase 1 and phase 2 studies, including with COSMIC. We're confident that its implementation in a central laboratory, that runs over 1 million such assays a year and is regulated by another branch of the Department of Health and Human Services, CLIA, is more than sufficient to ensure patient safety. We've submitted the extensive validation work performed to the FDA for

their review.

As you may end up discussing whether a PK test is essential, a word that seems simple has significant ramifications as to how drug tests are regulated. For instance, the word "essential" might apply to any routine therapeutic drug monitoring tests, tests you rely on everyday in your practices but are not considered companion diagnostics.

In the case of omecamtiv mecarbil, the PK modeling demonstrates the importance of PK testing to optimize benefit and risk only when using the 50-milligram dose in order to make a very small risk even smaller. The lower doses could be implemented without PK-guided dosing. For these reasons, we believe the tests are important, but not necessarily essential, at least given current precedence.

Finally, while it's unlikely that a test reviewed as a companion diagnostic would result in greater patient safety and essentially perform gold standard lab developed tests, its requirement would

substantially delay the approval of omecamtiv mecarbil and deprive patients of its benefits by a year or more. Nonetheless, we're committed and have communicated our commitment to FDA via our partner, and intend to submit the immunoassay used in GALACTIC-HF for review that could result in an FDA cleared test in the future that could be deployed in local laboratories.

In conclusion, we believe the totality of the evidence presented today provides a compelling case for the approval of omecamtiv mecarbil in patients with heart failure and reduced ejection fraction, addressing a significant unmet need in those patients at higher risk and providing physicians an option for their most difficult-to-treat patients. We thank you for your attention and we welcome your questions.

Clarifying Questions

DR. LEWIS: Thank you. Thank you for a few extra minutes.

We will now take clarifying questions for Cytokinetics. Please use the raise-hand icon to

indicate that you have a question and remember to lower your hand by clicking the raise-hand icon again after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so you can move on to the next panel member.

I'll take the liberty of asking the first question. This is Julia Lewis. To your credit with this first-in-class drug, your composite outcome, you designed it with an adequate power and an adequate number of events to assess for a signal for cardiovascular death.

What is your explanation for why you did not win on cardiovascular death? There were decreased heart failure events. Standing alone, it did not

win in terms of statistics but supported the composite outcome, and intuitively should have led to less cardiovascular deaths. That was not seen.

Why is the interpretation of this result -- not that there is a cardiac toxicity signal seen throughout your development program, from preclinical to phase 2 -- not the explanation? Thank you. That is the end of my question.

DR. MALIK: Thank you for your question. I think first I'll address the last part of the question in terms of cardiac toxicity. This is Fady Malik from Cytokinetics.

As we demonstrated, I think quite conclusively, at the exposures that we studied in GALACTIC-HF, there really was no signal of cardiac toxicity, even on preclinical models, in the phase 1 or phase 2 clinical studies, nor did any imbalance in cardiac toxicity or ischemic events occur in GALACTIC-HF, nor in COSMIC-HF.

This program probably was the the most thoroughly investigated program for a signal of cardiac toxicity related ischemia that I can

imagine. Our DMC was extremely diligent to this matter, and I would say that we haven't, at the exposures and concentrations that we targeted, seen any increased risk of cardiac toxicity.

The question in terms of why the improvements in heart failure hospitalizations didn't translate to an improvement in cardiac mortality, CV mortality, is a good one, and I think the answer really lies, again, in where is the benefit of this drug most greatly concentrated.

We treat patients with drugs in heart failure, for instance, that lower blood pressure, and it's apparent that at some degree of blood pressure, it's not a good idea to use those drugs because they potentially, as Dr. Michael Felker showed you, not only cause intolerance but also increase patient risk, as was demonstrated in that same trial, the LIFE trial.

If I could have slide 2, please? In GALACTIC-HF, this was the first trial of a drug that improved cardiac function that was studied in this manner and, a priori, we knew ejection

fraction was important but, at the top, what was the highest ejection fraction, perhaps, that would benefit? And the data I think are very clear that we were close but didn't quite hit that target, meaning we targeted 35 percent or less, which is lower than the definition of an HFrEF, which is 40 percent or less, but the evidence, I think fairly strongly, supports the conclusion that the benefits, both in hospitalization as well as in terms of cardiovascular death, as you can see here on the right, begin to emerge. And in fact, as ejection fraction gets lower again, you begin to see other accrued benefits in terms of other risk factors that are comorbid in these patients.

So I think our hypothesis is essentially the baseline ejection fraction of the patient.

DR. LEWIS: Thank you.

Dr. Bairey Merz?

DR. BAIREY MERZ: Thank you. Noel Bairey Merz. I have a question regarding efficacy. Clearly safety is an issue, but efficacy, also for heart failure, of course can include quality of

life. It was in the dossier in the box [indiscernible], but we didn't mention it.

This is to any of our three prior speakers; that in the box there was not a significant improvement in the Kansas City quality of life heart failure questionnaire. Can you please elaborate on this? And similar to Dr. Lewis' question, why was it not improved given the structural and functional NT-proBNP [indiscernible - audio distorted]?

Thank you. That's my question.

DR. MALIK: If I can have slide 2, please? This was the prespecified analysis of the Kansas City Cardiomyopathy Questionnaire in the GALACTIC-HF. On the left-hand side is shown the inpatient group, which had a much lower baseline score -- in the KCCQ, higher scores indicate less symptomatic patients -- than did the outpatients, and in that inpatient group one sees a 2 and a half point improvement in symptoms at 24 weeks with omecamtiv mecarbil. The overall test of both groups was actually nominally statistically

significant, but given the testing hierarchy we employed in GALACTIC-HF, did not meet the prespecified alpha level.

We looked at a another group of patients -- if I could have slide 2, please -- in the sense that these are patients in whom they self-reported their symptoms at baseline, using a patient global rating of severity, as moderate or greater, moderate or severe, and then we assessed for the increase in symptom improvement using the KCCQ as the number of those patients who had a 5-point or greater change, which is thought to be the minimally clinically important difference.

These showed the lower ejection fraction patients on the left and the higher ejection fraction patients on the right, and again you see in the group where we think this drug should be used was a 6.7 percent improvement in the proportion of patients who achieved that 5-point difference. And finally, on slide 3, if you'd please show me that, that relationship for KCCQ also appeared to be dependent on ejection fraction.

So I think just to wrap it up, we think that there are potentially symptom improvements here, again, concentrated in the patient population where we think this drug should be used.

DR. BAIREY MERZ: Thank you. That is all.

DR. LEWIS: Dr. O'Connor?

DR. O'CONNOR: Thank you, Dr. Lewis. Dr. Christopher O'Connor here. I have two quick questions, one for Dr. Malik on the heart failure events.

The signal, only in the heart failure events, was surprising, as Dr. Lewis said, but still very important in this patient population. It would be even more important if you could tell us that the heart failure events that were severe, that if those requiring vasoactive drugs, ICU, LVAD, or transplant, were reduced and whether length of stay was reduced.

Do you have any information on the severe heart failure events?

DR. MALIK: We did collect that information. I don't have it handy to show you at the moment.

My recollection is that for patients that went on to LVADs, and transplant, and such, that there was a numerical difference favoring omecamtiv mecarbil, however, obviously the numbers were reasonably small in that group, but we can look to see if we can pull those data during the break.

DR. O'CONNOR: And then second, quickly, to Drs. Felker or Solomon, the sponsor suggests that the wording for the low EF group would be benefits are increasingly evident the lower the EF. Is that wording strong enough or should there actually be a numerical cutoff?

DR. MALIK: Dr. Solomon, would you like to answer that question?

DR. SOLOMON: Sure. As an echocardiographer, I have to say that I'm not a fan of numerical cutoffs in general because of the uncertainty of that particular measurement. The wording that the sponsor is suggesting was very similar to the wording that's currently used for the sacubitril/valsartan expanded indication; that the benefit is greatest in patients with

LV ejection fraction below normal in that particular indication. And I think that clinicians who are going to be using this therapy, who take care of heart failure patients, with knowledge of the data will be able to make that determination.

With that said, I think that the data should be clearly outlined in the label so that clinicians are informed.

DR. O'CONNOR: Thank you --

(Crosstalk.)

DR. MALIK: Also, Dr. O'Connor -- I was just saying we would not be opposed to a more specific number, but I think, as Dr. Solomon stated, that creates its own uncertainty, so we'd be happy to discuss how to best describe that.

DR. O'CONNOR: Thank you, Dr. Lewis. No further questions.

DR. LEWIS: Thank you, Dr. O'Connor.

Dr. Kovesdy?

DR. KOVESDY: Yes. Thank you. Csaba Kovesdy. My question pertains to the results presented from the COSMIC-HF trial. I believe it

was slides 47 to 49. This trial had three arms, and one included the non-PK adjusted dosing arm, but the results presented here today only showed results from two of these arms.

Can you comment on the results from the non-PK directed arm, and how did this influence further decisions about planning GALACTIC?

DR. MALIK: Yes. Thanks for the question. We focused on the PK titration group in this presentation for simplicity, but the full data obviously are published in the paper, in the Lancet.

I will add in the 25-milligram group, which was a fixed dosing group, we did see pharmacodynamic signals. We saw the systolic ejection time go up. We saw other measures of cardiac function also increase. What really drove us to implement PK-guided titration was that the effects, particularly on cardiac structure and biomarkers, seemed to be somewhat larger in the PK titration group, and it also gave us the opportunity to ensure that we didn't have a lot of

patients that might be floating around at pharmacokinetic values that were really probably not beneficial at all.

I'll also add, I think in GALACTIC, when we looked at the treatment effect by dose, the patients that stayed on 25 milligrams didn't appear to have much of a clinical benefit.

DR. KOVESDY: So a quick follow-up to this. Normally when you don't have a benefit, the decision is to implement the higher dose as your minimum dose in clinical trials. So the fact that this was not done, does this mean that you are concerned that the higher dose would result in a new [indiscernible] perhaps, without PK monitoring?

DR. MALIK: No. To be clear, we did implement the higher doses of 37.5 and 50 in COSMIC when we examined just the 25-milligram dose. As I said, there was a pharmacodynamic effect, maybe not as large as at the higher doses; and that in GALACTIC, when we looked at the data in terms of the primary endpoint, there did seem to be an improvement with regards to a dose-response at the

higher doses.

If you'd show me slide 1, please? Here are the doses that patients ended up on in GALACTIC, and you see that the treatment benefit appeared largest in those patients that achieved the highest dose as opposed to those that received the 25-milligram dose. So we think we did a pretty good job of describing the therapeutic window, as well as the appropriate doses to be used. And perhaps with a more complicated PK-guided dosing strategy, one could even implement the higher dose, but that's not what we did in GALACTIC.

DR. KOVESDY: Thank you. This is the end of my question.

DR. LEWIS: Thank you.

Dr. Blaha?

DR. BLAHA: Hi. Michael Blaha, Johns Hopkins. I had a question that might follow up on company slide CC-121. Perhaps we could drop that slide as I ask my question.

Yes. I thought this side was interesting. The point was made here that the lower the ejection

fraction, the greater the benefit with multiple other drug classes that we use in heart failure. I just want to drop on one distinction here.

Here we see when that line would cross the line of unity, it appears to be more around a normal ejection fraction, which is something we're familiar with clinically, this distinction between a preserved and a reduced ejection fraction. But if maybe the company -- I don't have the number -- could pull up the slide of the benefit as a function of ejection fraction with this therapy, you see that line of unity is at a much lower ejection fraction when we already know that there's impairment in the systolic function as soon as we go below a normal ejection fraction.

So I just want to see if the company could comment a little bit more, other than a general statement, that if you have a really low ejection fraction, you benefit more. Why do you think that there's no benefit, even at ejection fractions, for example, of 30 or 35 percent, which clearly, clinically, we define as heart failure with reduced

ejection fraction with clear deficiencies of systolic function on echocardiography or many other tests we might do clinically? Thank you.

DR. MALIK: Yes. Could I have backup 45, please? While we're putting that slide up, please put slide 3 up.

This slide conceptually shows the determinants of cardiac output, and in this context, one sees that stroke volume is determined by three main characteristics: preload, which is the pressure inside of the heart prior to initiating the contractile cycle; the intrinsic contractility of the heart itself; and then afterload.

Some of those therapies that we've showed you earlier, they work on the afterload piece; some of them work on the preload piece. As heart failure gets worse, the compensatory mechanisms first work by increasing preload, and that becomes the heart's main mechanism of trying to compensate for the decrease in contractility.

So the question is, at what point do those

compensatory mechanisms run out and contractility becomes far more important in terms of compensatory mechanisms in heart failure? And I would say the answer was truly unknown until GALACTIC-HF. We never would propose using this drug in patients with higher ejection fraction, but where exactly that cutoff is, is not something that we had any preexisting data to help us assess. And I think GALACTIC-HF taught us where that transition begins, and it's probably when you get to what we call and what's classified as severely reduced ejection fraction, when EFs fall below about 30 percent.

DR. BLAHA: Thank you.

DR. LEWIS: Dr. Nissen?

DR. NISSEN: Thank you. I have a couple of quick questions. I'd like to see Kaplan-Meier curve hazard ratio and confidence intervals looking at only the hard endpoints; that is cardiovascular death and hospitalization for heart failure answering the outpatient urgent visits, which are clearly less severe events. So I want to see the KM curves for the heart events.

Then I have a second question, which is I would like to see the doses of ACE and ARB therapies used given the mean blood pressure of 116 in this patient population.

DR. MALIK: Alright. If you give me a moment, we'll try and pull those slides. If we don't have them immediately available, we'll produce them for you during the break. We have it by less than 28 percent, please.

DR. NISSEN: I want to see it for the whole population, not just --

DR. MALIK: Alright. What I have in front of me right now is slide 3, and we'll try and find the whole population as well. So this is heart failure hospitalization in the lower ejection fraction subgroup --

DR. NISSEN: We've already seen this. That doesn't help at all.

DR. MALIK: I'm sorry. That was heart failure events I showed you previously, so I was just trying to be responsive to your request.

DR. NISSEN: Yes. What I'm really --

DR. LEWIS: Do you want more time to find the data during lunch?

DR. MALIK: I think that would be helpful, Dr. Lewis.

DR. NISSEN: Okay.

DR. LEWIS: Okay.

(Crosstalk.)

DR. NISSEN: [Indiscernible] ACEs and ARBs used here, and the reason I'm asking is that the blood pressure here is 116. That means that there's a fair number of people whose blood pressures are in the normal range, and ordinarily we would titrate those patients to higher doses of ACEs and ARBs to maximize benefit. So I'm trying to understand whether background therapy was maximized prior to the randomization.

DR. MALIK: I'll describe qualitatively what we required, and then we'll try and pull the specific data for you during the break.

First of all, the blood pressure in this trial was substantially lower than what you see in all other heart failure trials. Average blood

pressure in most heart failure trials is about 120. We required two things that led to that lower baseline blood pressure. First of all, we allowed blood pressures lower than 100 millimeters of mercury into the trial, which is frequently where the exclusion criteria stopped, and we also capped the highest blood pressures in this trial at no more than 140, which, again, most heart failure trials don't have a cap on those, and the attempt there was to ensure that patients were maximally treated. The protocol also required -- and we queried at every visit -- whether patients not only were on background therapy but were they at maximum tolerated dose; and if not why?

So we have a fair amount of data. We may not have all that available to display today, but the trial made a substantial effort to ensure that patients were on maximally tolerated background medical therapy, including ACEs and ARBs.

DR. NISSEN: Sure, but I'm interested in seeing it. The actual doses used would be very informative about whether background therapy was

optimized adequately by the investigators. Investigators want to get patients into trials, so having them tell you they were on maximized therapies is not the same as being on maximized or on optimal therapy. So we really need to see that in order to understand the incremental value of omecamtiv.

DR. MALIK: We'll try and pull those data together for you, Dr. Nissen. Thank you.

DR. NISSEN: Okay.

DR. LEWIS: Thank you.

Dr. Wang?

DR. T. WANG: Yes. Thank you. Thomas Wang. I'll direct my question to Dr. Kupfer, who I believe presented the safety data.

I wonder if you could comment a bit further on the troponin increase in GALACTIC. Of course, there's the continuous relationship between troponin levels and adverse outcomes in heart failure. Is there any way to think about the magnitude of the troponin increase that was observed perhaps in observational studies, what

excess risk was that [indiscernible] been associated with?

My second question is whether the sponsor looked at subgroups like those with prior ischemic disease, those with higher levels of the drug, or those in the low EF group to see if the increase in troponin was higher in those groups.

DR. MALIK: Let me just start by mentioning one point, and I'll turn it over to Dr. Kupfer. The interesting question about putting the magnitude of troponin in context, we saw an increase of 0.004, which is about 10 times below the upper reference limit for the assay, and in fact is below the limit of detection of the assay in terms of its use. But as you average across lots of patients, obviously you can detect lower changes.

It's actually consistent with the daily magnitude of change as seen with diurnal variation. There was a nice study published that looked at troponin over 24 hours cycles in a fairly well-controlled study that showed, essentially, our

troponin varied by that much every day with diurnal variation. But let me turn it over to Dr. Kupfer to discuss the excess risk and whether we had any excess risk in ischemic patients or in the low EF patients.

DR. KUPFER: This is Stuart Kupfer, Cytokinetics.

Thank you, Dr. Wang. We very thoroughly evaluated changes in troponin in this program, as well as relationships to potential adverse effects. First of all, I want to show you the relationship between omecamtiv mecarbil concentration and changes in troponin.

If I could have slide 3, please?

Here we're looking at the relationship with omecamtiv mecarbil concentration, and in general we're not seeing an increase in troponin with higher omecamtiv mecarbil concentration. So that was an important analysis to conduct with respect to understanding the effect of troponin related to omecamtiv mecarbil.

With respect to potential adverse

effects -- if I can have slide 2, please -- we evaluated outcomes of major cardiac ischemic events, and in this case myocardial infarction, in relation to categorical increases in troponin in the GALACTIC trial. And no matter the category of increased troponin, we didn't see a difference in the incidence of myocardial infarction between omecamtiv mecarbil and placebo.

You had asked about changes in troponin in the low EF subgroup. We didn't see a difference of any greater magnitude of increase in troponin in that low EF subgroup compared to the population overall. Then you asked a question about were there particular subgroups that were at higher risk, and this is a question that we evaluated very carefully. In fact, we conducted a multivariate analysis, including all the prespecified subgroups, including baseline troponin.

If I could have slide 682, please? The bottom line is, in that multivariate analysis, we did not identify subgroups that were at particularly higher risk, and this is in slide 2.

The first point is that the global test for heterogeneity was not significant, 0.21, so that would tell us there really aren't any meaningful differences here. The closest one was inpatient versus outpatient status, which we reported previously was borderline p-value. But again, the global test was not significant, so our conclusion was that there weren't any subgroups that were at particularly high risk.

DR. T. WANG: Thanks. No further questions.

DR. LEWIS: Thank you.

Dr. Gillen?

DR. GILLEN: Great. Thank you very much. Daniel Gillen. This question I guess we can begin with maybe Dr. Solomon for response since he presented slide CO-120. This is in reference to the subgroup analyses, and I think the focus on the low EF group given the modest overall efficacy results that we have in the overall trial population.

One point of clarification is that the prespecification, which has been used somewhat

widely throughout the presentation of the subgroup for EF, can I just get some confirmation here? My reading of your document, from table 11, is that there were, in fact, 28 baseline covariates that you looked at interactions across in the study, and that these were done in what I would view as more of an exploratory fashion. They were not listed as the secondary analyses in your SAP; is that correct?

DR. MALIK: Dr. Solomon, would you like to comment on that?

DR. SOLOMON: These are prespecified subgroup analyses that were listed in the SAP, but as they would be for any clinical trial, there was no alpha ascribed to them if that's what you're asking specifically.

DR. GILLEN: That's part of what I'm asking. I'm also getting at the idea that when we say a prespecified interaction for a key secondary analysis, generally we would think of a covariate for which we have a mechanistic rationale as to why the treatment would behaved differentially in those

subpopulations.

Is it left to believe -- and you guys are using this term "prespecified" across these 28 covariates -- that you believed that there was a mechanistic rationale; that there would be differential treatment effect across these 28 covariates, essentially?

DR. SOLOMON: So as I said when I presented this, typically we use subgroups in clinical trials to demonstrate consistency not specifically to look for differences, and when we do find that there are potentially differences in the way individual patients behave and benefit, we do that with an abundance of caution. And what we've done in this case is we have looked at all the prespecified subgroups in a global model for heterogeneity, and I can turn over to Dr. Claggett to explain that in a little more detail.

Then we looked at the individual subgroups, accounting for all the other covariates and treatment interaction, and in doing that, in this case, two came out, as you've heard, highly

statistically significant, holding up to Bonferroni correction, as well as the multivariable adjustment.

So yes, we believe that these are real subgroup interactions, and then with ejection fraction, because we have the ability to look at this continuously, we can show that this does not just happen if you cut it at a median of 28 or any other specific cutpoint, but that it appears to be continuous.

So I think from a clinical point of view, it fulfills what we would say are the criteria for believing that there is true effect modification. We're happy to provide more details about this particular analysis if you want from Dr. Claggett.

DR. GILLEN: Thank you so much. Just to make sure that I've understood correctly, then, these 28 exploratory analyses were meant to assess homogeneity of treatment effect across these subpopulations, and there was no predefined a priori hypothesis that there would be a differential impact of the therapy across EF when

you began the trial.

I'm trying to gauge --

DR. SOLOMON: Yes --

DR. GILLEN: -- level of confidence inside of your subgroups.

DR. SOLOMON: I understand what you're saying. I think we can say there was no predefined hypothesis, but it is a finding that we certainly believe has biologic plausibility given everything we know. Now, we did not know whether or not -- we obviously went into the trial thinking that patients with lower ejection fraction would benefit greater than patients with higher ejection fraction, and that's why we started in patients with an EF under 35 percent. We didn't go higher than that for that particular reason, but we didn't know specifically where that cutoff would be, and we didn't know that we would see such a clear and profound gradient. That's something that we have learned from this trial, and I think will be important --

DR. LEWIS: Thank you, Dr. Solomon.

Dr. Gillen, does that answer your question?

DR. GILLEN: To some degree, although I will state one thing, is that a Bonferroni correction you stated was used. You quoted the Janet Wittes article. What has conveniently happened is the Bonferroni correction has been done on all subgroups that you've use, and Janet Wittes' article, if you read that carefully, would say that it's a correction on the test of interaction, in which case if you performed 28 of them, the Bonferroni correction would be 0.0017, and your interaction on the EF fraction would be 0.005.

So I don't think that we get to pick and choose which key values we put forward relative to an article, and I just want to make clear that that article that you have quoted on slide CC-120 is actually talking about presenting the interactions, which you have 28 tests, or on table 11, and then performing the Bonferroni correction on those, which actually you do not fall under there for EF. Thank you.

DR. LEWIS: Thank you, Dr. Gillen.

Dr. Nissen, I just want to be sure your hand didn't go up because you had a related question to Dr. Gillen; otherwise I'll get to you, but I'll go on to Dr. Moliterno.

DR. NISSEN: No, it's unrelated, and I'll come around again if we have time; otherwise I'll just wait till later.

DR. LEWIS: Okay. Thank you.

Dr. Moliterno?

DR. MOLITERNO: Thanks, Dr. Lewis. Thank you, and thanks to the presenters for doing a nice and organized job. I have a number of heart failure patients, though I'm not a heart failure specialist, so my question may be a little bit naive.

To begin with, this ejection fraction was only assessed at baseline and not necessarily at follow-up at systematic times throughout the study. I guess my concern is if we have a compound that we believe does improve myocardial performance, and we also believe the troponin levels could be affected and cause harm, then the next general concept is if

this ejection fraction is a continuous function of benefit, the one slide that stood out, to me at least, was that placebo was a superior drug for an EF above 28 percent without atrial fibrillation.

So I guess my question is, as a practitioner, what happens if I have somebody with an EF of, say, 28, but then it improves up to 35 or 40 with time and treatment, and potentially this drug; do I stop the drug, or what happens if they go in between atrial fibrillation and normal sinus rhythm? I guess the concern is, does placebos start to become superior?

That's the end of my question.

DR. MALIK: Thank you.

Well, with regards to the question around ejection fraction, certainly patients with a baseline ejection fraction that was less than 30 percent, we expected them to improve, and that shouldn't be a reason to discontinue therapy. But let me turn it over to Dr. Felker, who has a lot of experience in treating these sorts of patients as to what he would do.

DR. FELKER: Yes. Thanks, Dr. Malik.

I appreciate the question. Obviously, in clinical practice, ejection fraction can change over time, both randomly and also hopefully improve with good therapy. We don't typically reassess ejection fraction and then change drugs based on a drug that might no longer be indicated because the patient's ejection fraction has now changed.

Of course, the way we did the trial is we looked at baseline ejection fraction, we randomized patients, and then the data that's been shown about the subgroup of patients with lower ejection fraction is what happened, and probably some of those patients did improve their ejection fraction over time, but still that group showed the benefits that we described.

So I don't think this would be a situation where you need to reassess the ejection fraction and potentially stop or change therapy, just like we don't deal with any of our other drugs or devices in taking care of patients with HFrEF.

DR. MALIK: I'll just add, perhaps, that in

clinical practice, it's a question that is not infrequently asked with patients that come in with heart failure, and they're given excellent guideline-directed medical therapy, and their cardiac function improves as a consequence of that, and even potentially normalizes. That question of whether you could then withdraw background medical therapy was actually studied in a sizable trial, and the conclusion was that those patients still needed background therapy despite the improvement in their cardiac function.

DR. MOLITERNO: Sure. Thank you.

DR. LEWIS: Thank you --

DR. MOLITERNO: With a new compound being considered, a new drug class, I think we have to have, I guess, higher sensitivity to potential adverse effects with changes in cardiac performance. Thank you.

DR. LEWIS: Thank you.

Dr. Thadhani?

DR. THADHANI: Thank you. Dr. Thadhani speaking. Many of my questions have already been

addressed. It has to do with the subgroup of the 28 percent, as we've been talking about for the past few minutes.

One point I just wanted to highlight, or at least ask the sponsor, was there any evidence in prior studies, phase 2 studies, from echocardiographic results that there would be a differential effect between 28 percent and lower versus higher, acknowledging, of course, that the lower the ejection fraction, the more room there is to improve cardiac parameters?

In addition, if there were or were not, was there any evidence that there were changes in BNP and troponin to help us understand potential adverse events, either below or above median values? Thank you.

DR. MALIK: Thanks for the question. In some of the earlier studies, patients with lower stroke volumes appeared to have larger treatment effects. The patient I showed you, the echocardiogram, for instance, was someone whose baseline stroke volume was a third of normal,

25 mLs. They had a doubling of that, which is a very large treatment effect. We saw this as well in the studies where we could have a real good control over echocardiograms, smaller phase 1 and phase 2 studies.

I think the other question to ask, though, is not necessarily whether the magnitude of the treatment effect is what's important, but who are the patients that benefit the most from the treatment effect. You could have a similar treatment effect across the whole spectrum of ejection fraction, but you wouldn't expect patients with normal ejection fraction to drive benefits, and as the ejection fraction falls, I think you would, as we found.

We also have data for NT-proBNP; and if I could see slide 1?

These are the NT-proBNP data that you requested, and here you see in COSMIC how NT-proBNP cut baseline ejection fraction less than or equal to 28 percent, or greater than 28 percent, and in GALACTIC. And again, it's a quite variable

biomarker, but you see that the general pattern of the point estimate being greater in the lower ejection fraction group was true in GALACTIC -- or was consistent in GALACTIC with the finding in COSMIC, albeit more precise in GALACTIC given the number of patients.

DR. THADHANI: Thank you.

DR. LEWIS: I'm going to take a privilege to let Ms. Dunn ask her questions since she has not asked one yet, and then we'll hopefully get to everybody else's.

Ms. Dunn?

(No response.)

DR. LEWIS: Ms. Dunn, you probably need to unmute; if you go to the phone. Yes, there you go. You go to the phone on the top bar.

Got it? Great. Whoops. We lost her, I think.

Dr. Bairey Merz?

DR. BAIREY MERZ: Thank you, Dr. Lewis. Noel Bairey Merz. We're in a subgroup analysis, so I need to ask the question about sex stratified

analyses. This would be for Dr. Malik, and then Dr. Solomon. On slide 34, we don't need to see it, but there was no difference by sex, however, the female confidence intervals overlapped 1 substantially where the male did not.

Presumably in Drs. Solomon's and Malik's subgroup analyses with the Bonferroni interaction analyses, as recently discussed by Dr. Gillen, this was not a significant difference, yet we know from our recently approved heart failure drugs that the threshold for treatment benefit differs by sex by as much as 2 to 4 percent, acknowledging the variability, but it's a consistent sex difference, in that women benefit from a higher definition of reduced ejection fraction or even preserved.

So the question is, women have more atrial fibrillation, so long-winded rationale -- the question is, when you look specifically at spline curves of women with low ejection fraction, atrial fibrillation was the same harm signal seen at a different threshold. Thank you. That's my question.

DR. MALIK: Thanks for summarizing your question. We do not have those particular spline curves produced. We can perhaps produce them during the break. I think in GALACTIC-HF, we had --

DR. LEWIS: For time sake, I'm going to stop you there. Thank you.

Ms. Dunn, can you unmute? I want to give you a chance for your question.

MS. DUNN: Yes. Can you hear me?

DR. LEWIS: I can.

MS. DUNN: Yes. Thank you so much. I'm so sorry I'm having technical difficulties here. I did miss the question that I just came in on, so this may address what I'm going to ask. I needed a little clarification on the global study slide, where the 8,256 patients were enrolled globally. I neglected to write down the slide number, so I don't know if we could produce that.

My question was, 21 percent of the enrolled were female -- I don't believe it was that one. It might be the next study, the next slide. I don't

know if you can move that forward. It was a grid.

DR. MALIK: C-4, I think. Yes; slide 2, please.

MS. DUNN: It was a grid system with the breakout. Yes, there it is. It did address females.

The study there, it seems to be a wide disparity between the women represented in this study, the GALACTIC-HF study. Obviously women are different than men when it comes to clinical trials, so I was wondering if you could, A, answer why 21 percent, and then possibly if we could understand how women did fare in this clinical trial versus men. Thank you.

DR. MALIK: Thanks for the question.

The GALACTIC-HF, as you said, enrolled 21 percent. That was over 1700 patients in total that were women, which I think permitted an assessment at least of safety in that group. We found that women on this drug had lower rates of serious adverse events compared to men; or rather I should say at baseline. Their risks were somewhat

lower in terms of ischemic events, ventricular arrhythmias, rates of serious adverse events.

There was no significant treatment interaction in terms of the treatment effect based on sex and looking at it in the global effect, or the global analysis of the subgroup variables that we looked at. So I think the the answer to your question is maybe we haven't enrolled as many women as we would have liked. We tried. Many of the heart failure trials are challenged by the same issue. Heart failure with reduced ejection fraction maybe is not as common as it is in men, although I think it's more common than we achieved here, so I think that is one area of improvement for many of the trials.

DR. LEWIS: Thank you.

We'll take a five-minute break now. I have 11:25/11:24, so we'll be back at 11:30 and proceed with the FDA presentation. I and Rhea have kept a list of the remaining questions. We'll try to work them in later, and I know the company is going to be working on Dr. Nissen's questions that they need

to get material for.

Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break, and then again, we will reconvene at actually 11:29. Thank you.

(Whereupon, at 11:24 a.m., a recess was taken.)

DR. LEWIS: Okay. I apologize for that short break.

We will now proceed with the FDA presentations, starting with Tzu-Yun McDowell.

Dr. McDowell?

DR. McDOWELL: Yes. Hi.

FDA Presentation - Tzu-Yun McDowell

DR. McDOWELL: Good morning, everyone. My name is Tzu McDowell, and I'm a clinical reviewer in the Division of Cardiology and Nephrology. Together with my colleagues, Dr. William Koh, the statistical reviewer, and Dr. Li Wang, the clinical pharmacology reviewer, we will be presenting the FDA's review on efficacy and safety of omecamtiv

mecarbil.

I will start the presentation with the topics we would like the committee to address, and the first topic is to discuss the benefits of omecamtiv mecarbil and whether there is adequate evidence for concluding these benefits. We would like the committee to consider the findings for the heart failure and cardiovascular mortality components of the primary efficacy endpoint in the GALACTIC-HF trial. In addition, we would like the committee to discuss what role does the phase 2 trial play in their assessment of the benefits.

Second, if omecamtiv mecarbil were approved, we would like the committee to consider what should the labeling say regarding its use as a function of left ventricular ejection fraction, as well as its use in patients with atrial fibrillation or atrial flutter. The last topic is to discuss whether omecamtiv mecarbil is safe enough to support its proposed use. We would like the committee to consider safety with or without pharmacokinetic-based dosing.

Before delving into our review of the application, I would like to spend a few minutes on background by introducing the three approaches for establishing substantial evidence of effectiveness for a therapeutic product. In general, FDA requires at least two adequate and well-controlled trials to establish the effectiveness. This reflects the need for substantiation of experimental results and minimizes the possibility of bias or chance findings with a single trial.

Under certain circumstances, FDA has considered a single, large, multicenter adequate and well-controlled trial to satisfy the scientific and legal requirements of substantial evidence of the effectiveness. Using a single large multicenter trial to establish effectiveness should generally be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect of important clinical outcomes such as mortality and severe or irreversible morbidity.

The last approach to establish effectiveness

is based on one adequate and well-controlled trial plus confirmatory evidence. Confirmatory evidence could include, for example, clinical data from an adequate and well-controlled trial in a closely related disease area; compelling mechanistic evidence in the setting of well-understood disease pathophysiology.

I want to point out that FDA considers several factors when determining whether using this approach is appropriate. These factors may include the persuasiveness of a single trial; the robustness of the confirmatory evidence; the seriousness of the disease where there is an unmet medical need; the size of the patient population; and whether it is ethical and practicable to conduct more than one adequate and well-controlled study.

In the heart failure treatment space, a single large, multicenter, adequate and well-controlled cardiovascular outcome trial with a persuasive result over standard of care therapy is considered acceptable as the basis of substantial

evidence of effectiveness. Here, I would like to provide some perspectives on the evidence generated from the key phase 2 study, COSMIC-HF.

The primary objectives of this study were to select an oral formulation and dose, as well as to characterize omecamtiv mecarbil's PK over 20 weeks of the treatment. The effects of omecamtiv mecarbil compared with placebo on selected pharmacodynamic PD markers were evaluated as secondary or exploratory endpoints. This analysis was not controlled for multiplicity.

As discussed by the applicant, omecamtiv mecarbil was associated with improvements in several PD markers with a systolic ejection time as the most sensitive PD marker. Despite this positive finding, we noted that omecamtiv mecarbil was associated with a small increase in LVEF with an average increase of 1.6 percent compared with placebo. FDA questioned the clinical meaningfulness of this observed effect. Omecamtiv mecarbil also did not have an effect on increasing left ventricular cardiac output. There were no

differences between groups.

This phase 2 study overall provides data supporting a mechanism that is possibly related to outcomes in patients with heart failure with reduced ejection fraction, however, the degree of the clinical benefits associated with this mechanism and the changes of the study's PD markers are uncertain. None of the PD markers were studied in the phase 3 trial except for heart rate and NT-proBNP.

Here, I want to emphasize that the pivotal phase 3 trial, GALACTIC-HF, was sufficiently powered for cardiovascular [inaudible] and the composite of cardiovascular death and heart failure. This single large trial was designed to provide an adequate basis for an efficacy claim.

With this background, we will now move on to the main part of the presentation. Our presentation includes a discussion of the efficacy findings from the GALACTIC-HF trial and the related review issues, followed by a discussion of the main safety findings and the concerns from both

nonclinical and clinical data, including the issues related to the proposed dosing pathology. We will end with a discussion of the benefit-risk assessment.

Now, I will hand over the presentation to Dr. William Koh to start the discussion of efficacy.

FDA Presentation - William Koh

DR. KOH: Thank you, Dr. McDowell.

Good morning. My name is William Koh. I'm the statistical reviewer for omecamtiv mecarbil. I'll be presenting the efficacy findings.

Dr. Malik from Cytokinetics has nicely described the study design for GALACTIC-HF earlier. Just to recap, GALACTIC-HF was a randomized, double-blind, placebo-controlled, multicenter, event-driven study. We want to point out that GALACTIC-HF planned to randomize approximately 8,000 adult patients with chronic heart failure with reduced ejection fraction specifically with LVEF less than or equal to 35 percent. This number of subjects, together with the design assumptions,

will provide approximately 1590 subjects experiencing a CV death event to ensure at least 90 percent power for the CV death key secondary endpoint. The overall type 1 error of the study is specified at two-sided level of 0.05.

Patients were randomized equally to receive omecamtiv mecarbil or placebo. Randomization was stratified by randomization setting and regions. A randomization setting was categorized according to whether patients who were currently hospitalized with [inaudible - audio gap] primary reason as heart failure with those who were not currently hospitalized.

In GALACTIC-HF, patient demographics, baseline disease characteristics, and background standard of care were balanced across treatment arms. We listed the following baseline characteristics that are considered relevant for this presentation. The mean age is 65 years. Seventeen percent of the randomization was from the U.S., 66 percent of the patients were on all three standard of care therapies for heart failure. Only

2.6 percent of the patients used SGLT2 inhibitors. We want to point out that SGLT2 inhibitors only became available during the conduct of GALACTIC-HF.

Ninety-seven percent of the patients were categorized under New York Heart Association or NYHA class II or III. Only 3 percent were categorized under NYHA class IV. The mean LVEF was 27 percent. The median was 28 percent. At the time of randomization, LVEF ranged from 4 percent to 42 percent with 3 patients having values above 35 percent. Twenty-seven percent of the patients had atrial fibrillation at screening.

The primary endpoint was time to first adjudicated cardiovascular death or heart failure event. CV death included adjudicated cardiovascular death, presumed CV death or presumed sudden death. Unknown death was not included by this definition. Heart failure events included hospitalization for heart failure, urgent emergency room, emergency department, and office or clinic visit.

The applicant's primary endpoint for the

study was considered appropriate. The key secondary endpoint was time to CV deaths. Other secondary endpoints considered for multiplicity control included change from baseline in Kansas City Cardiomyopathy Questionnaire Total Symptom score at week 24; time to hospitalization for heart failure; and time to all-cause mortality. We want to point out that the applicant also listed multiple exploratory endpoints in the protocol, however, time to new atrial fibrillation among patients with absence of atrial fibrillation was prospectively included in the SAP or final protocol.

Based on the prespecified alpha level of 0.05, the primary endpoint for GALACTIC-HF was met. The estimated hazard ratio was 0.92. This translates to an 8 percent significant reduction on the relative scale in risk of composite CV death or heart failure event favoring OM. The 95 percent confidence interval ranged between 0.86 to 0.99. The 95 percent upper limit of the confidence interval of 0.99 adjusts throughout the null

hypothesis of no difference of 1.

As a reference, the risk difference per 100 patient-years, based on the difference in the incidence rates comparing omecamtiv mecarbil with placebo, are presented. On the absolute scale, this was two few events per 100 patient-years favoring omecamtiv mecarbil.

We looked at the components of the composite endpoint to understand whether the individual components trended in the same direction as the composite. Just as a reminder, CV death as a key secondary endpoint was adequately powered. There was not an observed treatment effect on CV death between arms. The estimated hazard ratio was 1.01. On the absolute scale, the estimated risk difference was 0.1 per 100 patient-years.

The hazard ratio for the first heart failure event was 0.93, translating to a numerical trend of reduction of 7 percent in risk of heart failure event. The majority of the first heart failure event was recorded as hospitalization for heart failure.

On this slide, we present a summary of the causes of CV death. There was no numerical imbalance in CV death between arms. The majority of the adjudicated CV deaths was noted to be due to heart failure. This was also similar between arms. We next looked at the key secondary endpoints that were prespecified according to the study's multiplicity hierarchy. In brief, if the primary efficacy endpoint was statistically significant at two-sided alpha of 0.05, the alpha was split to evaluate time to CV death at two-sided alpha level of 0.048.

The change from baseline in the Kansas City Cardiomyopathy Total Symptom score was evaluated at two-sided alpha level of 0.002. However, neither of the secondary endpoint CV death or change from baseline in KCCQ matched the specified level of significance. Therefore, none of the remaining secondary endpoints, namely hospitalization for heart failure and all-cause mortality, was evaluated.

In summary, according to the prespecified

alpha of 0.05, the primary efficacy endpoint for GALACTIC-HF was met. However, it was not clear to the review team whether the estimated treatment effect, either described on the relative scale or the absolute scale, was considered clinically meaningful. For the individual components, CV death was the key secondary endpoint. There was no difference in CV death between arms. There was an observed numerical trend, the reduction in risk of first heart failure event towards omecamtiv mecarbil.

Since the upper limit of the confidence interval for the primary endpoint was close to the null hypothesis of 1, we also conducted sensitivity analyses to understand whether these findings were robust to deviations in the assumption. These additional sensitivity analyses provided similar conclusions as the primary efficacy findings.

This is a summary of the findings for the remaining key secondary endpoints. Even though the prespecified multiplicity hierarchy failed to allow for the testing of the secondary endpoints, we

generally look at them descriptively to understand whether there were trends favoring omecamtiv mecarbil. There was no observed difference between arms in the change from baseline in KCCQ Total Symptom score at week 24. There was an observed numerical trend of reduction in risk of hospitalization for heart failure towards OM. There was no observed difference in all-cause mortality.

At the end of the phase 2 meeting, the agency specified two possible scenarios where the single study could provide support for an effectiveness claim. The first is as follows: if the primary endpoint was significant at a p-value of less than 0.01 and there was no adverse effect on mortality, or if CV mortality was significant at a p-value less than 0.05.

From our review of GALACTIC-HF, while we agree that the primary endpoint was met, the observed p-value of 0.025, a measure of the strength of evidence, did not meet the criteria we laid out during the end of phase 2 meeting. In

addition, the 95 percent upper limit of the confidence interval of 0.99 was close to the null hypothesis of no difference of 1. There was no difference in CV death and all-cause mortality. The review team concluded that the study findings did not quite meet the considerations for this scenario.

The second scenario is as follows. If the p-value for primary composite was driven by urgent heart failure disease -- i.e., emergency department/office visit -- a single study with a p-value of 0.05 would probably not be sufficient for approval in the absence of at least strong trends for the other components of the composite endpoint.

These are the key points for consideration. The primary composite endpoint was statistically significant at a two-sided alpha of 0.05. The majority of the first primary event endpoint came from hospitalization for heart failure. In the components of the composite endpoint, there was absence of trends for CV death. There was an

observed numerical trend for the heart failure event, however, the upper limit of the 95 percent confidence interval had just crossed the null hypothesis of no difference of 1. There was a numerical trend observed for the hospitalization for heart failure endpoint. The upper limit of the 95 percent confidence had also crossed the null hypothesis of no difference of 1.

There was absence of trends for all-cause mortality. In summary, based on the study, the review noted that the components of the composite endpoint did not show strong trends.

With that, I shall discuss some of the efficacy subgroup findings. In the applicant's proposed indication section, the following language was included to highlight the benefit of the drug. Specifically, it states that "benefits are increasingly evident the lower left ventricular ejection fraction or LVEF."

As a word of caution, we typically consider subgroup analysis results to be exploratory and not considered as definitive evidence for or against

the treatment effect within particular subgroups. The next few slides contain prespecified exploratory subgroup analysis results.

In GALACTIC-HF, heterogeneity of treatment effect was observed. In this forest plot, we included the following prespecified subgroup defined for the baseline LVEF and presence or absence of atrial fibrillation as screening for discussion. We want to point out that the categorization of LVEF was based on the median value of the full analysis population. The value of 28 percent was not predetermined.

These two subgroups were reported and emphasized because they were two of the most significant treatment interaction findings after looking at, at least 20 individual prespecified subgroup analyses. Acknowledging the lack of multiplicity control for these analyses, there was no difference in treatment effect among the subgroup of patients with baseline LVEF greater than 28 percent. There was also no observed difference among the subgroup of patients with

presence of AFib at screening.

For the context of the presentation later, we included exploratory subgroup findings defined by combination of LVEF and each presence and absence of atrial fibrillation at screening. In this exploratory subgroup analysis, among the subgroup of patients with presence of AFib at baseline and LVEF greater than a median value of 28 percent, and observed 20 percent higher risk of primary endpoint compared to placebo was noted. In the remaining subcategories, there was at least and observed numerical trend in the reduction in the risk of primary endpoint favoring OM.

We further support the proposed language in the indication section. The applicant conducted additional exploratory analysis after the data was unblinded. This also included the multivariate analysis that the applicant had done by including the treatment of prespecified subgroups and each subgroup and treatment interaction in the same model.

In this figure, this shows the applicant

included exploratory subgroup findings based on the regression [indiscernible] analysis between the primary endpoint with baseline LVEF. The applicant's results are shown in gold solid lines with the 95 percent confidence interval presented in gold dotted lines. This regression model allows the relationship between LVEF and the primary endpoint to be flexible, and in order to do that, knots were chosen to allow such flexibility.

The blue dots above the horizontal axes represent the LVEF value where the knots were chosen. In summary, there is observed trends of benefit for lower range of LVEF, based on their post hoc analysis. From the figure, for LVEF that is below 24 percent, there was an observed reduction in risk favoring OM. This is indicated by the confidence interval lines all below the null hypothesis of no difference of 1. However, only 32 percent of the randomized subjects had baseline LVEF below 24 percent. Also, subjects with baseline HFrEF greater than 24 percent, the observed treatment benefit was not clear.

Despite these observations, the review team has concerns with the proposed model used to describe the relationship between LVEF and the primary endpoint. In these exploratory analyses, it was not clear why only three knots were chosen at these specific LVEF values. We also questioned whether other regression models could be considered that describes the relationship between the primary endpoint with LVEF since this can impact the interpretation of the results. It is also unclear whether additional risk factors such as the presence or absence of atrial fibrillation could impact the relationships observed in this figure.

During the review, the clinical team expressed concerns with an apparent increase in risk of CV death for subjects with the presence of atrial fibrillation at baseline. As exploratory analysis, assuming that the applicant's exploratory model was sufficiently characterizing the relationship between the primary endpoint with LVEF, we've reported analogous results for each atrial fibrillation subgroup.

On this slide, we show the descriptive relationship for presence of AFib subgroup on the left and the absence of AFib subgroup on the right. In the subgroup of HFrEF subjects who had concomitant atrial fibrillation/atrial flutter at screening, there was no observed treatment benefit throughout the LVEF range. At certain ranges, it is unclear whether there's observed trends towards higher risk. On the right, in the subgroup of HFrEF patients who did not have atrial fibrillation at screening, an observed treatment effect was generally noted. The lower range of the reduced LVEF spectrum below 24 percent appeared to show more benefit.

The review team has concern with our own exploratory findings, too. Given the variabilities associated with echocardiographic measurements of LVEF, it is not clear whether the empirical value of LVEF of 24 percent, or even 28 percent, in the subgroup of subjects without AFib is considered reasonable. We acknowledge our analyses are also conducted post hoc. This presents additional

difficulty to the interpretation in an already post hoc issue of the subgroup analysis of subjects already categorically characterized as HFrEF.

This is a summary of the key issues noted with the applicant's proposal to include the language in the indication. We agree that the subgroup analysis suggests that there is evidence of a heterogeneous treatment effect observed in HFrEF and AFib cycles. There are issues with using baseline LVEF as a continuous measurement to determine or describe the subjects who may benefit. We know that there are limitations with the post hoc model used to describe the relationship.

The proposed language benefits are increasingly evident, the lower the left ventricular ejection fraction is considered vague and not readily actionable for healthcare providers. It is difficult to further use a specific LVEF value to describe what is lower in a patient population who already has low ejection fraction of 35 percent to begin with. Finding such a subpopulation of patients in and already low

ejection fraction subgroup is considered clinically arbitrary.

Given the variabilities associated with echocardiographic measurements of LVEF, they further underline uncertainty in the LVEF measurement that is unaccounted for. With respect to the AFib subgroup, we do observe a detrimental treatment effect for the subpopulation of subjects with concomitant AFib and LVEF greater than 28 percent.

The applicant noted that it is crucial to indicate OM for the group of patients that will benefit from the drug. It is important to understand whether there is any uncertainty in risk observed in the same group of patients, and with that, I'll turn the presentation back to Dr. McDowell, who will cover the safety findings.

FDA Presentation - Tzu-Yun McDowell

DR. McDOWELL: Hi. Thank you, Dr. Koh.

Now I will start the discussion of the safety findings from the nonclinical data.

Omecamtiv mecarbil was associated with a

dose-limiting cardiac toxicity in rats and dogs. Following short and chronic duration of the treatment, probably a related mortality in myocardial injuries, including myocardial degeneration, fibrosis, and necrosis, were found in both animal species. The effect of omecamtiv mecarbil on cardiac toxicity appears closely related to the plasma drug concentration.

The table on the slide shows the maximum concentration, Cmax, at the toxic dose that resulted in mortality and myocardial injuries, as well as the Cmax at the dose without cardiac toxicity. This finding clearly indicates a very slim separation, about 1.3-fold, between plasma drug levels associated with cardiac toxicity and the levels considered potentially efficacious with the absence of toxicity. Therefore, omecamtiv mecarbil appears to have a fairly narrow therapeutic window.

Based on this animal finding, there was a minimal safety margin for clinical exposure, about 2-fold. The calculation of the clinical exposure

was based on the estimated Cmax for the maximum recommended human dose of a 15-milligram BID from the GALACTIC-HF trial under PK-guided dosing. I want to point out that there would be nearly no safety margin if the calculation was based on the estimated Cmax of 50-milligram BID without the PK-guided dosing.

With the nonclinical data, an early clinical finding shows that myocardial ischemia, including myocardial infarction, occurs in healthy adults and patients with HFrEF on omecamtiv mecarbil. FDA has expressed concerns about cardiovascular safety in association with the dosing of omecamtiv mecarbil throughout the developmental program.

To mitigate the risk and ensure safety, the PK-guided titration was tested in the phase 2 study. A refined PK-guided posology was implemented in the GALACTIC-HF trial. The pathology used omecamtiv mecarbil plus mild concentration measures and the predefined time points to adjust the dose, and was designed to achieve the target concentration within a

predetermined range of 300 to 750 by minimizing the the frequency of excessive exposure.

Prior to the NDA submission, the applicant informed FDA that the immunoassay used in the GALACTIC-HF to measure omecamtiv mecarbil concentration for the purpose of the drug will not be commercialized. The applicant proposed to develop and validate an assay using the LC-MS/MS method. Nevertheless, the applicant subsequently submitted the NDA with the proposed scheduled dose titration without the need for PK guidance, with the understanding that the best regimen to inform dosing will be determined during the NDA review.

Next, I will discuss the key safety findings from the GALACTIC-HF trial and the main safety concerns. In GALACTIC-HF, under a PK-guided dosing strategy, the risk profile of omecamtiv mecarbil was similar to placebo with the exception among patients with AFib or flutter. The risk of myocardial ischemia is similar between groups. The hazard ratio for the prespecified safety endpoint for major cardiac ischemic event was 1.1.

Treatment with omecamtiv mecarbil was associated with a small increase in troponin and the creatine kinase-MB compared with the placebo. The clinical significance of this increase was unclear. The subgroup analysis of time to cardiovascular death shows that subjects with AFib or flutter on omecamtiv mecarbil had an increased risk compared with placebo.

This slide shows the subgroup analysis by AFib or flutter across the key efficacy endpoint. I'm showing the forest plot on the left. Patients with AFib or flutter, about 27 percent of the GALACTIC-HF population has no apparent treatment effect as measured by the primary efficacy endpoint and heart failure hospitalization.

This is a subset of the patients that also have an increased risk of cardiovascular death and all-cause death. The findings were concerning given the size of the observed effect. Patients with AFib or flutter on omecamtiv mecarbil were associated with the 26 percent increase in cardiovascular death, with the lower bound of the

95 percent confidence interval above 1. In contrast, patients without AFib or flutter in the forest plot on the right had a nominal significant risk reduction for primary efficacy endpoint and for heart failure hospitalization. There was also a trend favoring omecamtiv mecarbil for cardiovascular death.

The excess in cardiovascular death in patients with AFib or flutter was driven primarily by an increased incidence of heart failure death as opposite to sudden cardiac death. Safety data was consistent with this finding, indicating a higher instance of heart failure of the first event among AFib or flutter patients in the omecamtiv mecarbil group compared with placebo. The mechanism of this observation is unclear, but the possibility that this finding could be associated with cardiac toxicity of omecamtiv mecarbil cannot be ruled out.

Patients with AFib or flutter could be more susceptible to the potential cardiac toxicity related to omecamtiv mecarbil. Post hoc analysis conducted by the sponsor and FDA indicate that a

subset of the patients with AFib or flutter may have a higher risk of full cardiovascular death. AFib or flutter patients treated with digoxin, the omecamtiv mecarbil group was associated with a 70 percent increase in cardiovascular death compared with placebo.

Similarly, for AFib or flutter patients with baseline LVEF greater than 28 percent, omecamtiv mecarbil was associated with a 50 percent increase in cardiovascular risk compared with placebo. However, with the known limitation for this type of exploratory subgroup analysis, it is unclear whether AFib or flutter patients at risk should be prospectively and reliably identified.

Now, I would like to further discuss the clinical risk of omecamtiv mecarbil and some uncertainties. The principal safety concern of omecamtiv mecarbil is the potential risks of dose-limiting cardiotoxicity in the context of a narrow therapeutic window. As I just discussed, the risk appears to be contained in GALACTIC-HF under PK-guided dosing with exception among

subjects with AFib or flutter.

The applicant identified the risk of myocardial ischemia due to excessive exposure in early clinical studies and proposed a safety threshold of 1000. FDA considers this safety threshold arbitrary given that it was determined primarily based on limited clinical data from studies using an IV formulation following short duration of exposure. There are limited data to evaluate clinical risk associated with long-term excessive exposure of omecamtiv mecarbil. In the GALACTIC-HF trial under a PK-guided dosing strategy, the median plasma concentration was maintained in the range of 250 to 300, with limited experience at a higher exposure range.

Based on the available clinical data and the understanding of the toxicology profile of omecamtiv mecarbil, FDA has a concern that the exposure of omecamtiv mecarbil increases the risk of myocardial ischemia and heart failure. The applicant conducted an exposure-response analysis based on the data from GALACTIC-HF. There was a

positive exposure-response relationship for safety, showing that higher omecamtiv mecarbil exposure was associated with increased probability of serious adverse events. FDA's analysis further indicates that the positive exposure-response relationship was largely driven by increased probability of a cardiac failure and serious adverse events.

We also observed the safety signals from the case review in the phase 2 and 3 studies, indicating correlation between increased concentration of omecamtiv mecarbil with increased values of troponin and/or NT-proBNP in association with cardiac adverse events, including myocardial ischemia and heart failure.

FDA also considers that the optimal therapeutic range of omecamtiv mecarbil has not been well established. In GALACTIC-HF, the applicant predefined a therapeutic range of 300 to 750, however, there are limited data to support efficacy and safety of omecamtiv mecarbil at the higher end of this proposed therapeutic range. In addition, there was no apparent exposure-response

relationship for efficacy, which might imply that an increase in omecamtiv mecarbil exposure is not expected to improve efficacy.

FDA's main safety concern with real-world use is that the potential risks of omecamtiv mecarbil associated cardiotoxicity is likely to increase if there is no mandatory requirement of measuring plasma concentration for the purpose of dose adjustment. We also worry about the potential increased risk of cardiovascular death among patients with AFib or flutter.

Now, I will hand over the presentation to Dr. Li Wang to further discuss the issue related to the proposed dosing strategy.

FDA Presentation - Li Wang

DR. L. WANG: Thank you, Dr. Tzu McDowell.

Dear committee members and the staff, my name is Li Wang, and I'm the clinical pharmacology reviewer for this NDA submission. In this presentation, I would like to show you the observed and the predicted exposure of omecamtiv mecarbil with different dosing strategies to demonstrate

that the PK-guided pathology is critical for the safe and effective use of the drug.

As Dr. McDowell mentioned in the previous slides, the sponsor has proposed the target plasma concentrations of omecamtiv mecarbil as 300 to 750 nanograms per mL for safety and efficacy purpose [indiscernible]. Accordingly, in the pivotal trial GALACTIC-HF, the sponsor implemented the PK-guided dosing titration as shown in the table here.

All [indiscernible] subjects in the drug treatment group were started on a dose of 25-milligram BID. At week 2, plasma [indiscernible] concentration, or trough concentration in other words, were assessed for determining the target dose for each subject. These target doses were initiated from week 4. At week 6, trough concentrations were measured again to ensure they were reaching the desired range. If needed, the dose was further adjusted at week 8.

As shown in the pie chart on the right, 48 of the subjects were at the top dose of

50-milligram BID, while 29 percent and 13 percent of the subjects were receiving 25 milligrams and 37.5-milligram BID dose, respectively, as their final doses by week 12, according to the PK-guided dose adjustment. This PK-guided dosing posology was effective in limiting a high drug disorder, as we will present more data in the following slides.

Before we compare the PK-guided dosing posology, I would like to use the sponsor's initially proposed schedule of the forced dosing titration as an example. As shown in the figure here, all [indiscernible] subjects who received 25-milligram BID, 37.5-milligram BID, and 50-milligram BID with a 2-week interval, and everyone received 50-milligram BID as the final dose from week 5.

This is different from the pivotal with PK-guided dosing posology, in which only 48 percent of the patients received 50-milligram BID as the final dose. As this schedule of the forced dosing posology has not been applied in clinical studies, we used pharmacokinetic simulation to generate the

distribution of drug exposure.

As this schedule of the forced dosing posology has not been applied in clinical studies, we used pharmacokinetic simulation to generate the distribution of drug exposure. The distribution of trough concentration over time is shown in the two figures here. The left one represents the observed [indiscernible] trial from a phase 3 trial in which the PK-guided titration was applied, while the right one is from the simulation based on forced titration.

The red dashed lines label the three [indiscernible] levels, 750, 1000, and 1,200 nanograms per mL and weeks are on the X-axis. The patient population for the two scenarios share the same distribution of demographic characteristics. Let's start with observed [indiscernible] trial in the pivotal trial. In the left figure, you can see that the majority of the concentration is below the 750 nanogram per mL dashed line, only less than 0.1 percent of the point, about 1000 nanograms per mL. Clearly,

PK-guided titration is effective in limiting high drug plasma concentration.

Let's move to the right figure with forced titration. At week 6 and 12, everyone is on the 50-milligram BID dose. We can see the higher exposure of omecamtiv mecarbil compared with PK-guided titration. The percentage of the points above the 1000 nanogram per mL dashed line is at least 6- to 7-fold higher than that with the PK-guided titration.

According to the [indiscernible] phase 1 and phase 2 studies, myocardial ischemia events, including myocardial infarction, had occurred in both healthy adults and patients with heart failure, with reduced ejection fraction with excessive drug exposure. As there are more points shown as excessive exposure, there might be an increased risk for myocardial ischemia with forced titration.

Regarding efficacy, based on the limited exposure-response experience for omecamtiv mecarbil, the ER analysis for efficacy showed no

significant ER relationship for the primary endpoint, which might imply that an increase in drug exposure is not expected to improve efficacy. In summary, forced titration will lead to more safety concerns while no additional efficacy benefit.

These are the findings of the clinical pharmacology study of omecamtiv mecarbil. A number of intrinsic and extrinsic factors may increase the exposure of the drug. I would like to take CYP2D6 polymorphism for an example. CYP2D6 is one of the main enzymes that metabolizes omecamtiv mecarbil. The CYP2D6 gene is highly polymorphic.

The phenotype characterized includes ultra rapid metabolizers, normal metabolizers, intermediate metabolizers, and poor metabolizers in order of highest to lowest metabolizing ability. People recognized as poor metabolizers have no CYP2D6 activity. The CYP2D6 poor metabolizers are mainly found in European populations, about 6.5 percent, and lower in the female, African American, and Asian populations, around 1

to 3 percent.

In a dedicated clinical study, subjects with the CYP2D6 poor metabolizer genotype exhibit higher exposure compared with those with CYP2D6 normal metabolizer genotype. The AUC increased by 47 percent; therefore, we expect that the chance for patients as CYP2D6 poor metabolizers exhibiting excessive drug exposure might be high without PK-guided titration.

Now I want to summarize my presentation. We performed a simulation for forced titration initially proposed by the sponsor. We found that the forced titration was expected to lead to higher drug concentrations about 1000 nanograms per mL in more patients than PK-guided titration. In contrast, the concentration of omecamtiv mecarbil was well controlled in the pivotal trial with PK-guided titration. Finally, the PK-guided titration is also helpful to address potential safety concerns with elevated drug exposure due to intrinsic and extrinsic factors.

That's it for me. Thank you for your

attention, and now I will hand the presentation over to Dr. Tzu McDowell.

FDA Presentation - Tzu-Yun McDowell

DR. MCDOWELL: Thank you, Dr. Wang.

The FDA review team has communicated with the applicant about the concern with the initial proposed scheduled dose titration. During the review, the applicant subsequently agreed to implement a PK-guided dosing strategy that is similar to the strategy used in GALACTIC-HF. The applicant proposed to measure omecamtiv mecarbil plasma concentration using the Labcorp LC-MS/MS method instead of the immunoassay used in the phase 3 trial. This laboratory-developed test is not authorized by FDA.

Next, I will discuss the benefit and risk assessment of omecamtiv mecarbil. With the efficacy and the safety issues discussed in this presentation, the FDA review team is not certain whether the benefit of omecamtiv mecarbil outweighs the risk.

On the benefit side, there was a small

treatment effect from the single pivotal trial. The results were not statistically persuasive and may not provide an adequate basis for concluding the benefits. On the risk side, there was a concern regarding omecamtiv mecarbil's associated cardiac toxicity in the context of the narrow therapeutic window. Also, the risk could vary depending on whether or how well a PK-guided dosing strategy is followed in the real-world setting. The benefit and risk assessment is further complicated by differential results in certain subgroups, including baseline LVEF and the presence of AFib or flutter.

The table on this slide shows you the quantitative benefit-risk assessment. The effect of omecamtiv mecarbil compared with the placebo was evaluated by calculating the absolute difference in the incidence rate delta of the primary composite efficacy endpoint and the major cardiac ischemia event, the primary safety endpoint.

The negative delta risk difference indicates an absolute risk reduction in omecamtiv mecarbil

compared with the placebo. On the benefit side, compared with placebo, omecamtiv mecarbil reduced the incidence rate of the composite endpoint by 2 events per 100 patient-years. For the risk side, omecamtiv mecarbil increased the incidence rate of major cardiac ischemia events by 2 events per 1000 patient-years.

The overall benefit-risk was evaluated by calculating the incidence rate of the first primary composite endpoint or major cardiac ischemia event. A delta of a negative 2.5 indicates a potential net benefit of omecamtiv mecarbil, however, this small net benefit is uncertain given the issues we have stated in the presentation, as well as the limitation of this type of analysis which only considers the first event. Not all cardiovascular deaths in the trial were included.

The potential net benefit is also fragile because only three additional major cardiac ischemic events per 100 patient-years, or three additional cardiovascular deaths, or heart failure events are needed to render an unfavorable

benefit-risk profile for omecamtiv mecarbil.

With the expected increased exposure following the initial proposed posology of scheduled titration, and the concern that excessive exposure increases the risk of myocardial ischemia and heart failure, the FDA review team does not believe the benefit-risk profile is favorable to omecamtiv mecarbil without a PK-guided dosing strategy. The benefit-risk profile under the newly proposed PK-guided dosing with the LC-MS/MS assay should be similar to that in GALACTIC-HF if the PK-guided dosing is universally followed as it was in the trial.

This was a joint review with input from several members of our multidisciplinary review team. The members who are listed on the slide contributed to this presentation and our FDA briefing document.

Lastly, I would like to point out an error and the correction to FDA's briefing document. On page 53, the first line of the table 16 should be revised. The correction is shown in the bottom

table on this slide. This brings us to the end of the presentation, and we thank you for your attention.

Clarifying Questions

DR. LEWIS: Thank you.

We will now take clarifying questions for FDA. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your questions. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Dr. Blaha?

(No response.)

DR. LEWIS: Dr. Blaha, you're muted.

DR. BLAHA: I apologize about that. Can you all hear me now?

DR. LEWIS: Yes.

DR. BLAHA: Okay. Thank you.

I'd like to ask a clarifying question about FDA slide 36. If you could pull that up on the screen again, I'd like to clarify a statement that was made on slide 36. I'll wait for that to come up. And while it's being pulled up, I'll try to remember the exact phraseology.

But I thought that it said the FDA concluded -- let's go to the bottom here -- that there's no apparent exposure-response relationship for the primary efficacy composite endpoint. I was trying to reconcile that with some data that I saw from the sponsor, which seemed to show -- they seemed to claim -- that drug levels during the trial, that there did seem to be a dose response, I guess, at least up to some point.

If I can get the FDA to clarify that statement about what exactly they mean by no

apparent exposure-response relationship or perhaps the shape of that relationship, I'd be appreciative. Thank you.

DR. L. WANG: Hello, Dr. Blaha. This is Li Wang, the clin-pharm reviewer. Thank you very much for your question.

I want to clarify the exposure-response analysis we did. Basically, we used a time-to-event Cox model to describe the relationship between this exposure to the time-to-event efficacy endpoint. First, I want to emphasize that the drug exposure range in the ER analysis was really narrow, and that is because the data we got is from the pivotal trial, the GALACTIC-HF, which applied the PK-guided titration.

So the modeling work, results, showed no statistical significant ER relationship with any of the efficacy endpoint, based on a significant level of 0.05 after adjusting the baseline eGFR. That's why we claim that there's no apparent exposure-response relationship --

(Crosstalk.)

DR. BLAHA: Do you have the data or a graphic that we could see from your analysis?

DR. L. WANG: Sure.

(Pause.)

DR. L. WANG: Could I have slide [indiscernible]?

DR. McDOWELL: This is Tzu McDowell. I want to make some clarification that when we say the exposure-response analysis, the exposure was calculated based on the simulated concentration from the population PK model based on the dose that the patients received at week 12, and the applicant acknowledges this work based on the observed concentration in the GALACTIC-HF trial, and we also conducted exploratory analysis based on the observed concentration.

After Dr. Li Wang finishes his response, I would like to show our analysis from that perspective.

DR. BLAHA: Thank you.

DR. LEWIS: FDA I need you to pull up more slides -- there you go. Thank you.

DR. L. WANG: This is Li Wang again. This is a survival curve based on different quartiles of the trough at week 12. You can see we have different lines for quartile 1 to quartile 4, and also the placebo. You can see that, basically, the Kaplan-Meier survival curves are largely overlapping across these four quartiles of omecamtiv mecarbil trough concentration at week 12, and there's no monotonic pattern for the ER relationship. Also, the survival profile for quartile 4 has high exposure and the placebo has no exposure similar to each other.

This curve just demonstrates the typical values, and we also can further consider the uncertainty of these survival curves. We can also see an overlapping of these Kaplan-Meier curves with confidence intervals, which exhibit no apparent ER relationship or efficacy endpoint.

One more thing I would like to mention is that this kind of analysis is subject to a potential confounding effect, the other important clinical factors. Also, this is based on the

post-randomization information.

Does that answer your question?

DR. BLAHA: Yes. This is extremely helpful for me to see this data, and I think someone else is going to add a response as well. I'll give a moment for that.

DR. McDOWELL: This is Tzu McDowell. Let me find our backup slide regarding this.

This is the exploratory concentration response analysis that we performed based on the observed concentration in the GALACTIC-HF trial, and the difference between the applicant's analysis and our analysis is the difference in the definition for the concentration used.

For this particular FDA analysis, we used the last plasma concentration measured prior to or at week 12. This concentration at week 12 was the first concentration after the last scheduled titration at week 8. So the patients should remain at the same doses throughout the rest of the trial. So we think the concentration at week 12 reasonably represents the exposure for each subject during the

trial, and also the concentration at week 12 was early enough that we think it holds a temporary relationship between the exposure and the outcome for the majority of the patients.

So as you can see from the slide, this is the concentration response analysis for the primary efficacy endpoint on the top and for cardiovascular death on the bottom. And as you can see, there was no apparent concentration-dependent increase in efficacy. In fact, for patients in the high-risk category, concentration category, there's no apparent benefit from omecamtiv mecarbil.

I want to clarify that for the sponsor, this was actually the portion [indiscernible] proposed and used by the applicant at the time of the submission. After we communicated this analysis with the applicant, they came back to perform the concentration response analysis differently. For their particular analysis, they used the maximum concentration during the trial.

I want to point out that the maximum concentration could occur any time during the

trial. There was a temporary relationship, and also for a portion of the subjects who down-titrated at week 8, the maximum concentration can occur before that and [indiscernible] the patient's exposure for the majority of the time throughout the trial.

But having said that, both the analyses are post hoc and using the post-randomization information, but the take-home message I think is similar that there was no concentration-dependent increase in efficacy.

DR. LEWIS: Thank you.

DR. BLAHA: Thank you. This is very helpful.

DR. LEWIS: Thank you.

Dr. Nissen?

DR. NISSEN: Yes. Thank you, Dr. Lewis. I have a question for the FDA, and if time permits, Julia, there was a question --

DR. LEWIS: Could you say your name again, Dr. Nissen?

DR. NISSEN: I'm sorry. It's Dr. Steve

Nissen. Thank you. I have a question for the FDA reviewers, and if time permits, Julia, there was a question I did not get a chance to ask the sponsor.

For the FDA, I want to understand the potential for drug-drug interactions. Some of the drugs that we use, like SSRIs, do have an interaction with 2D6 metabolism. So what happens if a patient is on this drug, has high therapeutic concentrations, and then somebody, maybe their family practitioner, puts them on paroxetine? What is likely to happen? Do you have any simulation of that?

DR. L. WANG: Hello, Dr. Nissen. Thank you very much for your question. This is Li Wang, the clin-pharm reviewer. Yes. Based on the individual and the initial finding, CYP2D6 is one of the major enzymes which metabolizes omecamtiv mecarbil, and from the dedicated new [indiscernible] studies, we found that AUC increased by 47 percent, which may lead to [indiscernible] concern.

That's why, in this presentation, we want to emphasize the necessity for PK-guided titration,

and with the PK-guided titration, if the patient takes omecamtiv mecarbil, with drug as CYP2D6 inhibitors, basically they can re-take the whole PK-guided titration process and find the optimum dose to make sure the plasma [indiscernible] level is in the desired range.

DR. NISSEN: Okay. But what I'm asking, I guess, is, ok, they titrated with PK. Are they going to continue to get PK information throughout the course of the patient's therapy; or once they get to the stable dose, what happens if later somebody starts a 2D6 inhibitor?

DR. L. WANG: Yes. Thank you for your clarification. I think we would expect an increase of the concentration of omecamtiv mecarbil due to the inhibition of CYP2D6 if the patient starts to take -- if the concentration drops as CYP2D6 inhibitors; that is for sure.

DR. LEWIS: Dr. Nissen, can I ask you -- Dr. Blaha, then you, then Dr. Connor -- if you have remaining questions for the sponsor, can we do them at the end of the FDA?

DR. NISSEN: Yes, sure.

DR. LEWIS: Thank you.

Dr. Wang?

DR. T. WANG: Thanks very much. Thomas Wang. I wonder if the FDA could comment further on their perspective regarding the circumstances under which a single randomized trial may be sufficient for approval; and I want to refer specifically to slide 18 of their main presentation, if you don't mind pulling that up.

(Pause.)

DR. T. WANG: Thanks very much. This is helpful in providing some of the regulatory background in the discussions, after phase 2, that the FDA had with the sponsor, and it seems that the sponsor did not -- the phase 3 trial didn't meet these statistical criteria.

My question is whether there was any discussion about the possibility of pursuing approval with the use of a single trial using the criteria of confirmatory mechanistic evidence, whether that was raised, since obviously that's

what the sponsor has invoked in this circumstance.

The reason I ask that is because at the time of this phase 2 discussion, the results of their phase 2 trial were already known. So in a way, it strikes me that it's a little bit of a circular reasoning here that these phase 2 statistical criteria might not have been really -- these statistical criteria in these slides might not even have been necessarily proposed because the phase 2 data, the mechanistic data that are used as confirmatory evidence, were already available.

So was that brought up? Again, was this presented as these statistical criteria need to be met or that there could be another pathway?

DR. SENATORE: This is Fred Senatore. I'm the lead physician here, and I've been privileged with the task of triaging the questions, and I will take this particular question.

We had a discussion about ways to obtain substantial evidence. The first obvious requirement is a statistically significant and clinically meaningful result, and we feel that the

applicant did not meet that.

In terms of confirmatory evidence, normally in phase 2, if we saw some clinical benefit that informed on dose selection of phase 3, phase 2 could serve as confirmatory evidence. In this case, we saw echocardiographic parameters that generated a hypothesis for the information that would lead to the design of the phase 3 trial; and one could reasonably argue that the phase 2 results form a retrospective mechanistic thread to confirm the mechanism of action with some of the results in phase 3, and that was a reasonable argument to be made. But we felt that confirmatory evidence, not necessarily well defined in the statutes, would have been better defined if phase 2 had some clinical evidence that would have supported the results in the phase 3 study.

DR. T. WANG: Thanks very much.

DR. LEWIS: Thank you.

Dr. Gillen?

DR. GILLEN: Yes. Thank you. Daniel Gillen. I have a question for Dr. Koh, the FDA

reviewer, if we could. If you can bring up slide 24 from the FDA presentation?

Dr. Koh had mentioned that the choice of knots in this particular analysis, looking at the association between the treatments and the primary endpoint as a function of ejection fraction, was sensitive, or the results are sensitive to that choice of knots.

I wonder if there's any example of -- a standard thing to do, for example, would be to place these knots at quartiles, for example, of the distribution of either patients or events -- to be quite honest, probably events since that's how information is going to be measured here -- or any kind of an example to show why this particular choice of knots might have been chosen.

Maybe it somehow minimizes AIC, I don't know, but can we get a feel for how sensitive this relationship looks since that was stated?

(Pause.)

DR. LEWIS: FDA?

DR. KOH: Good afternoon. William Koh,

stats reviewer. Thank you, Dr. Gillen, for the question.

In our briefing document, we have an example of an analysis in figure 12 on page 54 that included knots at specific quartiles. I'm not sure whether you guys have the document to pull up in front of you, but we did look at it in a slightly different manner.

The relationship more or less holds that some trend -- it addresses whether it is considered to be so called linear or non-linear on the log scale. We did not have analysis based on the events; that means you would have to look at -- you have to select knots based on outcome. You only look at baseline LVEF.

DR. GILLEN: What I had seen on 54 is a slightly different, I think, analysis; probably similar but slightly different analysis to what the sponsor had presented, where they had done kind of a group Poisson model, I believe, and I think what I'm looking at on 54 is the Cox model.

Should I assume that there's roughly the

same amount of heterogeneity in the relationship as you change the knot points? Is that a reasonable statement? I don't have access to the data, so I'm trying to figure out how sensitive it is.

DR. KOH: Thank you for the question. This is William Koh, stats reviewer. For figure 12 of page 54 of the briefing document, there are two regression models included. One is based on the Poisson model that is actually equivalent to what the applicant had done, and one is based on the Cox model.

The results are generally quite similar. For the Poisson model, we relaxed the mean variance relationship assumption and had it at the robust confidence interval; otherwise, if you use the Cox model or the Poisson regression model, the model-based 95 percent confidence interval should coincide.

DR. GILLEN: Okay. That's great. That's very helpful. Thank you very much. I was caught up on the title of that slide saying "estimated hazard ratio," so I didn't see that you had also

the relative risk ratio in there. Thank you.

DR. LEWIS: Thank you.

(Crosstalk.)

DR. KOH: And I apologize --

DR. LEWIS: Dr. Kovesdy?

DR. KOVESDY: Yes. Thank you. Csaba Kovesdy. My question pertains again to the regulatory pre-condition as to the sponsor specifically, as shown on slide number 19, where it says that to the extent that, "if the p-value for the primary composite endpoint were driven by 'urgent heart failure visits' -- that is ED or office visit -- a single trial with a p-value of 0.05 would probably not be sufficient for approval in the absence of at least strong trends for other components of the composite endpoint."

Do you have information about whether or not urgent heart failure events were in fact driving the endpoint?

DR. KOH: William Koh, stats reviewer. Thank you for question.

Can we pull up backup slide --

(Pause.)

DR. KOH: So in this backup slide, we have the summary of the heart failure events. If you look at the number of first events for heart failure events, urgent heart failure, ER/ED, or urgent office or practice visit was relatively small.

DR. KOVESDY: So would it be fair to say that they were not driving this endpoint?

DR. KOH: William Koh, stats reviewer. I would say that hospitalization for heart failure contributed mainly to the first event, so urgent, ER/ED visit, office/practice visit were not the main contributors to the first event analysis.

DR. KOVESDY: Thank you. That's the end of my question.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Hi. Chris O'Connor. I have a question regarding slide 33. Our statistical, colleague, Dr. Gillian, cautioned us on the interpretation of interaction terms when there's

been multiple looks for efficacy, but mortality also stands as a safety endpoint.

Would you say that the atrial fibrillation cardiovascular death, a hazard ratio 1.26 -- I think slide 33 is what I wanted. Do you believe that is a true safety signal, true signal of harm, or do you think that could be a play of chance given the multiple looks?

DR. McDOWELL: Hi. This is Tzu McDowell. Thank you for your question.

Yes, we usually have to interpret caution for the subgroup analysis, AFib, a particular subgroup, because we show consistent results of both the primary efficacy endpoint and the cardiovascular death. And knowing the mechanisms of action for this drug and the toxicology profile, we think this finding could very likely be real, but again, we cannot rule out the possibility that this could be a chance finding.

DR. O'CONNOR: Thank you.

DR. LEWIS: Thank you.

Dr. Thadhani?

DR. THADHANI: Thank you. Ravi Thadhani.

A question to the agency regarding the PK data; they commented on the therapeutic window being narrow, and also, of course, the efficacy not necessarily related to concentrations.

Is it fair to say that the agency was not concerned about any potential for harm or toxicity at levels below 750 nanograms per mL? In other words, in the therapeutic window, as stated by the sponsor, was the FDA comfortable that toxicity events were either minimal, or not seen, or not as concerning? And hence, there technically could be a therapeutic window of benefit, albeit very narrow. Thank you.

DR. McDOWELL: Hi. This is Tzu McDowell. I will take this question first, but my colleagues can weigh in.

As I mentioned in the presentation, FDA does not think that the optimal therapeutic range has been identified. The exposure was tightly controlled in the phase 2 and phase 3 study, and we had very limited data at the higher end of the

predetermined exposure. More than 90 percent of the patients at each phase had a concentration less than 500, so we really do not have the clinical data to assess the efficacy and the safety at that highest end.

Having said that, if we err on the side of caution with the signals we saw, and with some exploratory analysis that we did, I do have the concern that the optimal therapeutic range from our review [indiscernible] could be lower or narrower than the sponsor originally determined.

DR. LEWIS: Thank you.

DR. THADHANI: Thank you.

Dr. Nissen?

DR. NISSEN: Thank you, Julia. It's Steve Nissen again. I just wanted to circle back with a question to the sponsor, if that's ok, Julia.

DR. LEWIS: Oh. Wait one second. I'm going to go back to the sponsor.

Dr. Kovesdy, is your hand still up or do you have another question for the FDA? And Dr. Thadhani, do you have another question for the

FDA?

DR. KOVESDY: I'm sorry. I forgot to lower my hand.

DR. LEWIS: Okay.

Dr. Nissen, Dr. Blaha also has a question. He was first, but I'll let you go. You can ask the sponsor.

DR. NISSEN: Sacubitril/valsartan was approved in 2015, before the start of this trial, but only 20 percent of the patients were on that drug, which had shown a decrease in death, among other things. I don't understand why the use of ARNi was so low in this trial, and I wonder if somebody could explain that to me.

DR. LEWIS: The sponsor may answer that specific question.

DR. MALIK: Am I on microphone now? Okay. Thank you. This is Fady Malik from the sponsor.

Dr. Nissen, during the trial, which started in 2017, the availability of sacubitril/valsartan around the world was not the same as maybe perhaps it was in the United States. Also, its

implementation was at the discretion of the prescribing physician. We've seen the uptake of ARNi's be relatively slow over time. In fact, the use of ARNi here was as high or higher than that in the recent SGLT2 trials, which were conducted in the same time frame, and others, and perhaps Dr. Solomon could expand on that.

DR. SOLOMON: Yes. Dr. Nissen --

DR. LEWIS: Excuse me.

Dr. Nissen, does that answer your question or do you want them to go on?

DR. NISSEN: Well no, it didn't actually answer my question. The question here is, with a new agent, was there [indiscernible] a benefit? The problem is that efficacy on top of ARNi doesn't look particularly favorable, so I'm concerned that in the contemporary environment, whether or not we can expect to see incremental benefit in people treated with ARNi.

I don't think you have an answer for this, but if you have an answer, I'd sure like to hear it.

DR. LEWIS: Dr. Nissen, do you want the sponsor to try to answer that question or is that a statement?

DR. NISSEN: No. I really would like an answer.

DR. LEWIS: Okay.

DR. NISSEN: I mean, you did look at the efficacy on top of ARNi, I believe.

DR. SOLOMON: Yes. Let me try to take that question, and this is Dr. Solomon speaking. There's no question that we would have all liked to have seen greater use of sacubitril/valsartan in this population, but for the reasons stated, its use and availability worldwide was less than would have hoped, starting in 2017.

With that said, the proportion of patients on sacubitril/valsartan in GALACTIC was higher than in any other contemporary HFrEF trial. It was about 11 percent in DAPA-HF; it was about 18 percent in the VICTORIA trial, so hitting roughly about 20 percent, we were a little bit higher than any other contemporary trial here.

In addition to that, as you know, the mechanism of sacubitril/valsartan is very distinct from the mechanism of action of omecamtiv mecarbil, and there's no a priori reason to think that there would be a diminution of benefit overall with that said. Now, the numbers are relatively small, but for the primary composite endpoint I think we don't see really any statistical heterogeneity in the patients who were or were not on ARNi as background therapy.

I don't have the exact interaction p-value. I'm sure we can get that for you, but there's no reason, I think, to think that if we had a higher proportion of patients on sacubitril/valsartan, we would not see a potential benefit in the patients in whom we believe benefit is shown in this study.

DR. LEWIS: Dr. Blaha, do you still have a question for the sponsor?

DR. BLAHA: Yes. I have a quick clarifying question.

As we think about this notion of substantial evidence of effectiveness and the pertinence of

subgroup analysis, of course the discussion of left ventricular ejection fraction takes center stage. I just want to get a clarifying question answered about the measurement of left ventricular ejection fraction in this study.

If the sponsor could just summarize, again, I believe these were clinical echos. Who read them, and how a single number was reported if not a range? And then for inpatients -- for example in patients who were enrolled in the inpatient setting -- was that ejection fraction taken at the time of their inpatient hospital admission? And a subsequent follow-up to that; how does that compare to the outpatients who their ejection fraction is also reported at the baseline?

DR. MALIK: This is Fady Malik for the sponsor. Ejection fraction could have been determined at any point in time within a year of enrollment. In general, we looked at this, whether, for instance, ejection fractions vary very much when patients are hospitalized. The literature didn't suggest that they did, so we

didn't require another echo in the inpatient setting.

These are echos, and there were other means of determining ejection fraction such as radionucleotide ventriculography, and other things. But essentially, these are assessments, clinical assessments, of left ventricular function done within a year of the time of enrollment; and the variability numbers would have certainly applied to the placebo group as much as it does to the active treatment group.

DR. BLAHA: Just to clarify, these are read at the site at the discretion of the site; right? There's no core lab read or no scheduled echocardiogram.

DR. MALIK: Correct. The COSMIC study was all core lab read, but in these 8,000 patients studied, these were not obtained as part of the study but rather were part of the patient's clinical record.

DR. BLAHA: Thank you. That's a helpful clarifying question.

DR. LEWIS: Thank you.

Dr. O'Connor?

DR. O'CONNOR: Yes. Chris O'Connor; one quick question to Dr. Malik.

Given the evidence that you're proposing in reduced EF, do you think that restricting the drug to those patients in sinus rhythm would help mitigate any safety signal that we saw from the analysis from the FDA? Thank you.

DR. MALIK: We think it's a matter of discussion and not unreasonable to assess. If you can show me slide 2, please?

We don't have slides up; do we? Okay. Show me slide 2, please. We'll be one second.

The treatment interaction by atrial fibrillation status in the low ejection fraction subgroup is shown here, and what you can see is that the adverse effect is confined to the patients with higher ejection fraction. If you, one, were to eliminate atrial fibrillation, you'd see a positive effect in all of the ejection fraction -- in both the ejection fraction

subgroups, so it is an alternative way of looking at it.

If you can bring up slide 3, we looked at the different means of assessing what would be the best strategy here, so these are four different ways of looking at it. The low ejection fraction group is at the top. If one were to eliminate atrial fibrillation and flutter from the study, from patient population and not have a cutpoint for ejection fraction, you see essentially the same point estimates for both CV death and the primary composite endpoint.

As Dr. Kupfer mentioned, we found a fairly strong interaction with atrial fibrillation and digoxin. You see in the third row the treatment effect there, and the whole population was a little bit to the left. But in the last row, in the low ejection fraction group, you see the strongest effect in terms of the point estimates.

So I think it's a question of how one wants to maximize benefit and minimize risk, but also enable the drug to be used in as many patients as

might benefit. So we're certainly flexible in terms of how we think about this, but these are the data I think that you were asking for.

DR. LEWIS: Thank you.

Dr. Wang?

DR. T. WANG: Hi. Thanks. Thomas Wang. About these subgroups, obviously the patients, as pointed out this morning, moved back and forth between these subgroups, and Dr. Moliterno, I think, asked specifically what happens if a patient's EF goes from below 28 percent to above 28 percent.

The reasonable response was that for other HFrEF drugs, we don't allow rises in EF to cause us to adjust our therapy. But it strikes me that the differences, to my knowledge, or in none of the other GDMT drugs that we use in HFrEF is there any evidence that when the EF starts to normalize, that there could be harm. In fact, many of the drugs have been tested and have been shown to be at least safe in patients with HFpEF.

So I guess my question as a follow-up of

Dr. Moliterno is, is this a different scenario in which there, at least theoretically, may be harm as EF gets close to normal from using this drug. And related to that, based on the slides that we just showed, would a patient who has AF, or who goes into AF subsequently, would that also affect your way of thinking about it if a patient has an EF that goes above 28 percent?

DR. LEWIS: Dr. Wang, that question is for the sponsor or the FDA?

DR. T. WANG: The sponsor, please.

DR. LEWIS: Or both?

DR. T. WANG: Well, it was meant for the sponsor. Thank you.

DR. MALIK: Thank you for the question, Dr. Wang. I think in regards to the ejection fraction question, we started this drug in patients with ejection fractions through the entire range, from 0 to 35, and we fully expect that many of those patients, their ejection fractions rose in the context of being given this therapy. So I think the benefits we saw in GALACTIC were a

consequence of that, and likely, many of them exceeded 30 percent or exceeded 35 percent.

It doesn't seem that the data would suggest that the response to the drug is something that should require termination of the drug. We've seen the safety in GALACTIC, and while we've talked a lot about it, it was an 8,000-patient trial and, overall, the risk of the drug was fairly balanced in the active and placebo groups, which is one of the reasons we did such a large trial.

The second part of your question had to do with new onset atrial fibrillation, and if you could show me slide 2, please? We did look at that as a potential issue, and we also looked at patients with a history of atrial fibrillation, assuming that the substrate was similar to those that were in atrial fibrillation.

But here's new onset atrial fibrillation, and we had about 7 percent of the patients who had new onset atrial fibrillation. The primary endpoint occurred in a small portion of those. You see that the effect is actually favorable with

regards to omecamtiv mecarbil for the primary endpoint and numerically favors omecamtiv mecarbil for all the other components as well, albeit the numbers are small.

DR. T. WANG: Thank you.

DR. LEWIS: Okay. We will now break for lunch. We will reconvene at 2:00 p.m. Eastern time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin at about 1:45 p.m. to ensure you are connected before we reconvene at 2:00 p.m. Thank you.

(Whereupon, at 1:07 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(2:00 p.m.)

Open Public Hearing

DR. LEWIS: We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please only speak when recognized by the chairperson. Thank you for your cooperation.

Public speaker number 1 has not checked in, so we will move to speaker number 2.

Your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. NELSON WILLIAMS: Good afternoon. My name is Nefertari Nelson Williams. I am a 49-year-old, and I live in New Jersey. I serve on the sponsor's Heart Failure and Caregiver Advisory Council. I am not receiving any compensation for speaking today.

I am here to share my experience as a woman who developed heart failure with reduced ejection fraction after suffering a spontaneous coronary artery dissection shortly before giving birth in 2008. I was not a participant in the GALACTIC Heart Failure study, but I hope my story and those of others will lead to more treatment options.

As a heart failure patient, I battle with several symptoms daily. Because my heart is weak, I have the common symptoms of heart failure such as fatigue, cough, lightheadedness, and swelling, but I also have some symptoms that may not be widely

discussed; for example, falling due to loss of balance and dizziness.

Not long ago, I needed to use the bathroom, which is only a few steps from my bed. I know that I always have to move slowly to avoid getting lightheaded and falling, but despite my best efforts, I fell, and I tore ligaments in my fingers. This caused me to wake my children, who then had to care for my injuries and clean up the mess that I've caused because I could not make it to the bathroom in time. To see the look in their eyes was very painful. Recently, I made the decision to wear adult diapers to bed.

Another symptom some heart failure patients may experience is coughing and difficulty breathing while laying down. I experience this, but I don't only cough; I also experience flash pulmonary edema, which is terrifying. It is when your lungs fill with fluid and you begin to drown. I have spent weeks afraid to fall asleep for fear of this happening.

I want to thank you for allowing me to share

a little of my battle with heart failure. On this day, I am hopeful that as a mother like myself could have a chance to have some type of normalcy in my life. As of now, I am weak, I'm slow, and I feel myself rapidly aging. It would be a dream come true to go back to being the bubbly, energetic woman that I once was, but I will be more than overjoyed with a blessing for treatment that would allow me to have just a little more time with my beautiful children. Thank you.

DR. LEWIS: Thank you.

Speaker number 3, your audio is connected now. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ZELDES: Good afternoon. I am Nina Zeldes, a health researcher at Public Citizen's Health Research Group. I have no financial conflicts of interest. Public Citizen strongly opposes FDA approval of omecamtiv mecarbil to reduce the risk of cardiovascular death and heart failure events in adults with symptomatic chronic

heart failure with reduced ejection fraction over two main concerns. First, the minimal benefits demonstrated in this single trial do not outweigh the significant risks, especially for some heart failure patients. Second, the evidence for the proposed benefits of omecamtiv are not accompanied by confirmatory evidence.

Although the clinical trial met its primary endpoint, the observed treatment effect was small and not clinically meaningful for patients. For instance, the relative reduction in risk for patients taking omecamtiv was 8 percent compared to placebo, however, the reduction of absolute risk was only 2 percent or 2 per 100 patient-years. Moreover, none of the secondary endpoints were met.

At the same time, patients taking omecamtiv had a 7.4 percent incidence rate of myocardial ischemia events compared to patients in the placebo group with 6.6 percent. And although the rate of cardiovascular deaths was similar between the groups with a hazard ratio of 1.01, the relative risk of patients with AFib or flutter at screening

was increased by 26 percent compared to placebo. We thus agree with FDA that, quote, "It is not certain whether the benefit of omecamtiv outweighs the risk," unquote.

The efficacy and safety of this drug are based on only one trial, and as FDA stated in the briefing materials, their information from the phase 2 trial may not be reliable to serve as confirmatory evidence. Given that the observed benefits of this drug were minimal, this is of particular concern.

This lack of reliable data and the limitations of post hoc analysis also make it difficult to evaluate potential benefits or additional risks in different subgroups. For instance, we agree with FDA that there is quote, "no scientific basis," unquote, for the observed benefit in patients whose LVEF at baseline was lower than 28 percent. Similarly, using post hoc analyses, it is not possible to establish the sponsor's claim that the increased risk for cardiovascular death seen in patients with AFib or

flutter was mainly concentrated in the subset of this patient group that was treated with digoxin.

In addition, it is important to keep in mind that although the post hoc analysis seemed to indicate that the risk was particularly high for this subset, patients with AFib or flutter not treated with digoxin also had a higher risk for cardiovascular death with omecamtiv compared to placebo.

In conclusion, the evidence for efficacy and safety of this drug is based on one single trial. No additional reliable confirmatory evidence was provided. The minimal absolute risk reduction of only 2 percent cannot be considered a clinically meaningful improvement for patients.

We also agree with FDA that, quote, "Given the limitations inherent in post hoc analyses, one cannot be certain about differential risk in patient subgroups, thus impacting regulatory decision making," unquote. We therefore urge the committee to vote no on the voting question and strongly recommend that FDA not approve omecamtiv

mecarbil. Thank you for your time.

DR. LEWIS: Thank you.

Speaker number 4, your audio is connected now. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. CALLENDER: Good afternoon. My name is Ealena Callender. I am a physician and senior fellow at the National Center for Health Research. Our think tank conducts, analyzes, and scrutinizes research on a range of health issues, with a particular focus on which prevention strategy from treatments are most effective for which patients and consumers. We do not accept funding from companies that make products that are the subject of our work, so we have no conflict of interest.

Thank you for the opportunity to express our views today on the new drug application for omecamtiv mecarbil. As you consider whether the data indicates substantial evidence of efficacy, let's think about the size of the study, as well as the statistical significance.

The phase 3 trial enrolled more than 8,000 patients. Such a large trial would be expected to achieve a statistically significant treatment effect if the drug does have a meaningful benefit. Although the trial did meet its prespecified primary endpoint, the composite of time to cardiovascular death or first heart failure event, the treatment effect is very small and only present in patients with severe heart failure.

Given the small benefit for a limited group of patients, a confirmatory study is needed to determine if the drug has meaningful benefits; and if so, for whom. It is also important to emphasize that the drug had no impact on any secondary outcomes such as cardiovascular death or the Kansas City Cardiomyopathy Questionnaire score, which is a measure of heart failure symptoms, physical and social limitations, and quality of life.

As you consider whether the benefits outweigh the risks, the main safety issue is cardiotoxicity, especially in patients with atrial fibrillation or flutter. With such a small

treatment effect, is any increased risk in their cardiotoxicity acceptable? Also, the fact that the assay the company used is not FDA approved or cleared means that it was not evaluated by an objective third party. The CLEAR program regulates labs that make these tests but not the tests themselves. As a result, we agree with the FDA, so we can't be confident about the accuracy of the assay, therefore raising additional concern about safety.

We respectfully encourage the advisory committee to require a confirmatory study before recommending approval of this new drug with significant risk and such a limited benefit. Thank you.

DR. LEWIS: Speaker number 6, your audio is connected now. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. ARCHER: Can you hear me?

DR. LEWIS: Yes. Go ahead, speaker number 6.

MR. ARCHER: I'm sorry.

My name is George Archer. I'm a 64-year-old retired insurance adjuster living near Harrisburg, Pennsylvania. I'm also a heart attack survivor who was treated with the drug you've been talking about today after my cardiologist enrolled me in a clinical trial. I'm not being paid for speaking to you. I'll keep this simple. I believe the drug worked for me, and I think you'll understand a little bit after I tell you what happened to me.

On Easter Sunday 2011, I had some bad indigestion and kept putting off doing anything about it other than taking antacids, which gave some mild temporary relief. Around 9 pm, I told my wife that I wasn't going to be able to sleep. I knew something was wrong, so she drove me to the hospital because I didn't want an ambulance.

I go walking in, tell them who I am, and why I'm there. They put me on a gurney. The young nurse who'd been there about a week hooks me up to the EKG and says, "Oh my God. That's what I thought." The next thing I know, my clothes are

being taken off, and I'm being rolled into an operating room with all kinds of stuff going on. I was scared and thought I was going to die. It was a major heart attack.

I had almost 100 percent blockage in my LAD. The doctor put a stent in, and a year later, he put another stent in. After a couple of years, he told me he did clinical studies and asked me if I'd be interested in participating. I said sure right away because anything that could help me or anybody else would be of a benefit.

I did several studies, but nothing like this. I was told some folks would get the real pill and others a placebo. Several weeks into the study, I was convinced I had the real pill. I felt a difference. Don't get me wrong. I couldn't go run a marathon, but I felt better. I had more energy. I wanted to do more because after the heart attack, I was just really taken down. When I was getting ready to go off, I asked if I could stay on this thing somehow, but they told me no; that it had to be approved. It's been about two

years since I took this pill, but I believe that it is good stuff.

What I'd like to leave you with is this. It restored a part of my life about how I felt and what I could do. I can say that the pill made a difference in me, and it helped me. I think it should be approved, and I would take it again because I believe that it was worth the risk. Thank you for listening to me, and have a good day.

DR. LEWIS: We're going to go back to speaker number 5.

Speaker number 5, your audio is connected now. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. G. LEWIS: Good afternoon. I'm Dr. Gregory Lewis. I chair the heart failure section and serve as a medical director of the heart transplant program here at Massachusetts General Hospital in Boston. I'm also an associate professor of medicine at Harvard Medical School. Although my hospital has received funding from the

sponsor, and I've served as an investigator in trials involving omecamtiv mecarbil, I have no financial relationship with the company.

I lead a team that takes care of patients across the spectrum of heart failure severity. Our hospital admits more than 1,500 patients a year with a primary diagnosis of heart failure, and cares for more than 5,000 patients with heart failure in total; and in my experience, I found that omecamtiv mecarbil seems to work particularly well in patients who have severe forms of heart failure, and two of my long-standing clinic patients immediately come to mind.

The first is a 57-year-old man who had long-standing non-ischemic cardiomyopathy. He was already on the heart transplant waiting list when he began taking omecamtiv mecarbil as part of a double-blind, placebo-controlled clinical trial. The second patient is a 57-year-old gentleman with similarities to the person that you just heard from, who had premature coronary artery disease and also participated in the same trial while also

being evaluated for consideration of heart transplantation or left ventricular assist device.

Both of these individuals had left ventricular ejection fractions below 20 percent. Both had regular assessments of their cardiac performance with heart pressure measurements, cardiac output measurements, and ultrasounds of the heart before, during, and after periods of omecamtiv mecarbil exposure. And for these patients, taking this medication had dramatic beneficial effects. Both tolerated the medication well. Both experienced marked improvement in their cardiac function.

My first patient actually asked to become inactive on the transplant list when his cardiac pressures and cardiac output improved markedly on the serial right heart catheterizations that were done when he was being exposed to this medication. The second patient also experienced subjective improvement in heart failure measures, while firmly believing that he derived unique improvement on this medication compared to other medications that

he takes for heart failure, including being involved in multiple trials of heart failure pharmacotherapies.

Since learning that they were on active study medication, omecamtiv mecarbil, like the gentleman we just heard from, both asked, and continue to ask regularly, if they'll be able to resume taking his medication, and it's these patient experiences that served as motivation for me to speak with all of you today.

While we're fortunate as a heart failure community to have available medications to treat heart failure, currently approved medications can be limited by blood pressure lowering and high potassium levels, which are not side effects of omecamtiv mecarbil.

It's important to put this into context of patients with severe heart failure in terms of what we currently have available to them. As heart failure progresses, we turn to therapies with very scarce resources such as heart transplantation or very invasive resource utilization such as left

ventricular assist devices, and I would like to remind everyone on the call that as an advanced heart failure community, we still use positive calcitropic medications. In fact, prescriptions for home dobutamine and milrinone number approximately 4,000 per year currently in the United States, yet we know that these medications increase arrhythmia, increase mortality, and have to be given continuously through an IV in an effort to improve cardiac performance.

So I think this frames the need for additional medications, particularly oral --

DR. LEWIS: Thank you, speaker number 5.

DR. G. LEWIS: Thank you.

DR. LEWIS: Speaker number 7, your audio is connected now. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. ASHWORTH: Hello. My name is Mike Ashworth. I'm 66 and live in Rhode Island. I'm a retired insurance executive, husband, father, grandfather, and a soccer coach. I have served as

the interim CEO of the HeartBrothers Foundation, a nonprofit that supports patients and their families as they deal with heart failure, mechanical circulatory support, and heart transplantation. I am on Cytokinetics Heart Failure Patient and Caregiver Advisory Council, but I'm not receiving compensation for speaking today.

I know what it's like to live with heart failure, and I believe the drug would make a big difference. Being very blunt, I speak directly to the root of congestive heart failure to transplant. It screwed up my life plans, my children's life plans, and my business associates' life plans. Before my illness, I used to go into the office; I believed [indiscernible] coach soccer; go golf or go fishing for nearly a decade until I received my transplant in 2004. I was in and out of the hospital, and everybody else's life around me went on hold.

Congestive heart failure changes everybody's life around you, and I'd like to share just a small portion of a very big story, which began nearly two

decades ago. I had a heart attack the night of Christmas 2003. I didn't realize it at the time. When I went in to get my right shoulder replaced on Valentine's Day in 2004, the surgeon looked at my EKG and said, "We're not doing this today. You had a heart attack," and that was at 7:00 in the morning. I was at my GP's office by noon and in front of a cardiologist by 4:00 that afternoon. I had massive damage to my left ventricle.

On April 4, 2004, I underwent surgery to try to deal with the damage. I was supposed to stay in the hospital for 10 days. I ended up staying 10 weeks. My left ventricle was rebuilt, and it gave me a life until 2010 when I got taken out of my office three times in the course of one month.

These medical challenges altered life plans within my family. My youngest daughter had intended on being a doctor. She ultimately became a nurse. She was going to school in Florida. She came home to Rhode Island. My three other kids basically put everything on hold, and in the interim, my wife had to take care of me. Luckily,

she's a nurse, but there were times when she would leave to go to work in the morning, start an IV, and I'd disconnect it myself.

I can't count how many infections I had. The whole thing is, it was a battle between staying healthy and not putting too much water weight on because the heart was failing, and trying to continue life. I managed to do that up until 2010, then I had a gout attack brought on by the diuretics I was taking, went into the hospital, and developer MRSA. Other MRSA related problems developed, including with my implantable cardioverter defibrillator.

The long and short of it is, after six months, I was told I needed a heart transplant.

DR. LEWIS: Thank you, speaker number 7.

Speaker number 8, your audio is connected now. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. TELISKA: Good afternoon. My name is Maggie Teliska. I am 49 years old and live outside

of Boston with my husband and cat. I serve on the sponsor's patient advisory committee for heart failure, but I am not being compensated for speaking to you today.

I've been living with heart failure for seven years. My heart failure results from suffering a sudden coronary artery dissection, or SCAD, at the age of 42. Overnight, I went from zero medications to managing taking over 10 pills a day to keep my blood from clotting, keep my vessels dilated, and my heart beating slower, ultimately making my heart beat more efficiently.

I have since become a patient and patient advocate for heart failure, SCAD, Women and Heart Disease, and I'm also a WomenHeart Champion, class of 2020. I am the co-founder of a private congestive heart failure group on Facebook. My co-founder and I started this group when we found an unmet need in the Facebook groups for people who had suffered from heart failure. There are plenty of groups for heart attack survivors but not for survivors who sustained heart failure, and we do

have different needs.

Since the group's inception, we have grown to over 20,000 in less than five years. In addition, the platform recognized us as having the most active health oriented group in 2018. While we couldn't articulate what we did to enable the group's activity, it does speak to the number of patients currently living with this disease and seeking guidance, information, and education on social media platforms.

Patient peers are the best source of information on living with heart failure because we are the ones living with heart failure. We deal with the symptoms and live daily with the reminders that our hearts are failing. Many of the conversations in our group are on how to feel better despite the many symptoms we deal with on a daily basis. We include dialogue on nutrition, exercise and medications, new and old, and how our lives could benefit from better and more therapeutic options. We are looking for better days.

While most of us are on the standard generic medications designed to keep our hearts small, yet efficient, we talk about and strive for better treatments to improve our quality of life. Even if it's a small benefit, that may mean one less bad day and one more good day, and that one day is significant.

The generic medications we are on today were designed to keep us stable. We still experience fatigue and shortness of breath, and we will never be what we were before our diagnosis. Many posed questions and responses in our group are around new medications and their experiences, whether we find out about them from the group, from commercials, or from our cardiologists.

I am currently on most generic heart medication, but I'm fortunate enough to take two branded new medications to improve my heart function, one of which I can attest makes me feel better. To feel better is hard to quantify, but my quality of life has improved. Unfortunately, so many of us, while under the care of our doctors,

are still looking for new treatments. We appreciate the research and development from companies trying to bridge that gap between restoring heart function, maintaining stability, and improving the quality of our lives.

Today I have more good days than bad, a stark contrast to when I started this journey. This is due to the medication regime I started, which has been modified as newer medications were introduced into the market. I am thankful there continue to be more options in the future thanks to the R&D and commercialization of new therapeutic options for heart failure.

My congestive heart failure co-founder and I will continue to enable patients to have a greater understanding of their conditions and bridge that gap, but we hope that more research companies will bridge the gap between current medication regimes and future therapeutic options to allow us a better quality of life. Thank you for your time.

DR. LEWIS: Thank you.

Speaker number 9, your audio is connected

now. Will speaker number 9 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ABRAHAM: Good afternoon. My name is Dr. Jacob Abraham, I'm an advanced heart failure and transplant cardiologist, infection head of the advanced heart failure division at the Providence Heart Institute in Portland, Oregon. I'm employed by the Providence St. Joseph Health system, so my comments today are mine alone and do not reflect the views of my employer. I have no conflicts of interest.

Over the past 13 years of clinical practice, I've been fortunate to witness important advances in the medical, surgical, and device treatment of chronic heart failure. Notable among these have been the approval of sacubitril/valsartan and the class of SGLT2 inhibitors, which in combination with beta blockers and MRAs constitute contemporary guideline-directed medical therapy for heart failure with reduced ejection fraction.

Yet, despite all these successes, there

remains an important treatment gap for patients with significant symptoms, impaired cardiac function, and hospitalizations for heart failure. Such patients are often unable to tolerate all components of GDMT due to symptomatic hypotension or renal insufficiency. These are patients that I routinely see in my practice and for whom treatment options are largely limited to invasive procedures, participation in clinical trials, or more advanced and aggressive therapies such as LVAD or heart transplant.

Our currently approved therapies appear to have less effectiveness in these patients with more advanced stage disease, a population that Drs. Clyde Yancy, Adrian Hernandez, and Gregg Fonarow have proposed labeling as stage C2 to signify symptomatic heart failure that is not yet end stage. The randomized LIFE study, for example, showed that sacubitril/valsartan did not reduce NT-proBNP levels compared to valsartan in a population of patients with severe symptoms. Similarly, vericiguat, the FDA-approved soluble

guanylate cyclase stimulator, was shown in post hoc analyses to be less effective in patients with the highest quartile of N-terminal proBNP.

This confluence of GDMT intolerance and loss of treatment effect result in the paradox that the highest risk patients may be least likely to receive evidence-based therapies. For these reasons, a drug that retains efficacy in sicker patients with no impact on renal function, potassium homeostasis, or blood pressure would be a welcomed addition.

The GALACTIC Heart Failure trial did demonstrate a modest benefit of omecamtiv mecarbil on the combined endpoint of time to heart failure event or cardiovascular death, and subsequent analysis of this trial has shown that these effects become more pronounced in patients with lower ejection fraction, lower blood pressure, greater than median NT-proBNP, and severe heart failure.

Given that these benefits are achieved without a clear increase in adverse clinical event, I would encourage the committee to approve

omecamtiv mecarbil as an important and novel agent for reducing events in this vulnerable population. Thank you.

DR. LEWIS: Thank you.

Speaker number 10, your audio is connected now. Will speaker number 10 begin and introduce yourself? Please state your name and any organization you are representing.

MS. DUCH WIDZGOWSKI: Good afternoon. My name is Denise Duch Widzgowski. I serve as the executive vice president of the board of The Mended Hearts, Inc., the largest peer-to-peer support organization for cardiovascular patients, caregivers, and families in the United States, with over 90,000 members and 200 chapters. I'm grateful for the opportunity to appear before the Cardiovascular and Renal Drugs Advisory Committee to speak about my journey as a heart failure patient and patient advocate, to underscore the need for new and improved treatment options for the heart failure community. Although Cytokinetics provides funding for Mended Hearts, I am not being

personally compensated for my appearance today.

Heart disease has been a central part of my life and my family for generations. My grandmother had mitral valve disease and my father underwent quadruple bypass surgery. My brothers are physicians, one of whom is a cardiologist, and my mother is a nurse, who retired at the age of 81, and my loving husband and daughter have served as caregivers in times of need.

In September 2012, I was diagnosed with an acute onset of cardiomyopathy, a disease of the heart muscle that makes it difficult for the heart to pump blood to the rest of the body. My health quickly deteriorated, and within two months my ejection fraction was down to just 15. I was taking upwards of five heart medications and was connected to a peripherally inserted central catheter, a PICC line, with round-the-clock infusion to stay alive.

On June 6, 2013, I got the life-saving call that a new heart was waiting for me. Some never get that call. I recently celebrated my nine-year

heart anniversary. I recognize that I've been given a second chance at life that others aren't afforded. I will continue to pay it forward by advocating for those navigating life with heart failure for the remainder of my life.

While life after successful transplant surgery has vastly improved, it still has its challenges. Organ rejection is a constant threat. Every day for the rest of my life I must take immunosuppressants to prevent the rejection of my new heart. These immunosuppressants increase my likelihood of renal failure, lymphoma, and osteoporosis.

The heart patient advocacy community wants more for heart failure patients. Through my life's journey and involvement in Mended Hearts' peer-to-peer support groups, what's become ever clear is that new treatments are needed for the heart failure community, even ones that provide modest improvement. The lack of new, improved FDA-approved treatments leaves heart failure patients and their families in a chronic state of

costly medical interventions. The cost of heart failure totals more than 30 billion dollars annually, with the vast majority of these costs, 75 to 80 percent, being attributable to hospitalizations and rehospitalizations.

The emotional burden is equally as vast. As heart failure progresses, the quality of life diminishes. Some must sacrifice extracurricular activities, cannot travel and spend time with loved ones, and must give up their careers to manage their condition due to exhaustion. Even simple tasks like walking up the stairs eventually become challenging.

That's why when I hear that investigational heart failure medications such as omecamtiv mecarbil have demonstrated even some success in treating heart failure patients, I get excited because any improvement in the treatment of heart failure can have significant impacts on the way people with the condition live their lives. Thus, I encourage this committee to recommend the approval --

DR. LEWIS: Thank you.

MS. DUCH WIDZGOWSKI: Thank you.

DR. LEWIS: Speaker number 11, your audio is connected now. Will speaker number 11 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MS. HACKER SMITH: Good afternoon. My name is Donna Hacker Smith. Thank you for allowing me the privilege of sharing with you some of my experiences as a caregiver to a husband with congestive heart failure, and also as a pastoral caregiver to many, many parishioners over the years who have dealt with this disease. I serve as a patient advocacy council member at Cytokinetics, and I'm not being compensated for speaking today.

My late husband, Lawrence A Smith, Jr., father of seven, grandfather and great-grandfather, retired judge and avid violinist, died on March 31, 2019 as a result of congestive heart failure. With comorbidities of diabetes and kidney disease, he was 82 years old at his death. We were married for 31 years, and part of my role as a wife was to

serve as a caregiver and cheerleader as he battled for his health and stamina.

Caregiving in this case involved tasks as varied as learning to prepare meals that were lower in sodium and fat, as well as sugar; regulating and administering medications, including IV milrinone at the end stage of his heart failure; and managing and accompanying my husband to his doctors and lab appointments. Over the years, as his heart disease progressed, I adjusted our lifestyle choices to accommodate the impairments caused by CHF. I dealt with the inevitable shifts and psychological and physical health from which Larry suffered.

I have come to realize that I've been among a privileged group in that my husband's employment offered him, along with his State of Illinois plan, an excellent medical insurance policy. As a provider of pastoral care, I have walked with those who have not been so generously provided for. CHF is more widespread than many realize, and is becoming an invisible epidemic among the many demographic groups among whom it takes root.

Thousands, if not millions, of Americans are crying out not only for new pharmaceutical therapies and treatment protocols, but are also expressing a desire for compassion and understanding on their CHF journey.

In addition to serving as a patient advocacy council member since my husband's death, I've also been able to reach out and support the many frightened and bewildered folks on Facebook and in other places who are seeking understanding and assistance. I have observed eagerly as Cytokinetics' researchers have shepherded their new therapeutic medication through the early stages of development, and have sought to help those who like my husband are told by their doctor, "There is nothing more we can try."

I have appreciated their compassionate dedication to listening to patients and caregivers, and utilizing that input in their efforts. I respectfully ask the committee to rule favorably on this application. Thank you again for allowing me to participate in this hearing.

DR. LEWIS: Thank you.

Speaker number 12, your audio is connected now. Will speaker number 12 begin and introduce yourself? Please state your name and any organization you are representing for the record.

(No response.)

DR. LEWIS: Speaker number 12? And our clock's not reset.

(No response.)

DR. LEWIS: Okay. I think we'll go on to speaker number 13 and return to speaker number 12. I'll ask our technical people to assist speaker number 12.

Speaker number 13, your audio is connected now. Speaker number 13, begin and introduce yourself. Please state your name and any organization you are representing.

MS. MOORE-GIBBS: Hi. Good afternoon, ladies and gentlemen, and this open public forum hearing. Thanks for allowing me the opportunity to speak to you this afternoon. My name is Ashley Moore-Gibbs, and I'm the president of the American

Association of Heart Failure Nurses. I've been a nurse for 29 years and a nurse practitioner for 18 of these. Throughout my professional career, I've provided care to the cardiovascular patients, with a focus on those with heart failure. I have no financial relationships with Cytokinetics, and I'm not being compensated to speak to you today.

You've been presented with a lot of scientific information about the benefits of this medical therapy and are no doubt aware of staggering statistics associated with this costly affliction. Today I want to share with you a different perspective that speaks to the devastating progression of this disease and the impact it has on the person's quality and longevity of life.

Two and a half decades ago, there were limited therapies available for heart failure patients. We simply practice in a desert in terms of medical options, leaving patients and providers at a painful standstill. This disease can be quite unpredictable. While some patients simply suffer

with swelling in their lower extremities, others are plagued with shortness of breath.

Time and time again, I've watched my patients continue to be progressively sicker and becoming more symptomatic, noting their swelling in their legs weighing them down to their bed; cherishing each and every breath they took throughout the days and night; dreaming simply of just bending over to pick up their grandchild, yet debilitated by fatigue.

Night after night, they're in the room next to the person they've loved so long, subject to sleeping in the recliner when all they desperately are wanting to have is just to feel better, knowing they will never be quite normal but grateful for anything that may resemble it.

These symptoms no longer allow them to foresee those family vacations with grandchildren or attend graduations and birthday parties, and during the darkest of times, they can't fathom walking their daughter down the aisle because to have that hope will cause their heart to hurt

further. They no longer are considered a part of society, as the daily list of things to do changes from going to work or to the grocery store, to pacing themselves, scheduling their activities so that they have enough energy to do what needs to get done.

Mrs. Smith is the patient that comes to my mind when I think about this progressive, deteriorating path that our patients walk on without advances in medical therapy. She was a beautiful 60-year-old woman who lived a quiet, private life in South Carolina with her loving husband of 35 years, 5 children, and 12 grandchildren.

Despite living a quiet life, she was originally from New York, an innate firecracker, as people would call her, who believed firmly in God and family. After she was diagnosed with dilated cardiomyopathy and end-stage heart failure, she would have joked that she had finally earned the honor of having her 13th grandchild take her name.

Unfortunately, her granddaughter's due date

fell on the week that she was admitted to the ICU. She had done everything right. By all means, she listened to medical advice and took the medications that were offered, but due to her low blood pressure and kidney function, she was limited in the medical therapy that she could continue to take, and her heart weakened further.

Her fierce spirit no longer coincided with her weak and fragile heart. She continued to grow weaker as her husband sat by her day in and day out, and there were words he would never allow himself to speak, yet his eyes grew sadder as he watched the love of his life decline day after day.

Providers at first would have a hint of hope in their voices as they saw her on daily rounds, but eventually this lapsed, as there was nothing else to offer her, and nothing could be done. And she died peacefully in the ICU next to the man she loved; and a granddaughter was born without a grandmother with the honor and blessing of her name; and her daughter celebrated and mourned all at once.

When we think about our patients and that drug that has been discussed today, I hope for more time for husbands and children. Over the years, we have seen advances in these medical therapies, but need additional treatment options for some of our patients. Thank you again for your time.

DR. LEWIS: Thank you.

Speaker number 1 has checked in, so we will go to speaker number 1. Your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. RUPP: Yes, ma'am. Thank you, and good afternoon, everyone. Thanks for having me. My name is Juddson Rupp. I'm 57 years old. I live in North Carolina, where I work as a senior manager in patient advocacy for a pharmaceutical company; not Cytokinetics, however. I do serve on a Cytokinetics' patient advisory board. Why? Because I received a heart transplant just over seven years ago, and know what it's like to have heart failure. I'm speaking here on my own time

and not being compensated for my remarks today. Thank you, again, for letting me share my story.

As we all know, the treatment you've been reviewing deals with the ejection fraction. If there had been such an option for treating ejection fraction years ago, I wonder whether I might have been able to avoid, or at least put off, a heart transplant. I was always a very healthy person, always exercised and played sports. I received a full athletic scholarship to the University of Virginia to play football. You might say I was pretty much an all American kid who worked hard at school and on the gridiron.

As a child, I had a heart murmur but seemed to grow out of it by high school. I underwent physical exams in college, but my hypertrophic cardiomyopathy wasn't diagnosed until after I graduated. All along, I kept up my exercise. I worked out at the YMCA like I'd always done, including playing pick-up basketball and flag football. I got married in 1995, and by 2000 was exercising at the YMCA very early in the morning

like I normally did. I fainted on two occasions, two different occasions, but I got up and kept going. I saw a doctor, and everything seemed to check out.

About two months later, I went into cardiac arrest at the YMCA. Fortunately, a good Samaritan who happened to be a physician came to my rescue and deployed a brand new AED. My heart stopped two other times in the ambulance to the hospital. I was a John Doe for literally 24 hours because I had no ID on me. My poor wife and small children had no idea what was going on until the highway patrol called her, which tracked me down based on my car still being in the gym's parking lot. I even became a local news story because I was literally this unknown man who had a sudden cardiac arrest.

I was in TV ad sales at the time, and even my own TV station did a story. They didn't normally do stories on employees, so I knew it was either a slow news day or truly a miracle I survived. I think it was definitely the latter. The American Heart Association saw the story and

told me, "Juddson, if you share your story, it will save thousands of lives."

It became an open book from that point on for me. Around 2005, I developed atrial fibrillation. That really made my HCM worse and I think contributed to my heart failure, and by 2014 I was also using a CPAP machine for sleep apnea. I was also in denial. I felt that the CPAP machine made me sleep better and feel better, and that I wasn't in heart failure like they thought. I was pretty selfish in thinking that, but I thought I was trying to really be selfless because I didn't want to burden my family. It was a difficult time.

I got my heart on July 22, 2015 at Duke University. Fortunately, I was able to work just up until the transplant and was out for just 3 weeks. Every day has been a great day. My wife has been an angel. I don't sweat the small things anymore, but again, before the transplant, I was in denial. I thought, "I'll be fine. I'll live like this, and I'm fine living with this."

They didn't know how long I would live with

that 10 percent ejection fraction, but if I'd had access to a drug for ejection fraction, I probably would not have had the heart transplant or would have held off for more years. If there had been a drug that could have helped me -- if I could have improved my ejection fraction, that is -- certainly that would have been a game changer. I know most heart patients don't want to go through a transplant. In hindsight, it's the best thing I could have done. But if I had had that option for an ejection fraction drug earlier in the process, I would have definitely taken that instead. Thank you for your time.

DR. LEWIS: Thank you.

Speaker number 12, your audio is connected now. Will speaker number 12 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ADAMS: My name is Kirkwood Adams, Jr., MD. I'm an associate professor of medicine and radiology at UNC Chapel Hill School of Medicine, but my views expressed are my own. My disclosure

is funding from Cytokinetics, and I'm not receiving any compensation for this presentation.

I would like to offer my in-the-trenches clinical perspective and support of omecamtiv mecarbil as a novel therapy for severe heart failure or HFrEF. I work as a clinical researcher in CHF, but much more importantly, I must address the dire state of many patients who are afflicted with severe heart failure despite currently available drug treatments. These patients often struggle with the simplest activities of daily living. They are frequently hospitalized for worsening heart failure, a dreaded event that they would like to avoid at almost any cost.

I and many of my colleagues have conducted extensive basic and clinical research for decades, aimed at developing effective drug treatments for this syndrome; however, the major pathophysiological problem in severe heart failure impaired cardiac contractility has proven very difficult to effectively and safely reverse by pharmacologic therapy. Classic inotropic agents

are not the answer. While they produce important improvements in LV function, their use comes at the cost of life-threatening side effects.

Another very important clinical consequence of severe heart failure is significant limitation of proven drug therapies for HFrEF. This includes all classes of neurohormonal antagonists and may worsen outcomes. The development of omecamtiv mecarbil addressing these two major limitations of current therapy for severe heart failure by directly targeting the active myosin interaction, this drug represents a novel approach to improve cardiomyocyte function without the adverse effects of classical inotropes.

In addition, omecamtiv mecarbil has proven to be safe without adverse effects on blood pressure, heart rate, renal function, and potassium that commonly limit the application of GDMT in HFrEF. This safety profile allows the addition of omecamtiv mecarbil without the risk of limiting important pharmacologic treatments for HFrEF.

The GALACTIC-HF met its primary endpoint of

reducing cardiovascular death and heart failure events. A number of secondary analyses suggest this drug may be even more effective in trial patients whose heart failure was particularly severe. Importantly, benefits and more severe subtypes of HFrEF are fully consistent with the mechanism of action of omecamtiv mecarbil. These findings are consistent with prior work with classical inotropes that indicate more favorable effects in patients with greater clinical severity of HFrEF.

In conclusion, patients with severe heart failure have dire needs that are not currently addressed by available pharmacological therapies. The demonstrated efficacy of omecamtiv mecarbil in GALACTIC-HF supports its approval to improve cardiovascular outcomes in patients with this debilitating and deadly condition. Thank you.

DR. LEWIS: Thank you, and I apologize to anyone I had to cut off, but I try to be fair with four minutes for everybody.

The open public hearing portion of this

meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will proceed with the FDA charge to the committee from Dr. Norman Stockbridge.

Charge to the Committee - Norman Stockbridge

DR. STOCKBRIDGE: Yes. This is Norman Stockbridge. I don't think I have any real comments to make. I think the discussion up to this point has been good, and I look forward to the further discussion coming up.

Questions to the Committee and Discussion

DR. LEWIS: Thanks for your help with my time.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and panel discussion. I would like

to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

After I read each question, we will pause for any questions or comments concerning its wording, then we will open the question to discussion. I'm going to read question number 1.

Discuss the proposed benefits of omecamtiv mecarbil and whether there is adequate evidence for concluding these benefits. Include a discussion comparing the findings for the heart failure and cardiovascular mortality components of the primary efficacy endpoint in the GALACTIC Heart Failure trial. What role does the phase 2 trial play in your assessment of the benefits?

Are there any questions or issues about the wording of the question?

(No response.)

DR. LEWIS: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Dr. Nissen?

DR. NISSEN: Thank you. We've had a lot of good discussion about this question.

DR. LEWIS: Dr. Nissen, will you say your name first, for the record?

DR. NISSEN: I'm sorry. It's Dr. Steve Nissen. Thank you, Julia.

So we've had some very good discussions. First of all, the proposed benefits are small, and I did not get an answer to my question from earlier, but it appears to me that they're driven, at least in large part, by the urgent outpatient visits, not by hospitalization or by death. If you look at the hard endpoints, hospitalization and death, and again, maybe at some point we can see those Kaplan-Meier curves, it does not appear that there's much of a benefit.

Now, the phase 2 trial I don't think is terribly informative, and there's a very important reason why, that we didn't discuss. If we had looked at cardiac function measures with dobutamine or milrinone, those drugs would have shown

benefits, but we know that, in fact, those benefits are not good predictors of the effect of drugs on morbidity and mortality. So using that as supportive evidence, in the case of this type of drug, is not nearly as compelling as it might be for some other indication where phase 2 might be very useful.

So without getting into some of the other issues here, a couple more things I'd like to say. One is the lack of quality-of-life benefits. There's no improvement in KCCQ. We really require a 5-point increase to be clinically significant, and that did not occur here. The final thing that I was very surprised about, even with Dr. Blaha's comment, which is that ejection fraction up to a year old could be used for qualifying patients.

Now, the proposed indication here is for people who have an EF of less than 28 percent. Those people could have had an EF of 28 percent a year ago, and who knows what's happened in the last year. So not having an EF proximate to the trial makes this post hoc analysis of the potential

benefits of low EF a much weaker argument. Thank you.

(Pause.)

DR. LEWIS: Thank you, Dr. Nissen.

I'm going to take a moment to ask the sponsor. Dr. Nissen had two outstanding questions for you to check if you could produce the data during the break. If you in fact have that data that specifically answered the questions -- not something that's sort of ancillary to it -- I'm happy to give you a moment to do that. Please be brief, though.

DR. MALIK: Yes. Certainly. We do have the Kaplan-Meier curves that Dr. Nissen requested, and if you can please bring up RR-21, please?

What are shown here are the Kaplan-Meier curves for the primary composite -- or rather the composite of heart failure, hospitalization, or CV death, whichever occurred first. On the left-hand side is the overall population and on the right-hand side is the population in the lower ejection fraction subgroup. You see an effect in

the overall population that's consistent with the primary results. You see a greater effect in the patients with lower ejection fraction.

DR. LEWIS: Dr. Nissen, does that address your question?

(No response.)

DR. LEWIS: Dr. Nissen?

DR. NISSEN: Sorry. Yes, it does. Just the other question I asked was on background therapy. If you have that listing, very quickly, I just wanted to see what the doses were of the ACEs and ARBs. I had asked that earlier as well.

DR. MALIK: If the chair would permit me to answer that, I can go ahead.

DR. LEWIS: Yes.

DR. MALIK: Can you show me slide 1?

This is an analysis that we did during the execution of the trial, so I would regard it as preliminary. We looked at the -- there are many different ACE inhibitors used, many different ARBs, and many different beta blockers and so forth. These are all normalized by their maximum

recommended dose, and you can see the dose intensity there for ACE, ARB, ARNi's -- we didn't split them out -- beta blockers, and MRAs.

If you can move to slide 2, please, or slide 1? These were the reasons for intolerance, and let me turn to Dr. Felker, perhaps, to comment on this slide.

DR. FELKER: Thanks, Dr. Malik.

To Dr. Nissen's point, these were actually collected by protocol for patients who are not on the maximum dose, why they weren't, and this is the data. As you can see, as I had referred to in my talk, this is a population with a huge amount of intolerance of traditional GDMT often due to hypotension, pre-syncope, and orthostasis, even in people often with a relatively normal or near normal blood pressure. So I think this just supports the difficulty of treating some of these high-risk patients with traditional GDMT.

DR. LEWIS: Thank you.

Dr. Bairey Merz?

DR. BAIREY MERZ: Thank you. Noel Bairey

Merz. I would also ask with respect to specific spline curves to evaluate whether or not a median or LVEF of 28 was similarly representative for women as well as the interaction of atrial fibrillation.

DR. LEWIS: I'll allow the sponsor to answer that question if they have the specific slide to answer it.

DR. MALIK: Yes. Could I get RR-19, please?

Dr. Merz, this is the spline curve for the treatment effect in women as a function of baseline left ventricular ejection fraction, and you see generally a similar shape to what we saw in the primary results that we displayed. Perhaps it shifted a little bit to the left, although I wouldn't overinterpret that, as this is a smaller group than the overall population, but consistent with the overall results I think is the key message.

DR. BAIREY MERZ: But I would agree that could be that your [indiscernible] sample size -- go ahead.

DR. MALIK: Yes. I was also going to show -- let's see if I could have slide 3 shown please. With regard to your question about the effects in atrial fibrillation women, this is the same slide we showed in the overall population, but now just women are represented on this slide.

You see there the overall study population at the top. In the low ejection fraction population, there in the middle, you see a reduction in the primary composite endpoint, and very few events really do evaluate the difference between atrial fibrillation in that group. There were only 44 events in the omecamtiv group and 40 in the placebo group, and similar findings to the overall study in the higher ejection fraction group.

DR. BAIREY MERZ: Thank you.

DR. LEWIS: Thank you. I appreciate you putting that together quickly during our shortened lunch break.

Dr. Bairey Merz, do you have a comment to our discussion question 1?

DR. BAIREY MERZ: Obviously, we're dealing with sub-subgroup, but I do find this as satisfactory, and thanks to the sponsor for putting it together so quickly. Thank you.

DR. LEWIS: Okay. Thank you.

Dr. O'Connor?

DR. O'CONNOR: Yes. Hi. Chris O'Connor here. I'd like to comment on discussion question 1, and really ask the committee to look through the lens differently than we traditionally look at heart failure programs that have come to us or have come to the agency without a committee.

This is a very unique population of advanced heart failure, and there's a very strong unmet need here. I think the presentations have been made that while GDMT was quite good in this population, it's hard to maintain GDMT in the very severe population, so there's not many therapeutic options for this population.

The second thing I would say is that not all studies are the same, so when we talk about a study that's 1,000 patients or 2,000 patients with

several hundred events, that's not equivalent to the study we have here, which is the second largest study ever done in heart failure, where you have significant power to look in subgroups. And the interaction p-value was pretty strong for -- it may not have met Dr. Gillen's 0.001, but it was pretty daggone strong for an interaction p-value. So I want the committee to recognize that not all studies are the same, and this was a very large number of events.

Finally, I think the sponsor has presented guardrails. I don't think they've presented all the guardrails of a path forward, but if this was an oncology drug, I think we would be having a very different discussion than we're having now, and the patient population that we're talking about is very much like the oncology population. So I'll leave it at that. Thank you.

DR. LEWIS: Thank you.

Dr. Gillen?

DR. GILLEN: Yes. Thank you. Daniel Gillen. I genuinely appreciate the open public remarks and

Dr. O'Connor's statements about the difficulty in treating such a population. Despite that, my general feeling is that there is a truly modest effect here on the combined endpoints, and that's really primarily driven by the non-fatal events when we look at this and see no difference in the slight increased point estimate, at least in cardiac-specific mortality.

With respect to the subgroups, while the sample size is large, that simply increases the precision inside of each subgroup. That does not obfuscate the issue with multiple comparisons and multiplicity in general. I think I've stated pretty clearly, and I think the sponsor has alluded to the fact that this was not a hypothesis-driven effect modification analysis. This was one of 28 covariates that was looked at, and then deemed to be significant after that analysis, and then a post hoc adjustment for multiplicity was made through a Bonferroni correction.

With respect to the way that I'm judging the evidence here in the overall population, where we

have a very modest effect, no effect on survival, I am somewhat dubious about the subgroup effects. And then with respect to the phase 2 data, while it is supportive to some degree, I think it's important to keep in mind that the phase 3 study was only done because the phase 2 study showed some promise. So therefore, these are not independent trials. There's a conditioning that takes place, that phase 3 only gets completed because phase 2 showed some hints of efficacy through there. So while I can take it as supportive evidence, I do not take it as independent evidence of benefits. Thank you.

DR. LEWIS: Dr. Wang?

DR. T. WANG: Thanks. Thomas Wang. Actually, my point was just now made by Dr. Gillen, which is my comment regarding the phase 2 trial data. I view that as not at all independent of the phase 3 program. I suspect the phase 3 trial wouldn't have happened without the phase 2 data. So in terms of whether I would view that as confirmatory evidence, I would say it's consistent,

but I'm not sure it fits the spirit of the FDA guidance for truly confirmatory evidence that would allow confidence to move ahead with a single trial.

The second comment regarding phase 2 mirrors off of Dr. Nissen's earlier comment, which is the profile that was seen in the phase 2 trial would likely be the same profile seen with all of the inotropic drugs that we've evaluated in the past, including some to which we know that there is an adverse signal with regard to heart of events. Thanks.

DR. LEWIS: I'm going to make a comment. I think what has struck me the most and hasn't already been commented on is forgetting that the preclinical data in the healthy volunteers, and in phase 2, and I believe in phase 3, is a suggestion of cardiac toxicity. This study had excellent power, and as you mentioned, Dr. O'Connor, many, many events to evaluate cardiovascular death. And indeed this did not in any way help or reduce cardiovascular death, which is a bit of a disconnect if it's helping heart failure in

reducing symptomatic admissions.

So I think the absence of that when it was powered to do it, and plenty of events, really troubles me as a stand-alone trial, and the suggestion of cardiac toxicity in the phase 2, and in the healthy volunteers, and in the preclinical data all give me pause.

Dr. Blaha?

DR. BLAHA: Yes. Hi. Mike Blaha, Johns Hopkins. I largely, I think, agree with what was said by my colleagues, Dr. Nissen and Dr. Wang. Personally, I don't find the phase 2 data to be confirmatory. I find it to be very interesting and mechanistic of nature, understanding the way this drug works, but to me not confirmatory of any clinical benefit; and what I mean by that is clinical benefit on outcomes that are meaningful to patients, including, of course, heart outcomes.

I think the phase 3 trial was a great trial and was a large study from which we can draw lots of interesting observations. But largely, it's driven -- or our discussion today, and even the

presentation by the company, was largely a discussion of subgroups. It was largely even presented as a subgroup, and I think that's a very important subgroup.

I think Dr. O'Connor makes a very important point about clinically important is that particular subgroup of advanced heart failure, advanced, I should say, HFrEF is, with severely reduced ejection fraction. And still, this study was driven by heart failure events, and even so, many of those were the softer, urgent outpatient visits or ER visits for heart failure, and it didn't lead to hospitalization.

So all the concerns, of course, that have been stated about subgroups, I also share those concerns, but to me, as far as that goes, it didn't reach the standard of substantial evidence. But for me, a strong rationale to look closer, maybe in a future study, is at this important subgroup of advanced systolic heart failure, and we'll come back to it later.

What gives me quite a bit of pause was when

I heard the proposed label indication from the sponsor, which had lots of deficiencies, in my view, but we can come back to that, I'm sure, at another point in the discussion. Thank you very much.

DR. LEWIS: Thank you.

If there are no further comments -- Dr. Bairey Merz, do you want to make a comment or is your hand just up?

DR. BAIREY MERZ: Yes.

DR. LEWIS: Oh, okay. Sorry. Go ahead.

DR. BAIREY MERZ: Thank you, Julia. Noel Bairey Merz. I did not address the question.

I see that there's an innovative drug, but basically we're revisiting history. This is a squeeze drug, even though the mechanism is different. That likely explains the very mild benefit and the potential harm.

Then I agree with Dr. Blaha. We're doing subgroup comparisons to subgroup comparisons. When we have prespecified subgroups, because we know something about the biology, then we can prespecify

28 and get away without multiplicity correction. When we see a sub-subgroup that appears to be harmed, we're much more alarmed by that because we didn't know it. We didn't anticipate it, even though we might have hypothesized it because this was a contractility drug. Anyone -- even I grew up treating people with dig [ph], treating people with an IV inotrope, and watching them die. So I think we need to keep all of that in mind, not over emphasize any of these subgroups, or even sub-subgroups.

I don't think the phase 2 trial contributes much, in my mind, and at the end of the day, the overall trial had a very mild -- and to the FDA's requirement, did not meet their specification. So we're going to then go to the discussion of need, and those are my comments. Thank you.

DR. LEWIS: Thank you.

I'll try to summarize our comments. I'll begin with the comment that this is a very sick population of people with advanced heart failure. They have an unmet need because of often having

intolerance to existing therapies, so there's no question that it's a very important group to study, and if able, to potentially help. However, I think concerns are being expressed about this as a first-in-class drug, stand-alone trial.

I think the consensus -- for often the same reasons but actually several reasons -- was that the phase 2 trial does not provide sufficient supportive evidence for a single trial that does not meet the specified p-value.

The proposed benefit being small is another negative factor; that very modest effect on the primary event; a concern of why there was no benefit for the cardiovascular death outcome despite being powered for that; a concern about subgroups and sub-subgroups being used to argue that it justifies the label or approving the drug for those subgroups, expressed for all the usual reasons why, but also there were over 20 or so subgroups looked at, which really limits the interpretation of it, and it was not a pre-hypothesized rationale.

Then lastly, one of those major subgroups was determined by an echo that could have been done any time in the first year, so it makes it also more complex to accept as supporting evidence.

I will now read question 2. If omecamtiv mecarbil were approved, what should the labeling say about use as a function of left ventricular [sic - ejection] fraction? Are there any issues or questions about the wording of the question?

(No response.)

DR. LEWIS: I didn't put my hand down.

If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

Dr. O'Connor?

DR. O'CONNOR: Yes. Chris O'Connor. Specifically about left ventricular ejection fraction, I think all of us have concerns about echo EFs of 28, which it's the median, but it's an unusual number in clinical practice. I very much like the analysis that the FDA did looking at the knots, where they saw 25, which echo EFs are often

measured in ordinal components of 5, even the distribution in Teerlink's paper, EFs as steps on ordinal measurements, intervals of 5.

So if this were approved, I would advocate an LVEF less than or equal to 25, which is much more user-friendly in practice and helps prevent against some of the variability that one might have that could reach over the 28 boundary. Thank you.

DR. LEWIS: Thank you.

Dr. Blaha?

DR. BLAHA: Yes. Hi. Mike Blaha, Johns Hopkins. I agree with much of what has just been said. I was going to return back to the indication proposed in the NDA from the company, which said omecamtiv mecarbil is a cardiac myosin activator, indicated to reduce the risk of cardiovascular death and heart failure events in patients with symptomatic chronic heart failure with reduced ejection fraction, but then sort of the caveat that benefits are increasingly evident the lower the ejection fraction.

So I had a lot of concerns about that. Both

the mention of cardiovascular death gives me some pause. I realize that was in the primary endpoint, but we've discussed the nature of that endpoint already. Then the statement that it was only sort of a secondary comment that the benefit was increasingly noted with lower ejection fraction, to me, doesn't seem supported. We could even have the discussion was it only present when the ejection fraction was severely reduced. So I guess that's the nature of the question here.

So taking the question here as asked, if it was approved, what should the labeling say about the use of ejection fraction, I tend to agree with Dr. O'Connor here, that the only way I could see an indication being supported, based on the single trial that we've seen presented, would be to have severely reduced left ventricular ejection fraction mentioned, and maybe specifically, as was mentioned, less than 25 percent I think would be somewhat supported by the spline analysis, and actually seems fairly robust to me across lots of different ways of doing that same analysis; so

again, only in those patients with severely reduced ejection fraction, and maybe with another risk factor -- that could be discussed perhaps later -- with an ejection fraction less than 25 percent. So I agree with what's been said. Thank you very much.

DR. LEWIS: Thank you.

Dr. Gillen?

DR. GILLEN: Yes. Just a little bit to add. I agree with the two prior comments on that. The one thing I would say -- I guess two points to add, one, is that the way that the current labeling, proposed labeling, is worded with the increased benefit with lower ejection fraction assumes monotonicity, and I think actually relies a little bit on the linearity of what that assumption is.

I think that as you saw some of the different non-parametric smoothing of that effect, it's not necessarily non-linear, so I don't agree with that method. And while I don't agree with arbitrary cutpoints such as 28, where that's the median, I do agree with Dr. O'Connor in stating

that there should be an emphasis on something lower, and part of that is driven by just the recent data that was shown in females, where we saw a shift to the left in that ejection fraction, where the estimated benefit is pulled to the left of the lower ejection fraction, lower than 25 in fact.

So I disagree with the current wording on both of those principles. If we did a more extreme wording on the ejection fraction -- if this were approved given all the caveats that we already discussed -- that should be made. Thank you.

DR. LEWIS: Dr. Gillen, I'm sorry. I forgot to remind you to state your name into the record.

DR. GILLEN: I apologize. Daniel Gillen. Sorry about that.

DR. LEWIS: Thank you. I appreciate it.

Dr. Thadhani?

DR. THADHANI: Thank you. Ravi Thadhani. The comment made by Dr. Solomon regarding how a label would translate to clinical practice and the reticence for a specific cutpoint, per se, just

given the variation, certainly struck me.

Obviously, I'm not a cardiologist, but is there precedence where a label actually states a specific cutpoint, and necessarily then adherence to that in clinical practice, especially in the context where when we look at those curves, when we get above some of the cutpoints you've described, like 25 and 28, there seems to be the potential, actually, for harm above some of those numbers? Thank you.

DR. LEWIS: I will make a comment. One could argue that the label should say that it was potentially only a benefit at a low ejection fraction and in fact shouldn't be used in patients with a higher ejection fraction, for the reasons others have stated.

Dr. Bairey Merz, your hand is raised.

Okay. Dr. Gillen, do you have another comment?

DR. BAIREY MERZ: Yes. No, I have a small --

DR. LEWIS: Oh, sorry, Dr. Bairey Merz.

State your name, please.

DR. BAIREY MERZ? Yes. Thank you, Dr. Lewis. I have a comment, and then an answer to Dr. Thadhani's question.

My comment is I very much agree with the suggestions of Dr. O'Connor, Blaha, and Gillen of more stringent labeling if approved. And then to Dr. Thadhani, yes, CMS has a threshold of a left ventricular ejection fraction measured by any means, less than 35, to be able to pay for cardiac rehab, just as an example. So there certainly are thresholds that are used clinically. Thank you.

DR. LEWIS: Okay. I don't see any other hands raised.

Dr. Bairey Merz, do you have another comment?

DR. BAIREY MERZ: No. Noel Bairey Merz. I'm trying to pull it down, Dr. Lewis. Apologies.

DR. LEWIS: It's so hard to tell on this one, isn't it?

Okay. Then I'll summarize question 3. The point's been made that an ejection fraction of

28 percent is an unusual number, and that perhaps 25 percent would be more compatible with clinical practice, and also represents whether the FDA knots, and might be a more appropriate recommendation.

It's also been brought up that there is an issue with what to say about the people with higher ejection fractions. Do we just say it works better at lower, or do we even make a suggestion that it is, in fact, non-helpful at higher ejection fractions or perhaps harmful?

Cardiovascular death might not belong in the label since it was powered and has sufficient events to show no benefit, even though it was part of a composite, and that's a very unusual aspect of a composite. Do we actually prospectively power it for one element of it? So I think we don't often see that.

Also, Dr. Gillen -- and I might not quite get it right, but that the lower ejection fraction, due to the shift of the left in women, makes you concerned about picking a precise one, and also

that the analysis for the currently labeling assumes monotonicity and linearity, and you're not necessarily in agreement that it is linear.

I will go on and actually read question 3. Actually, I think we get a break, and we have time for a break, or do you guys want to go on to question 4 and get done early?

Anybody want to vote?

MALE VOICE: Well, we need question 3 still.

DR. LEWIS: Oh, I apologize. My fault. Okay. Sorry about that. I've got too many things I'm trying to do at once here.

I'm going to go ahead and read question 3. Thank you for whoever reminded me.

If omecamtiv mecarbil were approved, what should the labeling say about the use in patients with atrial fibrillation or atrial flutter?

Are there any questions or issues in regards to the wording of the question?

(No response.)

DR. LEWIS: If there are no questions or comments concerning the wording of the question, we

will now open the question to discussion.

Dr. O'Connor?

DR. O'CONNOR: Chris O'Connor. This one is, I think, important because we view mortality not only as efficacy, but safety, and I think the FDA provided a nice analysis on a worrisome signal on cardiovascular death. And since it's easy to obtain a rhythm status at time of drug initiation, I think the labeling should say normal sinus rhythm or the absence of atrial fibrillation/flutter. Thank you.

DR. LEWIS: Dr. Blaha?

DR. BLAHA: Yes. Mike Blaha, Johns Hopkins. I agree. I think this one is fairly straightforward for me, based on the data from this single study and the concerns about safety. Then also, the clinical context for this drug, where that could be used, I think it would make sense, for this drug, if it were to be indicated, for the label to mention in patients in the absence of evident atrial fibrillation or atrial flutter.

I say that both because of the harm that was

potentially seen in patients with a higher ejection fraction with atrial fibrillation or atrial flutter, but also it's seemingly a less potential benefit, even on the softer endpoints, in the patients with lower ejection fraction.

Just as a side note, I think it's intriguing, and I'm sure the sponsor's quite interested in this signal where 5 patients in sinus rhythm might actually have reduced instant atrial fibrillation. That's an intriguing side note. But yes, as far as this goes, I agree that the label should exclude patients with atrial fibrillation or atrial flutter that's clinically evident. Thank you.

DR. LEWIS: Dr. Thadhani?

DR. THADHANI: Ravi Thadhani. I agree with my colleagues. We did see an analysis that highlighted that if people developed new onset AFib, as was indicated or at least -- the results were in the same direction as the overall study. So while the label, if this were approved, should highlight, when the agent is started,

contraindication with AFib and AFlutter, I think subsequent development of that, after being in normal sinus rhythm when the drug is started, does not appear to alter the outcome. Thank you.

DR. LEWIS: Dr. Thadhani, can I ask you to clarify that for me? You would say that if they develop subsequent AFib, what would you recommend?

DR. THADHANI: I believe we saw an analysis -- and please correct me if I misread it. But we saw an analysis where individuals who did not have AFib at the onset when the agent was started, if they subsequently developed AFib or AFlutter thereafter, there did not appear to be adverse effects on those individuals.

So while the label should highlight that it should only be started in individuals with normal sinus rhythm, that once they're on the agent and they develop AFib and AFlutter, there was no evidence that coming off the agent would be harmful; at least that's what I remember seeing. Again, please correct me if I misstated that.

DR. LEWIS: I think I'm going to let the FDA

clarify that question.

Did you guys look at whether if AFib was -- not at the beginning of the trial at baseline, but later developed, if there was an impact of it with an adverse effect?

DR. McDOWELL: This is Tzu McDowell. I think that particular analysis is from the sponsor. We did not look at that in our assessment specifically.

DR. LEWIS: Okay. Then I'm going to let the sponsor comment.

Do you confirm Dr. Thadhani's recollection of your analysis?

DR. MALIK: Yes. The data we showed were for people that had new atrial fibrillation during the course of the study, and not seeing any emergent adverse imbalance in clinical events.

DR. LEWIS: Thank you very much.

Dr. Wang?

DR. T. WANG: Yes. Thomas Wang. I agree with my colleague that it's difficult for me to ignore the signal with AF and AFlutter, even though

I'm not sure I really understand what the source of the signal was, if it's real. The fact that the sponsor pointed out that when you are nested within the group with low EF, that adverse signal seems to go away reassures me only slightly, again, because it's a subgroup of a subgroup. But again, my initial impression is that if there were a labeling, that AF and AFlutter would have to be addressed.

As for Dr. Thadhani's point and the sponsor's point about infinite AF in people who had sinus rhythm at baseline, I appreciate the sponsor providing that data. I still wonder whether that would be confusing for clinicians and also not intuitive. Again, it's not intuitive why AF at only one point in time -- i.e., when they were enrolled in the trial -- should matter, but AF at some future point in time wouldn't matter, and is it a true interaction of the drug. So there clearly are a lot of unknowns in this area. Thank you.

DR. LEWIS: Thank you.

Dr. Bairey Merz?

DR. BAIREY MERZ: Noel Bairey Merz. I agree with my colleagues, and I would add the phrase, "particularly in patients concomitantly on digoxin." Thank you.

DR. LEWIS: Thank you.

Dr. Nissen?

DR. NISSEN: Steve Nissen. I don't think we know enough about what happens to patients that develop atrial fibrillation while on therapy, so we're looking at very limited amounts of data. So my thought here would be, if it's contraindicated in patients with AF at baseline, unless we can see better evidence that it's safe in people that develop atrial fibrillation, we should impute to those patients the potential for the drug to do harm. Thank you.

DR. LEWIS: Thank you.

Dr. Wang, do you have another comment?

Okay. Ms. Dunn?

DR. T. WANG: No. I apologize.

DR. LEWIS: Ms. Dunn?

(No response.)

DR. LEWIS: Ms. Dunn, you're on mute at the top bar. So if you go to the top bar where the phone is, you can unmute yourself with the arrow.

(No response.)

DR. LEWIS: Ms. Dunn, while you're doing that, I'm going to go ahead to Dr. Moliterno.

MS. DUNN: Yes. I'm here.

DR. LEWIS: Oh, there you go. Thank you.

MS. DUNN: Yes. Thank you.

DR. LEWIS: Go ahead.

MS. DUNN: This is Debra Dunn, and I just wanted to weigh in that I do agree with the panel. This is very concerning as a patient. This is in a very gray area. Patients do go in and out of atrial fibrillation, so I feel full disclosure, and hopefully a patient will partner with her care provider. And if they're ever told that they have been going in and out of AFib, that when this drug may be discussed with them, that they will be able to strike up a conversation and remind the clinician that this possibly may be a risk factor.

Thank you.

DR. LEWIS: Thank you, Ms. Dunn.

Dr. Moliterno?

(No response.)

DR. LEWIS: Dr. Moliterno, you're also muted in the upper bar.

Can we unmute him or does he have to do it?

DR. MOLITERNO: Julia, are you able to hear me now?

DR. LEWIS: I am.

DR. MOLITERNO: Good. I must have been shut off centrally, which is why you don't like any of my comments, I guess, because you can't hear them.

(Laughter.)

DR. MOLITERNO: I'll be brief.

I was just going to say I agree with Ms. Dunn and also Steve Nissen. I think that this needs to be in the label and needs to be rather straightforward given the real modest benefit and no benefit to quality of life, and no benefit with mortality; that if there is some residual concern with regard to atrial fibrillation, I think we

can't let it go unsaid.

There's just not enough data to know what would happen for patients who are going in and out of AFib or who go permanently into atrial fibrillation, that I do think it would need to be stated that there is inadequate evidence for certainty of safety and some concern for adverse outcome. Thank you.

DR. LEWIS: Okay. I'm going to, I think, attempt to summarize. And, Ms. Dunn, I assume your hand is just still up.

I think everybody was in agreement that the label should include some comment about the potential harm in patients with atrial fib, and although there is some data that it's only atrial fib or flutter at the onset of therapy, that the subgroup analysis, the numbers are small. There isn't a rationale for why that would be true. Certainly patients go in and out of flutter; it's not an uncommon phenomena. It's a very gray area.

With the benefit side of this drug being limited by the mortality data, the quality-of-life

data, for example, to err on the safe side of warning about a patient who is in AFib/AFlutter, ever, particularly on digoxin, and perhaps even requiring them to be in normal sinus rhythm.

Now that I've managed to get us back on track with the right question number, we can take a 10-minute break. I have roughly 3:40. Panel members, please remember that there should be no chatting or discussion of the meeting topic with anyone during the break, and we will resume at 3:50.

(Whereupon, at 3:40 p.m., a recess was taken.)

DR. LEWIS: We will now move on to question 4. Discuss whether omecamtiv mecarbil is safe enough to support its proposed use. Consider safety with and without pharmacokinetic-based dosing.

Are there issues or questions about the wording of the question?

(No response.)

DR. LEWIS: If there are no questions or

comments concerning the wording of the question, we will now open the question to discussion.

Dr. Nissen?

DR. NISSEN: This is Steve Nissen. I do have safety concerns, and I also have concerns about the posology.

First of all, because the drug is a 2D6 metabolized drug, there's high potential for drug-drug interactions, and I would point out that regardless of whether it's dosed by fixed dosing or pharmacokinetic-based dosing, there's nothing to prevent a physician from starting an SSRI while patients are on this therapy. And if there's a lack of awareness of that potential, given the fact that there is potential harm from the therapy with excess pharmacology, that potential is fairly high.

We didn't talk about it very much, but I was troubled by the troponin I elevations. If you look at elevations greater than 10 times the upper limit of normal, there is a significant excess; not [indiscernible] significant, but there's quite an excess in patients that we see omecamtiv.

What does that mean? Well, in general, when troponin and also CKMB goes up, that means myocyte injury, and we do know that there are lots of preclinical data and other data that suggests that can be ischemic damage from the drug; so now we have a drug that's difficult to administer, the pharmacokinetic-based modeling is really quite difficult, and the assay that has been developed is not an assay that's been fully evaluated and approved by the FDA.

So for all of those reasons, I think because dosing is so difficult, and because there are safety issues with excess pharmacology, I do have significant concerns about safety. Thank you.

DR. LEWIS: Thank you, Dr. Nissen.

Dr. O'Connor?

DR. O'CONNOR: Yes. Chris O'Connor. I'd differ just a little bit with my colleague, Dr. Nissen, and say this trial of GALACTIC-HF, with over 8,000 patients, I'm sure had drop-in of drugs post-randomization that may have been metabolized through those pathways. And by using a

pharmacokinetic-based dosing strategy, as they did in that trial, they averted the safety concerns of myocardial injury and drug-drug interactions that may have caused torsades or significant ventricular arrhythmia.

So I think, in totality, what we're talking about is, is there a pathway by putting guardrails up both on the efficacy and safety side? And I think pharmacokinetic-based dosing is one of the additional components of the pathway that we've just talked about. Thank you.

DR. LEWIS: Dr. Blaha?

DR. BLAHA: Hi. Mike Blaha, Johns Hopkins. I agree with much of what I heard from Dr. O'Connor. I was actually fairly reassured by the safety profile from the large clinical trial, of course, that had the guardrails that we just spoke of, where this drug appeared fairly safe. I admit that there are some signals of potential harm. We talked about the atrial fibrillation question already, but this is -- at least the way I have it in my mind, where this would go -- a very

sick population of patients with few other options and lots of other competing risks, where small elevations in troponin perhaps might not be as prognostic.

But anyway, as far as this question goes, do I think it's safe enough to support its proposed use? I think that's a subtle one because the proposed use we're still discussing. But considering its safety with or without pharmacokinetic-based dosing, I would say it appears, to me, to be safe enough, from a large clinical trial with pharmacokinetic-based dosing, to consider that a reasonable strategy. So I come down a little bit on the side of, yes, I think pharmacokinetic-based strategy can be a safe way to administer this drug if it's determined that that's a thing that will lead to net clinical benefit. Thank you.

DR. LEWIS: Dr. Bairey Merz?

DR. BAIREY MERZ: Noel Bairey Merz. I agree with my colleague. I'm also not concerned of high sensitivity to troponin now. There's a lot of

injury in people walking around with diabetes, people walking around with CKD. These are seriously ill heart failure patients. That does not worry that much, and there were not large group differences.

This is to return to pharmacokinetic testing, which I would support if approval was indicated, and it's for toxicity and requires there be availability at that testing, and the sponsor seems to say that it is [indiscernible]. Similar to theophylline, similar to digoxin, and other medications that have very narrow therapeutic toxicity windows, this is fairly easily managed, particularly in this type of patient who will likely be seeing a heart failure cardiologist due to the severity of their disease. Thank you.

DR. LEWIS: May I ask the panel a question. Would you feel that it would be safe to use this drug without pharmacokinetic-based dosing? Would anyone advocate for that? Because I think that's part of this question.

Dr. Blaha?

DR. BLAHA: Yes. It's Mike Blaha, Hopkins. As far as that goes, I'd just say we do not have enough data to evaluate that question. I couldn't in the affirmative say that I feel comfortable using this drug without any pharmacokinetic-based dosing or dosing check levels, et cetera. That may be the case, but I don't have the evidence to support that. Thank you.

DR. LEWIS: Thank you.

Dr. Bairey Merz?

DR. BAIREY MERZ: Noel Bairey Merz, just to endorse what Dr. Blaha said. Thank you.

DR. LEWIS: Okay.

Dr. Wang?

DR. T. WANG: Thomas Wang. Yes, similarly I think we have no data to support the safety without PK-based dosing, and in fact, I don't think the sponsor was proposing that either. Thank you.

DR. LEWIS: Thank you.

Dr. Kovesdy?

DR. KOVESDY: Yes. Correct me if I'm wrong, but I think there's a number that the FDA

presented, some data that without pharmacokinetic dosing, the blood levels of the drug tended to be in ranges where one could expect safety concerns. Correct me if I'm wrong, but if I remember correctly, that data would tell me that it may not be safe to use it without pharmacokinetic dosing. Thank you.

DR. LEWIS: Thank you.

Does anyone want to comment on the change in the assay? Are there any concerns about that?

Dr. Nissen?

(No response.)

DR. LEWIS: Dr. Nissen?

DR. NISSEN: Yes. Thank you. Steve Nissen here. Yes, I have concerns. There is considerable evidence that excess pharmacology here has the potential to cause harm, so having a validated assay is an important component of the safe use of this drug. Without a validated assay, it is very difficult to be sure that the drug is going to be used safely.

I also do have to comment on this issue of

the troponin elevations. Please look at page 71 of the briefing document, table 27, and look at the differences between placebo and omecamtiv on elevations at troponin I [indiscernible], including elevations that are 10 times the upper limit of normal. Yes, these patients do tend to have higher troponin Is and CKs, but when you see an excess of increases more than 10 times the upper limits of normal, you have to notice. So I would reiterate the concerns I expressed a little bit earlier.

DR. LEWIS: Dr. Wang and Dr. Kovesdy, do you have your hands up for further comment?

(No response.)

DR. LEWIS: Okey-doke.

If there are no -- oops. Dr. O'Connor?

DR. O'CONNOR: Chris O'Connor. I would just say that the assay used in the trial was effective in maintaining safety of the patients. And the way it was used, the way it was conducted was in over 8,000 patients all over the world, different health systems, different countries. So to me, that's very good evidence that the assay used worked.

Thank you.

DR. LEWIS: Dr. O'Connor, correct me if I'm wrong, but that's not the assay that they're going to propose using going forward. They're switching to a different assay.

DR. O'CONNOR: Yes. My comment is the assay that they they used in the trial is the one that I think affords the best safety; right.

DR. LEWIS: Okay. Thank you.

Dr. Bairey Merz?

DR. O'CONNOR: But --

DR. LEWIS: Oh, I'm sorry, Dr. O'Connor. Go ahead.

DR. O'CONNOR: No, I'm finished. Thank you.

DR. BAIREY MERZ: Noel Bairey Merz. To address Dr. Nissen's legitimate concern, the prognostic value of a high sensitivity TnI or TnP in a high-risk group would have been evidenced by increased safety signals, which we didn't see in the total population. But to address Dr. Nissen's concern, I would suggest that we look in another subgroup to see if that bears out. But overall,

again, I think safety in the overall group suggested that these were not highly significant. Thank you.

DR. LEWIS: Dr. Rossert, I'd like to encourage you to make a comment on any of our discussion questions we have mentioned so far. I'm not trying to put you on the spot.

DR. ROSSERT: Thank you very much, Dr. Lewis. I'm the industry representative, and my comment will be around the size and quality of the study that has been done. It has been mentioned, 8,000 patients. I think it's something to keep in mind. And also Dr. O'Connor mentioned the severity of the patients in people with very low ejection fraction. There is severe heart failure who have very high [indiscernible]. These would be my two comments.

DR. LEWIS: Thank you, Dr. Rossert. I appreciate it.

I'll try to summarize question 4. We've got a little bit of a divided group. I think that everybody feels that pharmacokinetic-based dosing,

if the drug were to be approved, would be an important component of safety. The assay that was used in the study was the one that was validated, and at least most panelists supported that assay.

Dr. Nissen, which was also echoed by some others, said there are still safety and posology concerns, drug-drug interactions concerns, catching a patient at the level at the same time that a doctor starts a drug that could potentially increase drug concentration, which has been shown to be associated with increased toxicity is a concern. On the other hand, others felt that in the large 8,000-patient study worldwide, this must have happened. I guess we don't know if it happened and bad things happened, or it happened and not bad things happened.

I think the significance of the biomarker measures -- which I believe were a disconnect from phase 2, by the way -- the troponins and the CPK-MB elevations, some were not troubled by those because they are elevated in other populations and not necessarily as prognostic as they would be in

perhaps a different population. I think that, overall, there was a large degree of support for some sort of pharmacokinetic monitoring.

We will now move on to the next question, which is a voting question. Rhea Bhatt will provide the instructions for the voting.

Rhea?

MS. BHATT: Thank you, Dr. Lewis.

Question 5 is a voting question. Voting members will use the Adobe Connect platform to submit their vote for this meeting. After Dr. Lewis has read the voting question into the record, and all questions and discussion regarding the wording of the vote question are complete, Dr. Lewis will announce that voting will begin.

If you are a voting member, you will be moved into a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button, the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote"

choice selected.

Please note that you do not need to submit or send your vote. Again, you only need to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, Dr. Lewis will go down the roster, and each voting number will state their name and their vote into the record. You can also state the reason why you voted as you did, if you wish to, however, you should also address any subparts of the voting question.

Are there any questions about the voting process before we begin?

(No response.)

DR. LEWIS: Okay. I will read question 5.

Do the benefits of omecamtiv mecarbil outweigh its risk for the treatment of heart

failure with reduced ejection fraction? Provide a rationale for your vote. If you voted yes, comment on whether pharmacokinetic-based dosing is essential for the safe and effective use. If you voted no, provide recommendations for additional data or analyses that may support a positive benefit-risk assessment.

Are there any issues or questions about the wording of the question?

(No response.)

DR. LEWIS: If there are no questions or comments concerning the wording of the question, we will now begin voting on question 5.

MS. BHATT: We will now move voting numbers to the voting breakout room to vote. There will be no discussion in the voting breakout room.

(Voting.)

MS. BHATT: Voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

MS. BHATT: The vote results are displayed.

I will read the vote totals into the record. Dr. Lewis will go down the list, and each voting number will state their name and their vote into the record. You can also state the reason why you voted as you did, if you wish to. You should also address any subparts of the voting question.

There are 3 yeses, 8 noes, and zero abstentions.

DR. LEWIS: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote, if you wish to. We'll start with the first person on the list, Dr. Bairey Merz.

DR. BAIREY MERZ: Thank you. Noel Bairey Merz. I voted yes. For the rationale, this is a novel mechanism but an old-fashioned contractility squeeze drug that are known to have narrow benefit to toxicity ratios. The overall trial, as designed with the FDA, had a small benefit and similar risks compared to placebo, and therefore I say yes on the basis of need. My personal experience, as well as

the data presented today, that up to half of severe heart failure patients are intolerant of guideline-directed medical therapy to the max.

I also strongly suggest that there be assays required for keeping this as safe as the clinical trial was conducted, and I anticipate, given all of the barriers, this likely will be used in a small subset by advanced heart failure cardiologists offering, at least to me, a little more bit of safety. Thank you.

DR. LEWIS: Thank you, Dr. Bairey Merz. You're not proposing that it be limited to heart failure specialists in some way, but you're projecting that it might be.

DR. BAIREY MERZ: No, I am not. But again, in my experience, it's the centers of excellence, as well as the larger groups, that have the subspecialties that can deal with the assays, the authorization, the patient phone calls, et cetera. This is my experience. Thank you.

DR. LEWIS: Thank you. Thanks for the clarification.

Dr. O'Connor?

DR. O'CONNOR: Dr. Chris O'Connor. I voted yes, and like cancer patients, I think this high-risk heart failure patient population represents an important unmet need. And like oncology drug approval, which often occurs for subgroups within the overall clinical trial, this trial represented one of the largest clinical trials ever done in heart failure, with a large number of severe heart failure patients.

Therefore, I believe that a path was constructed in which one could go forward safely and with enhanced efficacy by stating that the patient population for the use of this drug would be those with an ejection fraction, for example, less than 25 in sinus rhythm and with pharmacokinetic-guided dosing. Therefore, it may be a narrow path, but I think it's a path that would afford a lot of benefit to this high-risk patient population. Thank you.

DR. LEWIS: Thank you, Dr. O'Connor.

Dr. Kovesdy?

DR. KOVESDY: Yes. Csaba Kovesdy, and I voted no because the treatment effect and the benefits of this drug in this population were small and were limited to the heart failure outcome with no benefit on cardiovascular mortality or on any secondary outcomes, including subjective outcomes and quality-of-life benefits, and also with the potential that there may be potential harm in certain subgroups.

The level of evidence afforded by this single clinical trial does not give me sufficient comfort to state that the benefit outweighs the risk. Thank you.

DR. LEWIS: Dr. Kovesdy, do you have any recommendations for additional data or analyses?

DR. KOVESDY: I would say probably a second large randomized-controlled trial, maybe targeting specifically the groups that are supposedly benefiting from this.

DR. LEWIS: Okay. Thank you.

Dr. Gillen?

DR. GILLEN: Yes. Daniel Gillen. I voted

no for many reasons that I've already stated. I believe that the overall point estimate is a modest effect, again, primarily driven by HF events and limited to no signal on cardiovascular mortality. I do have issues with the subgroup analysis, if that's pointed to as the primary reason for approval, and lack of prespecification in terms of, A, an a priori hypothesis in that subgroup.

Going forward, I do believe that that subgroup should be validated in a future trial. If it were to be done, then I would suggest excluding the AFib population given what we've seen and potential harm that we've seen in those patients. Thank you.

DR. LEWIS: Thank you.

Dr. Moliterno?

DR. MOLITERNO: Hi. David Moliterno. I also voted no. When I considered the benefits, I thought they were more singular, and that being a modest reduction primarily limited to fewer outpatient visits. So I agree this is a severe heart failure population, and you can liken it to

oncology patients -- and no disrespect to anyone on the call -- but I wouldn't vote for the drug either if it were for oncology if it were only to reduce outpatient visits and not affect quality of life, and not affect mortality.

So I think there's no fault of the investigators or the sponsor, but new drugs are available that weren't at that time, and that a very small portion, under 1 in 5, received, for example, ARNi, and that a substantial portion of patients still had a reasonable blood pressure, the 115 and 116 range systolically, meaning they probably could have had other therapies. I think all these things in totality led me to vote against the drug, and that I do still have some concerns about its safety.

I know studies are timely and expensive. I don't think it would need to be a very large study. It would need to be a respectable size. It would be one in a similar cohort, but it would be restricted to those with an ejection fraction less than 30 percent. That ejection fraction would need

to have been measured probably within the last month or two, certainly without an interval of substantial times at therapies or the patients could have changed. It would need to be in sinus rhythm, and preferably on optimal guideline-directed medical therapy, including, just as an example again, ARNi. That's all my comment. Thank you.

DR. LEWIS: Thank you.

Ms. Dunn?

MS. DUNN: Yes. Debra Dunn. I will admit this is a hard one. I am a heart failure patient myself, and I do work with numerous heart failure patients and transplant patients. I personally know the quality of life diminished, and I know all of the different types of resources out there, which are somewhat limited and do have risks. All of them have risks, one form or another.

So I did have to step back. I voted no, then I voted yes, but I did vote yes. I feel that, hopefully, with the FDA's expertise and help, and the sponsor, that maybe we could refine something a

little bit here. My big concern is the clinicians who are administering. I think that they need to certainly evaluate their patient, and dig deep, and know if this is really a good drug for them.

I think it does give hope to patients, and we are progressing with medical care by passing this, or passing it in time, to give an option for quality of life. I would say that the pharmacokinetics definitely would play an important part in this, and I did defer back to 8,256 patients. I'm not happy that it was a small number of women, but I do feel that that was a broad spectrum like my colleagues on the panel had discussed at length also.

Ejection fraction, I'm a heart patient. I actively have echocardiograms, and it usually is a 5 number, and I do agree with that, and maybe reducing that to the 25. What I've heard was no harm to renal, and a lot of the drugs that we do take could possibly have renal effects on us. I heard some positive things. I'm encouraged. I hope that we keep advancing here, so thank you for

the opportunity.

DR. LEWIS: It's Julia Lewis. I voted no. Actually, the size of the trial, in a way, concerned me, that a more positive effect could not have been found. Both the effect size in the heart failure part of the composite was very modest. There was no effect despite the powering and the large number of events -- and, by the way, a really well-done trial with great follow up -- and there was no benefit, no benefit and quality of life or any of the other secondary outcomes.

I think the trial opens more hypothesis-generating questions. Who is it harming? Who is it helping? How do we identify those people safely? I'm not confident that the not prespecified and not particularly rationalized subgroups that were identified reassure me.

I think that it does leave open -- also, again, it's a first-in-class drug, and I think it's very different than it being the second or third in a class. Also, I will say the SGLT2 inhibitors -- again, not any fault of this trial

that it had low penetration, but many of the limitations of the other heart failure drugs aren't present with those drugs.

So I would encourage a study perhaps using the hypothesis-generating data. If you enrich your population for the lower ejection fraction, if you eliminate people who are not in sinus rhythm, do pharmacokinetic modeling as you would do it in the real world, and assure a certain penetration of SGLT2 inhibitors, that would be an excellent second study to be done to support this first-in-class drug.

Dr. Blaha?

DR. BLAHA: Yes. Thank you, Julia.

This is Mike Blaha, Hopkins. I voted no. For the record, to make it clear, I was responding to the question as phrased, which was, do the benefits of omecamtiv mecarbil outweigh its risks for the treatment of heart failure with reduced ejection fraction? This is a very broad prompt, which I think is appropriate given the very broad label put forth by the sponsor.

The sponsor stated that this drug might be indicated to reduce cardiovascular death or heart failure in patients with heart failure reduced ejection fractions. I vote no specific to that prompt because I think that's far too broad of a claim and far too broad of a label for the data that we saw, and I basically say that because of the small effect that we saw on the primary endpoint that was driven by heart failure hospitalizations, or actually, in that case, even urgent heart failure outpatient visits or ER visits that did not result in hospitalization. All the data did not meet the FDA's prespecified criteria for substantial evidence supporting approval of this drug.

I agree with Dr. Lewis that the large trial here is both reassuring for safety, but also raises some questions about why we don't see greater efficacy. That's a very large number of patients powered for cardiovascular mortality, and we didn't see any signal on cardiovascular mortality at all; in fact, in my view, a little bit of disappointing

outcomes as far as quality of life, which I would have loved to see improved with a drug with this mechanism of action.

It wouldn't seem like you would need a very long follow-up to see a benefit with this mechanism of action. I would have thought that if this mechanism of action, or if this mechanism of action were strongly supported in this trial, you would see a benefit early given the increased contractile function. In fact, with drugs like the SGLT2 inhibitors, we see quality-of-life improvement and heart failure hospitalization benefits very early after initiation.

So the absence of that large effect and only seeing a small effect driven by urgent heart failure, but it's no effect on mortality, led me to vote no for this question. But I actually have quite a bit of interest in the very low ejection fraction group, particularly patients maybe with a very low ejection fraction, let's say, less than 25 percent, with an additional risk factor like many of the folks would have, for example, high BNP

or another one that was tested by the sponsor. I think that's a very intriguing group to specifically target a therapy like this in the future for reducing heart failure hospitalization, which becomes a crippling outcome for patients in that group.

So I would strongly encourage there to be a dedicated trial in that specific patient group with patients with severely reduced ejection fraction in the absence of AFib or AFlutter. I would love to see such a trial have a dedicated core lab read of the echocardiograms so we all can be quite certain about this start phenotype where we think this drug might have benefits. And I do agree that, likely, this drug, should it reach the marketplace, would be mostly used by heart failure specialists who could become quite savvy with pharmacokinetic dosing, and I think do that quite safely.

So as you can see, my vote is no, but with several caveats about specific subgroups of interest for future study or future consideration. Thank you.

DR. LEWIS: Thank you.

Dr. Thadhani?

DR. THADHANI: Thank you. Ravi Thadhani, and I voted no for the reasons my colleagues have stated. I believe the risks outweigh the benefits as stated.

That said, I want to point out a few items, which gets to the if you voted no recommendations. One, I don't think we can dismiss the fact that this is one of the largest studies in its kind. I want to commend certainly the sponsor for conducting this in the way it did.

I also believe that we can't dismiss the data from these subgroups; and yes, in typical subgroup analysis, we are rather careful and weary. Dr. Solomon laid out the rationale for some of the subgroups, which I was moved by. These are very large subgroups in which significant signal was evident, and therefore cannot be dismissed.

When we think about the challenges here with regards to AFib ejection fraction cutoffs and PK, I do believe that some of this can actually be put

into more focus. And as a result, clarity with the agency and discussions with the sponsor can get to a population that would benefit and, hence, then have the benefit outweigh the risks.

Apropos to this was the discussion we had on atrial fibrillation and whether somebody had a baseline, and whether they developed it. I think clarification on some of those parameters; again, in addition to PK dosing, as well as ejection fraction cutoffs; with the discussion with the agency, again, to provide the guardrails, may provide a pathway forward. Thank you.

DR. LEWIS: Dr. Nissen?

DR. NISSEN: Steve Nissen here. As mentioned by others, the benefits here were small, and in my view --

DR. LEWIS: Dr. Nissen, could you read your vote?

DR. NISSEN: Oh, I'm sorry. I voted no. Thank you. I voted no. As mentioned by others, the benefits were small, and if you remove the less severe events, that is the urgent outpatient

visits, no longer statistically significant. This is really insufficient for a single trial.

Now, let me compliment the sponsor on doing a very large and comprehensive trial, but I want to remind everybody about the vesnarinone story. What happens when you have a single trial is it needs to be replicated. Was there supporting data? I would have been encouraged if there was a quality-of-life benefit.

Why did patients want to take medications? Well, they certainly want to stay out of the hospital, they certainly don't want to die, but they want to feel better, and there wasn't any evidence, despite the 8,000 patients studied here, of a meaningful quality-of-life benefit, and that makes this less attractive.

There were some deficiencies in the study design that need to be corrected in a new trial. Using a year-old echo [indiscernible - audio gap] in this very dynamic population is really not acceptable. They need to have an echo contemporaneously, and could be done locally, but

it has to be read out within a few weeks to a month of when they're actually enrolled. Old echos may not reflect the current situation.

Approving a drug for a subgroup of a subgroup; that is having a low ejection fraction and not having atrial fibrillation is just for me a bridge too far. I have concerns about the posology, I have concerns about using an assay that was not used in the clinical trial, and I have concerns about the background therapy. I do not find it plausible that people that had blood pressures of over 120 could not tolerate full doses of ACEs or ARBs or ARNi's. So in a new trial, I would want to see very clear efforts to get people on national medical therapy, including, if indicated, an ARNi.

Lastly, the safety issues, including troponin and CKMB, are not trivial in my view. When you see a 10-fold increase in enzymes, that to me is very likely myocyte injury. So if the posology is wrong, and people get excess exposure, the risk of injury is not ruled out. So this is a

good, big hypothesis-generating study that might lead to a better trial done in a more focused population, without atrial fibrillation and with a low enough ejection fraction to see clinical benefits. Thank you.

DR. LEWIS: Thank you.

Dr. Wang?

DR. T. WANG: Hi. Thomas Wang. I voted no. I also want to start by commending the sponsor both for the development of this new class of medication and also for their thoughtful development program.

I certainly could see a role for this medication, especially in the subset of patients who aren't fully served by existing therapies. I also want to note that I think I was more persuaded by the data on the hard heart failure than simply my colleagues. I think the data showed by both the sponsor and the FDA indicate that the vast majority of the heart failure events that were part of the heart failure endpoint were hard hospitalizations and not just urgent visits, and thus the reduction was likely driven by these events.

But that said, the reduction was modest, as has been pointed out. So leading to the reasons for my no vote, I think the issue is whether there's enough here to move ahead on the basis of what we've seen from this single clinical trial, and given the modest potential benefit and the residual uncertainties, I'm not sure that's justified yet.

So like many of my colleagues, I do believe that there'd be value in a true confirmatory trial likely targeted at patients with very low EF. And as also noted, I think the confirmatory trial may not be as large or as long as the prior trial, given the more focused questions being addressed and the more focused population. Thank you.

DR. LEWIS: Thank you.

I will now try to summarize the reasons for the votes. I think that the votes that were in favor of the single trial leading to label were really emphasizing that this is a very sick, unmet population not unlike very ill cancer patients; that this is somewhat a novel mechanism, but on the

other hand an old-fashioned squeeze drug that commonly have narrow margins, and that half of heart failure patients are currently intolerant to many of the medications that are available to them now.

Again, I think whether you voted yes or no, everybody was impressed with the size of the trial, the quality of the follow-up, and the efforts of the sponsor folks to develop a novel drug and to conduct such a wide-ranging trial.

I think the overwhelming support, if the drug was approved, was for continuing the pharmacokinetic monitoring and the anticipation that its use would be in the hands of heart failure specialists in a natural system.

The no votes I think had a series of things that were in common with them: again, the small treatment effect size despite a very large trial; the absence of the cardiovascular mortality benefit; and what's even more troubling to many of the panelists was that there was no quality-of-life improvement and a modest effect on heart failure

hospitalization.

The other thing -- let me glance to make sure I haven't missed anything before I go in to what the suggestions were -- is one of the panelists did vote no because of the aggressive label, I guess implying that perhaps if it was a less aggressive label, he might have voted differently. But it did include decreased cardiovascular death, and it was a very broad claim for such a small effect, and then again, concerns about benefit, quality of life, and CV death.

The subgroup data and subgroup of a subgroup data were just not compelling enough for many of the panelists, and if you removed the urgent visits, although they were the minority visits, you lost your statistical significance for the heart failure outcome.

There were some suggestions, in a way, for a new trial; criticism of how this trial was conducted; and old echos as being acceptable, suggesting that really contemporaneous echos with the time of enrollment would be the best; the

subgroup of the subgroup showing benefit, the low ejection fraction with no AFib; was the bridge too far for a first-in-class drug; and still a deep concern with the mean blood pressures being above 115; that there wasn't better penetration for even the available background therapy at the time, and the concern for evidence of myocardial toxicity from the troponin and CPK [indiscernible].

Again, I think people were suggesting, that voted no, that an enriched population could be done in a much smaller study over a shorter period of time since it would be an enriched population, and that data from this study could be used as hypothesis-generating data to look at the low ejection fraction patients who did not have AFib or flutter, and, again, a strong support for PK monitoring and a parallel validation process for that as well.

I think that summarizes most of this. Before we adjourn, are there any last comments from the FDA?

DR. STOCKBRIDGE: This is Norman

Stockbridge. I just want to thank the committee for its work today, the issues that got discussed, and the insights that got offered. I think you've given us a number of things that warrant at least internal discussion and probably some other analyses that can be done.

I want to point out a very interesting suggestion that isn't even product-specific here. There was some discussion about when we should rely on phase 2 results to support a phase 3 result, which you wouldn't have even tested this if the phase 2 data hadn't been positive. I think that warrants some further consideration on our part, too. But in general, it's been a very productive and helpful session, and I very much appreciate everybody's time and effort.

Adjournment

DR. LEWIS: I want to, once again, thank the FDA for their diligent work and thoughtful presentation; the sponsor for a well-conducted trial and presentation; the public for sharing their views; and, of course, our panel for

benefiting the public with their expertise.

We will now adjourn the meeting. Thank you.

(Whereupon, at 4:43 p.m., the meeting was adjourned.)