UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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CIRCULATORY SYSTEM DEVICES PANEL ADVISORY COMMITTEE MEETING

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V-WAVE VENTURA INTERATRIAL SHUNT SYSTEM

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December 3, 2025

09:00 a.m. EST

Virtual

Transcript Produced By:

ACSI Translations

1025 Connecticut Avenue, NW, Suite 1000, Washington, DC 20036

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Participants

Richard Lange, M.D., M.B.A.	President, Texas Tech University, Health Sciences Center El Paso El Paso, TX	Temporary Voting Chair
James Blankenship, M.D.	Professor of Medicine, Director of Cardiac Catheterization Laboratory and Director of Division of Cardiology, University of New Mexico Albuquerque, NM	Voting Member
Mladen I. Vidovich, M.D.	Professor of Medicine Division of Cardiology, Department of Medicine, University of Illinois at Chicago Chicago, IL	Voting Member
David D. Yuh, M.D., FACS, FACC	Cardiothoracic Surgeon Division of Cardiac Surgery Brown University Health Providence, RI	Voting Member
Eric Leifer, Ph.D.	Mathematical Statistician, Office of Biostatistics Research, National Heart, Lung, and Blood Institute Bethesda, MD	Temporary Voting Member
Janet T. Wittes, Ph.D.	Principal, Wittes LLC, Affiliate Professor Florida Atlantic Washington DC	Temporary Voting Member
Paul J. Hauptman, M.D.	Dean and Professor at University of Nevada, Reno School of Medicine Reno, NV	Temporary Voting Member
Christopher O'Connor, M.D.	President, Inova Schar Heart and Vascular, Primary Academic, Inova Schar Heart and Vascular Falls Church, VA	Temporary Voting Member
Antoinette Gomes, M.D.	Professor of Radiology & Medicine, David Geffen School of Medicine at UCLA Los Angeles, CA	Temporary Voting Member
Vakhtang Tchantchaleishvili, M.D., FASC	Associate Professor, Department of Cardiac Surgery, Thomas Jefferson University	Temporary Voting Member

	Philadelphia, PA	
Clyde W. Yancy, M.D., M.Sc., MACC, FAHA, MACP, FHFSA, FRCP, FASPC (Hon.), FPCNA (Hon.)	Vice Dean, Health Equity Magerstadt Professor, Professor of Medicine, Professor of Medical Social Sciences, Chief, Division of Cardiology, Northwestern University, Feinberg School of Medicine, Associate Director, Bluhm Cardiovascular Institute, Northwestern Memorial Hospital, Deputy Editor, JAMA Cardiology Chicago, IL	Temporary Voting Member
Robert Yeh, M.D., M.Sc., M.B.A.	Section Chief, Interventional Cardiology, Beth Israel Deaconess Medical Center; Director, Smith Center for Outcomes Research, Katz-Silver Family Professor of Medicine, Harvard Medical School Boston, MA	Temporary Voting Member
Mitchell Krucoff, M.D., F.A.C.C.	Professor, Medicine/Cardiology, Duke University Medical Center, Director, Cardiovascular Devices Unit and Director, eECG Core Laboratories, Duke Clinical Research Institute Durham, NC	Temporary Voting Member
Richard Page, M.D.	Dean, Larner College of Medicine, Professor of Medicine (Cardiology), Chief, Medical Affairs Officer, University of Vermont Burlington, VT	Temporary Voting Member
Amit Shanker, M.D.	Attending Physician, St. Lawrence Health System Potsdam, NY	Temporary Voting Member
Dharam J. Kumbhani, M.D., SM	Professor Section Chief, Interventional Cardiology, University of Texas Southwestern Medical	Temporary Voting Member

	School, Internal Medicine/Cardiology Dallas, TX	
Wes Cetnarowski, M.D.	Interim CMO – B. Braun Medical, Inc. Senior Consultant & Fractional/Contract Resource Bethlehem, PA	Industry Representative (IR)
Kathleen O'Sullivan-Fortin	Co-Founder, ALD Connect, Inc Wenham, MA	Consumer Representative (CR)
Debra Dunn	WomenHeart Champion – Mayo Clinic, Support Group Lead, Patient Advocate Washington DC	Patient Representative (PR)
Bram Zuckerman, M.D.	U.S. Food and Drug Administration Silver Spring, MD	Office Director CDRH/OPEQ/OHTII
Kendra L. Brooks, MHA	U.S. Food and Drug Administration Silver Spring, MD	Designated Federal Officer

Table of Contents

Call to Order

00:06:28 Dr. Lange: I would like to call this meeting of the Circulatory Systems Devices Panel to order. It is now 9:00 a.m. I'm Dr. Richard Lange, the Temporary Chairperson of this Panel. I have expertise in interventional cardiology, adult congenital heart disease. I'm currently President at Texas Tech Health Science Center El Paso, where I practice in general cardiology. I note for the record that the voting members present constitute a quorum as required by 21 C.F.R., part 14. I would also like to add that the panel members participating in today's meeting have received training in FDA device law and regulations. Please be aware that this meeting is being recorded and will be accessible to the public, including the Zoom chat.

00:07:11 For today's meeting, the Committee will discuss, make recommendations, and vote on information regarding the premarket approval application, the PMA, sponsored by V-Wave, Inc. for the V-Wave Ventura Interatrial Shunt System, which is a first-of-a-kind device permanent implant designed to shunt blood from the left to the right atrium to improve symptoms in patients with advanced chronic heart failure.

00:07:37 The proposed indication for use statement is as follows: The V-Wave Ventura Interatrial Shunt System is indicated for New York Heart Association Class III heart failure patients who remain symptomatic despite guideline-directed medical therapy and have a left ventricular ejection fraction of less and/or equal to 40%, and who are judged by a Heart Team to be appropriate for shunt therapy in order to reduce the risk of hospitalization for heart failure. The device is proposed to be used in patients who have already been treated with all other device and drug treatment options appropriate for them.

Introduction of Panel/Committee

00:08:12 Before we begin, I would like to ask our distinguished Committee members and FDA representatives attending virtually to introduce themselves. Committee

members please turn on your video monitors if you have not already done so and unmute your microphone before you speak. When I call your name, please state your area of expertise, your position, and affiliation. We'll start with Dr. Blankenship.

00:08:37 Dr. Blankenship: Good morning. My area of expertise is interventional cardiology. I'm currently Director of the Division of Cardiology at the University of New Mexico and Director of the Cardiac Catheterization Laboratory there in Albuquerque, New Mexico.

00:08:53 Dr. Lange: Thank you, Jim. Dr. Vidovich.

00:08:57 Dr. Vidovich: Good morning. I'm an Interventional Cardiologist. I'm currently Professor of Medicine at the University of Illinois at Chicago and I'm Chief of Cardiology at the Jesse Brown VA Medical Center in Chicago.

00:09:09 Dr. Lange: Thank you, Mladen. Dr. Yuh.

00:09:11 Dr. Yuh: Good morning, everybody. I'm an Adult Cardiac Surgeon at Brown University. My expertise is primarily in valvular interventions, but I have significant past experience in surgical therapies for end-stage heart failure. Thank you.

00:09:27 Dr. Lange: Thank you, David. Dr. Leifer.

00:09:29 Dr. Leifer: Good morning. My name is Eric Leifer. I'm a Mathematical Statistician at the National Institutes of Health. I have a lot of experience in heart failure clinical trials.

00:09:40 Dr. Lange: Thank you, Eric. Dr. Wittes.

00:09:42 Dr. Wittes: Yes. I'm Janet Wittes. I'm a Statistician currently mostly consulting, but I am a Faculty Member of the BAIM Institute and Affiliate Professor of Epidemiology at Florida Atlantic University. [Indiscernible - 00:09:58] in DC.

00:09:58 Dr. Lange: Thank you. I'm sorry. Thank you, Janet. My apologies. Dr. Hauptman.

00:10:04 Dr. Hauptman: Yes, good morning. I'm a Heart Failure and Transplant Cardiologist by training and currently serve as Dean at the University of Nevada, Reno School of Medicine and Chief Academic Officer at Renown Health.

00:10:15 Dr. Lange: Thank you, Paul. Dr. O'Connor.

00:10:18 Dr. O'Connor: Good morning. I'm Chris O'Connor. I'm trained as a Heart Failure Cardiologist and currently President of the Inova Schar Heart and Vascular Institute in Northern Virginia.

00:10:28 Dr. Lange: Thank you, Chris. Dr. Yancy.

00:10:30 Dr. Yancy: Good morning. Clyde Yancy. My expertise is in heart failure and cardiovascular disease prevention. I'm Professor and Chief of Cardiology at Northwestern University Feinberg School of Medicine, Vice Dean of the same institution, and a former Chair of this Cardiovascular Devices Panel for the FDA.

00:10:46 Dr. Lange: [It] Just proves you never really got off of it, Clyde. Dr. Yeh.

00:10:52 Dr. Yeh: Good morning. Robert Yeh. I am the Section Chief of Interventional Cardiology at Beth Israel Deaconess Medical Center where I also direct the Richard and Susan Smith Center for Outcomes Research.

00:11:00 Dr. Lange: Thank you, Bob. Dr. Krucoff.

00:11:04 Dr. Krucoff: Good morning. My name is Mitch Krucoff. I'm an Interventional Cardiologist, Professor of Medicine at Duke University in Durham, North Carolina, and Director of the Cardiovascular Devices Unit at the Duke Clinical Research Institute.

00:11:18 Dr. Lange: Thank you, Mitch. Dr. Page.

00:11:21 Dr. Page: Morning. My name is Richard Page. I'm a Clinical Cardiac Electrophysiologist, still practicing non-invasive. I'm Professor of Medicine, Dean of

the Larner College of Medicine and Chief Medical Affairs Officer for the University of Vermont.

00:11:36 Dr. Lange: Yeah, talk about distinguished--

00:11:37 Dr. Page: And a former Chair of this Panel.

00:11:39 Dr. Lange: I was going to say we've got two former Chairs, so this is a really distinguished Panel. Thank you, Rick. Dr. Tchantchaleishvili.

00:11:47 Dr. Tchantchaleishvili: Good morning. I'm a Cardiac Surgeon and Associate Professor of Surgery at Thomas Jefferson University in Philadelphia and my expertise is adult cardiac surgery, heart failure surgery, and cardiac transplantation.

00:11:58 Dr. Lange: Thank you, Vakhtang. Dr. Gomes?

00:12:01 Dr. Gomes: Good morning. I'm Antoinette Gomes. I'm a Professor of Radiology and Medicine at UCLA Medical Center in Los Angeles. I'm a Trained Cardiovascular Interventional Radiologist and my primary activities right now are in interventional radiology and non-invasive cardiac imaging.

00:12:18 Dr. Lange: Thank you, Antoinette. Dr. Shanker.

00:12:21 Dr. Shanker: Thank you for having me. My name is Amit Shanker. I'm a Trained Cardiac Electrophysiologist and Attending Physician at St. Lawrence Health System in upstate New York.

00:12:29 Dr. Lange: Thank you, Amit. Dr. Kumbhani.

00:12:33 Dr. Kumbhani: Hi, good morning. My name is Dharam Kumbhani. I'm the Section Chief for Interventional Cardiology at UT Southwestern in Dallas. I'm honored to be here.

00:12:42 Dr. Lange: Thank you, Dharam. We have our Industry Rep, Wes Cetnarowski. Wes?

00:12:49 Dr. Cetnarowski: Good morning. Yep. Wes Cetnarowski. Chief Medical Officer for B. Braun Medical at this point and the Industry Rep on the Panel. Thank you.

00:12:57 Dr. Lange: Terrific. Ms. Fortin?

00:12:59 Ms. O'Sullivan-Fortin: Hi, I am Kathleen O'Sullivan-Fortin. I am-- Today I am the Consumer Rep on this Panel. I'm the Co-Founder and Patient Advocate at a rare disease organization, ALD Connect.

00:13:11 Dr. Lange: Thank you, Kathleen, for joining us. Ms. Dunn.

00:13:15 Ms. Dunn: Good morning. My name is Debra Dunn and I am a 24-year heart failure patient. I am a National Patient Advocate, trained by WomenHeart at Washington DC and I am on my eighth ICD device and I've had many, many long journeys with being a heart failure patient over 24 years.

00:13:38 Dr. Lange: So, Debra, thank you for joining us as our Patient Representative.

00:13:42 Ms. Dunn: Thank you.

00:13:43 Dr. Lange: Dr. Zuckerman.

00:13:45 Dr. Bram Zuckerman: Good morning. I am Bram Zuckerman, Director, FDA Office of Cardiovascular Devices. Thank you.

00:13:52 Dr. Lange: Thank you. Dr. Neubrander.

00:13:58 Dr. Neubrander: Good morning. I'm Rachel Neubrander. I'm the Division Director for the Division of Circulatory Support, Structural and Vascular Devices in the Office of Cardiovascular Devices at FDA.

00:14:09 Dr. Lange: Thank you. And then Ms. Brooks.

00:14:12 Ms. Brooks: Good morning. I'm Kendra Brooks. I'm the Designated Federal Officer for this meeting.

00:14:17 Dr. Lange: Thank you. Once again, I'd like to thank everybody. I'm going to go off script for just a moment. One of the values of the Panel is not only getting expertise but we're colleagues and we work together with similar goals for advancing healthcare for our patients with heart disease. We lost a colleague this past week, Mike Briscoe, and Paul Hopman suggested, and I really appreciate it, that we just spent a moment of silence in recognition of his contribution as a colleague and his contribution to the field of heart failure. So, I'm going to ask that we take a ten-second moment of silence to recognize him and his contribution. Thank you very much, and Paul, thanks for that suggestion by the way. [I] appreciate that.

00:15:10 Once again, I want to remind all attendees to mute their microphones until they're called upon to speak. If you have a question, please use the raised-hand feature and unmute your microphone and I will call on you. Ms. Kendra Brooks, the Designated Federal Officer for today's Circulatory System Devices Panel will now provide the Conflict of Interest Statement and some introductory remarks. Kendra, it's to you.

Conflict of Interest Statement

00:15:34 Ms. Brooks: Good morning. I will now read the Conflict of Interest Statement. The Food and Drug Administration is convening today's meeting of the Medical Devices Advisory Committee under the Federal Advisory Committee Act, FACA, of 1972. The Medical Devices Advisory Committee will discuss and make recommendations on information regarding the benefit-risk profile for the premarket approval application, PMA, for the V-Wave Ventura Shunt System. The Agency is seeking Panel input on the interpretation of the clinical data, indications for use, labeling and post-approval studies.

00:16:24 With the exception of the Industry Representative, the members of the Committee are either Special or Regular Government Employees and are subject to federal conflict of interest laws and regulations. Accordingly, FDA has reviewed the financial interests of the Committee members for compliance with federal ethics and

conflict of interest laws. We have screened the members for potential financial conflicts of interest related to today's meeting agenda, both their own interest and those that are imputed to them, including those of their spouses, minor children, and employers. Based on the agenda for today's meeting and all financial interests reported by the Committee members, no conflict of interest waivers under 18 U.S.C., subsection 208, have been issued in connection with this meeting.

00:17:26 Doctor Wes Cetnarowski of B. Braun Medical is participating in the meeting as a Non-Voting Industry Representative acting on behalf of regulated industry. Consistent with Commissioner Makary's April 17, 2025, statement, FDA is only including Industry Representatives in Advisory Committee meetings where required by statute. FDA is required to include an Industry Representative in today's meeting under 21 U.S.C., subsection 360c(b)(2). Industry Representatives are not appointed as Special Government Employees nor are they Regular Government Employees. Industry Representatives serve as Non-Voting Members of the Committee. Non-Voting Industry Representatives represent all regulated industry, and not a particular association, company, product, or ingredient, and bring general industry perspective to the Committee. Under FDA regulations, although a Non-Voting Member serves in a representative capacity, the Non-Voting Member shall exercise restraint in performing such functions and may not engage in unseemly advocacy or attempt to exert undue influence over the other members of the Committee.

00:19:03 Kathleen O'Sullivan-Fortin is serving as the Consumer Representative for this Committee. Consumer Representatives are appointed Special Government Employees and are screened and cleared prior to participation in the meeting. They are Non-Voting Members of the Committee.

00:19:24 FDA asks that all other participants, including the Open Public Hearing speakers, advise the Committee of any financial relationship that they have with any affected firm, its products and, if known, its direct competitors. We would like to remind the

members that if the discussions involve any products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from the discussion and their exclusion will be noted for the record.

00:20:07 A copy of this statement will be available for review and will be included as part of the official transcript.

00:20:14 Please be advised that all participants should turn on their cameras and mute their microphones. If you wish to speak, use the raised-hand feature at the bottom of the Zoom screen and wait to be acknowledged by the Chair. Once acknowledged, you should unmute your microphone. When you are done speaking, click the raised-hand button to lower the hand and mute yourself again.

00:20:40 Likewise, use this feature to notify Dr. Lange when you need to step away from your computer and be sure to turn your camera off. Please unmute your microphone before you speak and mute it again when you are done.

00:20:58 To assist the transcriber with identifying who is speaking, please be sure to identify yourself each time that you speak. For press inquiries, please contact the HHS Press Room at www.hhs.gov/press-room/index.html or at 202-690-6343. Thank you.

V-Wave Presentation

00:21:37 Dr. Lange: Well, thank you, Kendra, to model that. I'm Rick Lange and I will identify that we will now proceed to the sponsor's presentation. I would like to invite the sponsor to begin and I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair. That would be me. The sponsor will have 90 minutes to present and the sponsor may now begin their presentation.

00:22:11 Dr. Abraham: Good morning, Chair, members of the Panel and members of the FDA. My name is Bill Abraham and I'm a Professor of Medicine at the Ohio

State University and Chief Medical Officer at V-Wave. We're pleased to be here today to share our data supporting the Ventura Interatrial Shunt System. During this presentation, we'll demonstrate that the totality of evidence provides reasonable assurance of safety and effectiveness, resulting in a highly favorable benefit-risk profile, supporting approval of this novel device.

00:22:50 We're seeking a limited indication for New York Heart Association Class III heart failure patients who are persistently symptomatic despite guideline-directed medical therapy and have a left ventricular ejection fraction of 40% or less, which is usually referred to as HFrEF, and who are judged by a Heart Team to be appropriate for shunt therapy. In this population, the Ventura shunt was very safe and shown to reduce the risk of heart failure events, including heart failure hospitalizations. As you will see during this presentation, the reduction in heart failure hospitalizations is supported by the concordant effects of the device on all heart-- Heart failure clinical outcomes, including terminal events, namely death, cardiac transplantation, and LVAD implantation, and all heart failure hospitalizations and all outpatient worsening heart failure events.

00:23:56 In support of this indication today, we will present the following. I will provide the Committee with an overview of our presentation and outline the design of the RELIEVE-HF trial. Next, Dr. Gregg Stone will present the safety and effectiveness results. Then, Dr. Michael Zile will present the mechanistic basis for the differential effects of shunt treatment in patients with HFrEF versus HFpEF. Importantly, Dr. Zile will show you published echocardiographic results from RELIEVE-HF that demonstrate a mechanism by which shunting improved clinical outcomes in HFrEF patients. Then, Dr. JoAnn Lindenfeld will summarize the benefit-risk profile and provide her clinical perspective. I will return to moderate the Question and Answer Session after our presentation.

00:24:57 In addition to our presenters, Dr. Suzanne Hendrix, our Biostatistical Consultant and Founder of Pantera, will be available to assist in answering questions. All external participants have been paid for their time in preparing for and attending today's meeting.

00:25:18 There is a significant unmet need for therapies that improve prognosis in patients with heart failure with reduced ejection fraction, as these patients continue to be at significant risk for heart failure hospitalization and mortality, despite current treatment options. Dr. Lindenfeld will speak about this unmet need in her presentation. Increased left atrial pressure and pulmonary venous congestion drive this residual risk by causing worsening heart failure symptoms, resulting in heart failure hospitalization and often death. While lowering left atrial pressure improves clinical outcomes in heart failure, it is difficult to achieve through medical therapy. Importantly, no alternative therapies exist which improve clinical outcomes in New York Heart Association Class III HFrEF patients who are treated with optimal GDMT, including left atrial pressure lowering medications such as diuretics and vasodilators, and remain at risk of poor outcomes.

00:26:31 An alternative non-pharmacological approach to lowering elevated left atrial pressure is through the use of the V-Wave Ventura interatrial shunt. The shunt is a medical device that is permanently implanted across the fossa ovalis inside the heart. The shunt has a small opening in the middle of the device with a diameter of approximately five millimeters. Following transseptal puncture, the shunt is delivered using a 14 French catheter delivery system in the cardiac catheterization laboratory. Skin-to-skin procedure time is about one hour.

00:27:12 While diuretics reduce left atrial pressure by reducing intravascular volume, in contrast, interatrial shunting redistributes a small amount of blood volume from the left atrium to the right atrium to lower left atrial pressure. When left and right atrial pressures are normal, the left atrial pressure is usually slightly higher than the right

atrial pressure, which results in a small amount of left-to-right shunting. If heart failure worsens or there is volume overload for any reason, left atrial pressure rises. This causes the shunt flow to increase because the pressure gradient from the left to the right atrium increases. In other words, the shunt flow increases automatically when left atrial pressure increases. This is a desirable characteristic of the shunt, since increased shunting occurs only when it's needed. The result is lowering of left atrial pressure.

00:28:16 As a novel technology in the treatment of heart failure, a life-threatening and debilitating disease, the shunt was granted Breakthrough Device designation in 2019 because it met FDA's criteria. The device can provide a more effective treatment for a life-threatening and irreversibly debilitating human disease, namely heart failure, and it meets all FDA criteria shown on this slide.

00:28:48 Under this program, the FDA may accept a greater extent of uncertainty of the benefit-risk profile. Uncertainty needs to be balanced by other factors, such as the probable benefits for patients to have earlier access to the device. As we'll present today, given the strong clinical signal, clear safety results and large unmet need, the benefit-risk calculus supports approval of the shunt device for the proposed population of HFrEF patients. As a framework for the presentation, I would like to summarize the trial and the key findings before we go into detail.

00:29:33 The RELIEVE-HF trial was a well-executed multicenter, randomized, double-blind sham-controlled study where patients with symptomatic heart failure on optimal, that is, maximally tolerated, GDMT, as assessed by a Central Eligibility Committee, received either the shunt or the sham control procedure. 508 patients were randomized over a four-year period. More than 95% of the patients were in New York Heart Association Class III, representing a very high-risk patient group. The median follow-up was 22 months and we have data through primary analysis on

more than 98% of the patients enrolled. There were very few protocol deviations and there were no confounding interventions.

00:30:27 From preclinical data and early feasibility studies of the shunt, we anticipated that both HFrEF and HFpEF patients could potentially benefit from the device. As a result, the RELIEVE-HF study design included patients across the full spectrum of LVEF. However, it was also understood that functional differences in the two clinical heart failure phenotypes could potentially affect the response to shunting. For this reason, randomization was stratified by LVEF group with the goal of ensuring a balanced representation of treatment assignment within each stratum in RELIEVE-HF. Interaction testing between these two strata was pre-specified to assess the homogeneity of the treatment effect in the ITT population.

00:31:27 The safety of the device and the procedure have been clearly demonstrated. The primary safety endpoint at 30 days was achieved for the ITT cohort. In fact, there were no device- or procedure-related, major adverse cardiovascular or neurological events at 30 days and through two years of follow-up in either the HFrEF or HFpEF strata. In addition, stroke, MI and thromboembolic events occurred infrequently and at similar rates in the HFrEF shunt group and control groups.

00:32:06 The primary effectiveness endpoint was not met. A significant interaction was observed between the two LVEF strata and therefore the strata could not be pulled for the analysis of effectiveness. Consequently, each LVEF stratum was separately analyzed, which demonstrated directionally opposite outcomes. There was a signal for benefit in HFrEF patients and for harm in HFpEF patients. The benefit of treatment in the HFrEF patients was quite clear, as you will see.

00:32:46 Shunt treatment was associated with a concordant and clinically meaningful reduction in heart failure events, including all-cause death, LVAD placement or heart transplantation, all heart failure hospitalizations and all outpatient worsening heart failure events. As Dr. Stone will present in more detail, these data, which

represent an all-event analysis reflective of the total burden of disease, support the benefit of treatment in HFrEF patients.

00:33:18 In an effort to understand the biological mechanisms of the observed discordant effects between HFrEF and HFpEF patients in RELIEVE-HF, additional analyses were conducted to examine cardiac structure and function using serial echocardiograms read by an independent echocardiographic core laboratory. These findings showed marked differences in baseline cardiac structure and function, as well as differences in changes in cardiac structure and function in response to shunt treatment in the two groups.

00:33:56 This schematic depicts the differences in left ventricular structure and function in patients with HFrEF on the left and HFpEF on the right that may affect the response to shunt treatment. At baseline, patients with HFrEF are characterized by an enlarged left ventricle with increased LV compliance. Patients with HFpEF are characterized by normal LV size and a noncompliant LV. As Dr. Zile will present in more detail, after shunt placement, patients with HFrEF undergo favorable LV reverse remodeling, as evidenced by a decrease in LV and diastolic volume. In contrast, patients with HFrEF do not undergo favorable LV reverse remodeling and instead are characterized by no change in LV and diastolic volume.

00:34:57 A second determinant of mortality and morbidity after shunt placement is change in right heart structure and function. At baseline, patients with HFrEF have an enlarged RV and increased RV compliance, while patients with HFpEF have a more normal RV size and noncompliant right ventricle. After shunt placement in HFrEF patients, a compliant right heart may be able to accept an increase in redistributed blood volume from the left atrium to the right atrium without resulting changes in right heart size or increased PA pressure. By contrast, after shunt placement in HFpEF patients, a less compliant right heart may not be able to accept an increase in

redistributed blood volume and thus result in increased right heart size and increased PA pressure.

00:35:56 In summary, RELIEVE-HF demonstrates that the Ventura shunt device will benefit New York Heart Association Class III HFrEF patients in whom there is a critical unmet need for therapies that improve clinical outcomes. HFrEF is associated with very high rates of heart failure events, especially heart failure hospitalization, despite treatment with guideline-directed medical therapy. In fact, the rate of heart failure hospitalization has been increasing for more than a decade.

00:36:31 These observations are supported by the RELIEVE-HF trial, which demonstrates very high rates of worsening heart failure events, including heart failure hospitalization in HFrEF control patients treated with optimal GDMT alone. Currently, there are no alternative therapies to improve clinical outcomes in New York Heart Association Class III HFrEF patients who are treated with optimal GDMT along with ICDs and cardiac resynchronization therapy devices when indicated. Therefore, approval of the Ventura shunt is in the best interest of patients with heart failure and a reduced ejection fraction.

00:37:16 I'd also like to touch upon our commitment to postmarket controls, which are touched upon in the Breakthrough designation guidance. The guidance speaks to these controls supporting premarket approval. In addition to a proposed indication restricted to patients with LVEF less than or equal to 40%, V-Wave is proposing an extensive list of conditions of approval to support a safe and responsible commercial rollout as well as ongoing robust evidence generation and data collection.

00:37:52 These proposals are like those post-approval requirements for structural heart devices and include a requirement for a local Heart Team and extensive physician training to make sure the right patients receive the device. A slow and controlled commercial rollout, a robust post-approval study to be designed collaboratively with FDA, and a registry enrolling all U.S. patients treated with the commercial device.

We're in discussions with the American College of Cardiology Real-World Evidence Generation Group on the development of such a registry.

00:38:32 In summary, the safety profile of the shunt was excellent, with no device- or procedure-related major adverse cardiovascular or neurological events through two years of follow-up. As we'll present in detail today, patients with HFrEF treated with the shunt achieve consistent benefits across multiple clinically relevant endpoints. As Dr. Zile will present in detail, there is a plausible mechanism to explain the benefits seen in shunt-treated HFrEF patients. Taken together, the safety effectiveness and mechanistic findings result in a favorable benefit-risk profile. This is especially the case when taken in the context of the high unmet clinical need for new treatments for patients with HFrEF who have a high risk for heart-failure-related events despite GDMT, supporting approval under the Breakthrough Devices designation.

00:39:30 And as I just mentioned, to help assure that approval of the V-Wave shunt will continue to offer HFrEF patients benefits that outweigh the risks, V-Wave is committed to work with FDA to establish robust postmarket controls to support premarket approval.

00:39:50 With this overview in mind, let me go into more detail on the RELIEVE-HF trial design. RELIEVE-HF was a randomized, double-blind, sham-controlled trial conducted in patients with symptomatic heart failure treated with maximally tolerated guideline-directed medical and device therapy as adjudicated by a Central Eligibility Committee. After screening, 605 patients were enrolled in the study, 97 of whom were roll-in patients. The remaining 508 were stratified by left ventricular rejection fraction, the only clinical variable that we believed might determine shunt effectiveness.

00:40:31 While we anticipated that the two LVEF strata would respond similarly to shunting, we also appreciated the known differences between HFrEF and HFpEF and the possibility that they would not. In this regard, the stratified randomization is a

critically important differentiator in our trial and one that reduces the risk of type I error on subsequent analysis. Patients with an LVEF of 40% or less were allocated to the HFrEF strata. Patients with an LVEF of greater than 40% were allocated to the HFpEF strata. Patients in each of the LVEF strata were randomized one-to-one to receive the shunt or undergo a mock transseptal catheterization and device placement using a script and they served as controls. The ITT population and related analysis are based on the combined shunt group versus the combined control group of 250 versus 258 patients respectively. However, I would like to emphasize that formal interaction testing was pre-specified for the HFrEF versus HFpEF strata so that we would still have meaningful data if the group results differed.

00:41:55 Quality control was assured throughout the trial in multiple ways, including sponsor-independent processes and a built-in blinding assessment. Sponsor-independent processes included an independent Eligibility Committee which confirmed all patients met the enrollment criteria, including that they were treated with maximally-tolerated guideline-directed medical and device therapy and remain symptomatic. An independent Clinical Events Committee and a Data and Safety Monitoring Board met to adjudicate adverse events and monitor trial safety respectively. The CEC was blinded to treatment assignment during the adjudication of events. There was also an independent echocardiographic core laboratory that evaluated all echo imaging performed during the study. Data management and biostatistics were performed independently from the sponsor. Finally, strict blinding procedures were put in place per protocol and blinding assessments were performed twice during the study.

00:43:06 The key inclusion criterion was heart failure of at least six months duration. Patients could have ischemic or non-ischemic cardiomyopathy, and importantly, any left ventricular rejection fraction with no lower or upper bound. Patients had to be symptomatic with New York Heart Association Class II, III or ambulatory IV, despite being on all maximally-tolerated Class I guideline-directed medical and

device therapies, including implantable cardiac defibrillators and cardiac resynchronization therapy. They also had to have either a heart failure hospitalization within the prior 12 months or elevated natriuretic peptide levels to enrich for clinical events. Their six-minute whole walk distance had to be depressed by at least 100 meters and had to be limited by symptoms related to heart failure.

00:44:06 Key exclusion criteria included hemodynamic instability with a systolic blood pressure of less than 90 or greater than 160 millimeters of mercury, severe pulmonary hypertension and/or severe right ventricular dysfunction, according to the criteria detailed on this slide, severe left ventricular dilation, as well as any anatomic abnormalities of the atrial septum, which might preclude shunt implantation. Once key inclusion and exclusion criteria were reviewed and approved by the Clinical Eligibility Committee, the patient was scheduled for right heart catheterization and either transesophageal or intracardiac echocardiography.

00:44:53 The right heart catheterization and either transesophageal or intracardiac echocardiography was done to confirm that patients were hemodynamically stable without severe pulmonary hypertension or other listed exclusions, and that they did not have any anatomic abnormalities or thrombus that would preclude shunt implantation. If these criteria were still met, then the patients were immediately randomized while on the table.

00:45:25 The primary safety endpoint was the composite of device-related or procedure-related major adverse cardiovascular and neurological events, or MACNE, occurring within 30 days after randomization. This is the composite of all-cause death, stroke, systemic embolization, need for open cardiac surgery or major endovascular surgical repair. The proportion of patients with MACNE within 30 days was tested against a performance goal of 11%, which was predicated on studies of left atrial appendage occlusion with the WATCHMAN device. The exact binomial test with a one-sided significance level of 0.025 was used to assess this safety endpoint.

00:46:09 The primary effectiveness endpoint was the hierarchical composite of five components, the first four representing hard heart-failure-related outcomes, and the fifth representing health status. They were ranked in order as all-cause death, then heart transplantation or left ventricular assist device implantation, then all heart failure hospitalizations, then all outpatient worsening heart failure events, then the change in health status from baseline through the longest blinded follow-up period measured using the KCCQ overall summary score. The hierarchy shown here was analyzed using the win ratio when the last enrolled patient reached 12 months, with the longest follow-up through 24 months. Dr. Stone, who did a lot of the early work in developing the win ratio method, will further describe the method as well as its advantages and limitations in his presentation of the RELIEVE-HF results.

00:47:17 The study also evaluated several secondary endpoints listed here, inclusive of the four hard clinical outcomes assessed singularly and in various combinations. Effectiveness was powered for all randomized patients in an ITT analysis. However, randomization was stratified by baseline LVEF to assess whether these two strata were poolable. The study protocol stated that safety and effectiveness according to pre-specified LVEF strata would be assessed by interaction testing. This was pre-specified. And similarly, the primary effectiveness analysis would be performed on a combined HFrEF and HFpEF population with the homogeneity of the treatment effect examined by interaction testing.

00:48:13 I'll now turn the presentation over to Dr. Stone to present the study results.

00:48:19 Dr. Stone: Thank you. I'm Gregg Stone, Professor of Medicine and Professor of Population Health Sciences and Policy, and Director of Academic Affairs at the Mount Sinai Heart Health System in New York.

00:48:32 Let's turn to the RELIEVE-HF results, starting with patient disposition. A total of 1,136 patients were screened at 114 sites in 11 countries over approximately four years. 531 patients did not meet the eligibility criteria and 97 patients comprised the

role and cohort. Thus, 508 patients were randomized one-to-one to the shunt or a placebo procedure. There were 206 HFrEF patients and 302 HFpEF patients in the two separately randomized LVEF strata. The rate of compliance with follow-up visits was very high, greater than 98%, and did not differ between the treatment groups in either strata.

00:49:19 This slide shows selected baseline characteristics of the entire population stratified by HFrEF versus HFpEF. Patients in both groups were elderly with multiple comorbidities reflective of a real-world heart failure population. Nearly all patients had severe heart failure. 96.5% were NYHA functional Class III, natriuretic peptide levels were markedly elevated and baseline KCCQ scores were low. As expected, there were substantial differences between the HFrEF and HFpEF cohorts. Of note, the median LVEF was 30.5% in patients with HFrEF and 55.5% in patients with HFpEF.

00:50:01 Baseline guideline-directed medical therapies are shown here. Notably, patients with HFrEF received Class I recommended drug therapies at rates exceeding most other contemporary heart failure clinical trials. As anticipated based on treatment guidelines, these agents were used less commonly in patients with HFpEF. SGLT2 inhibitors were used less frequently than the other agents. However, SGLT2 inhibitors did not have a Class I indication in the U.S. for HFrEF and HFpEF until 2022 and 23 respectively, at which time most patients had already been enrolled in RELIEVE-HF. Thus, the usage rates of these agents were quite high for the time. The use of defibrillators and cardiac resynchronization devices was also very high in the HFrEF cohort, 89% and 45% respectively.

00:50:51 Now, let's review the implant procedure. Implantation of the Ventura interatrial shunt is a straightforward non-complex procedure for a structural interventional cardiologist and EP physician. In the shunt arm, the procedure was attempted and the shunt was implanted in all 250 patients. A 100% shunt implant success rate. The

procedure took an average of 80 minutes to complete within the study. The procedures were performed with heparin anticoagulation, a relatively small amount of fluoroscopy time was required, and no contrast was administered. Most patients went home the day after the procedure. In the control arm, one patient did have a shunt implanted due to a site randomization error. This patient remained in the control group by intention to treat.

00:51:41 Now, let's review the principle safety results. The primary safety outcome is shown on this slide. The incidence of device- or procedure-related major adverse cardiovascular or neurologic events, or MACNE, at 30 days was 0%. The upper 97.5% confidence limit for the 0% event rate was 1.5%, which was well under the performance goal of 11%. Thus, the primary safety endpoint was met with a statistically significant p-value of less than 0.0001.

00:52:18 When we assessed the same endpoints through two-year follow-up in the 250 randomized shunt-treated patients, there were again no device- or procedure-related MACNE events. This was a pre-specified secondary safety endpoint. In addition, MACNE did not occur through two-year follow-up in the 97 patients treated with the shunt in the roll-in cohort or the one randomized control group patient who was treated with a shunt. Thus, among 348 total patients treated with the Ventura interatrial shunt, the two-year rate of device- or procedure-related MACNE was 0%.

00:52:55 Additional safety outcomes were examined in the HFrEF strata, the patient group for which we are seeking an indication. First, we looked at all MACNE events through two years in HFrEF patients regardless of whether they were adjudicated to be device- or procedure-related. There were no significant differences between the shunt and control groups and all MACNE events. Indeed, if anything, these adverse events tend to be less frequent in shunt-treated compared with control group patients; 16.6% versus 32.7%.

00:53:28 Considering other possible shunt-related adverse outcomes among patients with HFrEF, there were no pericardial effusions or tamponade, no shunt implant embolizations and no shunt-related thrombus. Indeed, all event types that might be ascribed to shunt-related procedural complications or embolic phenomena were very rare and occurred with similar frequency in the shunt group and the blinded control group.

00:53:53 Finally, the rates of site-reported serious adverse events are shown on this slide. In patients with HFrEF, all serious adverse events were less frequent with shunt treatment compared with control. Moreover, in this blinded trial, not only were there fewer cardiovascular SAEs, there were also fewer non-cardiovascular SAEs with shunt treatment compared with placebo treatment. Specifically, there were fewer infections, injuries, cancers, respiratory illnesses, and other non-cardiovascular SAEs. It's possible that the 40% reduction in cardiovascular heart-failure-related SAEs contributed to the reduction in these non-cardiovascular events. Whatever the mechanism, there clearly were no safety concerns with atrial shunt implantation in patients with HFrEF, nor were any unexpected adverse device effects reported.

00:54:46 In summary, the safety profile of the Ventura atrial shunt was excellent. The primary 30-day safety endpoint of device- or procedure-related MACNE was met with a p-value of less than 0.0001, and there were no MACNE occurrences through two years of follow-up in 348 randomized or roll-in shunt-treated patients. Shunt implant success was a hundred percent. Periprocedural complications were rare and not increased in the shunt group, and shunt embolization did not occur during two years of follow-up. Other thromboembolic events that may be attributed to an interatrial shunt occurred infrequently and at similar rates in both the shunt and control groups.

00:55:28 Now, let's review the effectiveness results. As a reminder, the primary effectiveness endpoint was a hierarchical composite of five components, as seen in the left column. All-cause death, cardiac transplantation or LVAD implantation, all heart

failure hospitalizations, that is first in recurrent events, all outpatient worsening heart failure events, first in recurrent, and change in health status as measured by a difference of greater or equal to five points in the Kansas City Cardiomyopathy Questionnaire score from baseline through longest blinded follow-up. This hierarchy was analyzed by the Finkelstein-Schoenfeld method when the last enrolled patient reached 12 months, with the longest follow-up to 24 months, and was expressed as the win ratio with a 95% confidence interval.

00:56:15 For the win ratio analysis, every patient in the treatment group is compared with every patient in the control group, with 250 patients randomized to shunt treatment and the 258 patients randomized to the blinded control, a total of 64,500 patient pairs were present to compare. To calculate the win ratio, we first examine the outcomes of each patient pair during each pair's longest common follow-up duration, starting at the top of the hierarchy, all-cause death. In these 64,500 patient pairs, there were 5,424 shunt group wins, that is, a death in the control group patient, but not in the shunt group patient, or an earlier death in the control group patient than in the shunt group patient. And there were 7,615 control group wins. There were 51,461 ties, in which there were no deaths in each patient pair comparison during their longest common follow-up period.

00:57:12 The patient pairs that tied were then compared in the second level of the hierarchy for cardiac transplantation or LVAD implantation. This procedure was then continued through the fifth level of the hierarchy. To generate the win ratio, we then add up all of the wins in the treatment arm and divide by all of the wins in the control arm. Thus, the win ratio was 0.86 with a 95% confidence interval that included 1.0. The p-value was 0.20. Please also note in the last column that 69% of the decisions, the wins, were based on the first four levels of the hierarchy representing objective hard heart-failure-related outcomes. 31% of the decisions were attributed to changes or lack thereof in quality of life based on the KCCQ

score. This will become important as we assess the win ratio outcomes stratified by LVEF.

00:58:09 FDA has expressed concern that this extensive analysis based on LVEF may not be justified because the HFrEF versus HFpEF subgroup was just 1 of 15 pre-specified subgroups and these analyses have not been adjusted for multiple testing. However, this is not the case.

00:58:26 As you see here, LVEF stands apart from the remaining subgroups in many ways. First, it was the only clinical variable that was used for stratification resulting in two separate randomized groups ensuring covariate balance. Second, it was included in the scientific rationale for study design section of the protocol. Third, the sample size calculations were based on the separate HFrEF and HFpEF groups in the protocol. Fourth, the LVEF strata analysis was included in the top line analysis prior to unblinding for primary and secondary endpoints. And finally, this grouping was also included in the primary effectiveness endpoint section of the SAP, section 4.1.2, with an interaction analysis pre-specified.

00:59:13 In contrast, all other subgroup analyses were performed for descriptive purposes only, not adjusted for multiplicity. In addition, as we have demonstrated, the observed interaction between LVEF strata and treatment group for the primary endpoint was confirmed by the GST analysis of the totality of the data from the trial with a minimal chance of a false positive finding given the strength and consistency of the data across multiple endpoints.

00:59:42 There's biologic plausibility for the difference in outcomes between the HFrEF and HFpEF groups supported by the internal echocardiographic data, and there was a continuous monotonic relationship between LVEF and outcomes, further supporting this pathophysiologic mechanism as valid. Thus, given the strong interaction between HFrEF and HFpEF, the present separate analysis of the HFrEF and HFpEF strata is justified and consistent with the protocol.

01:00:09 Per the protocol, to assess whether the two LVEF strata were poolable, a test for interaction would be performed regardless of the ITT outcome in the entire population. The win ratio analysis in the randomized HFrEF stratum appears on the left. The win ratio is 1.40. That is, there were 40% more wins with shunt treatment, a high value signifying a substantial improvement favoring the shunt. However, among these 206 randomized patients, the 95% conference interval included 1.0. Examining these outcomes in more detail, for the first four components of the hierarchy, the hard heart-failure-related clinical event outcomes, there were substantially more wins in the shunt group than in the control group. However, for the KCCQ outcome, there were a similar number of wins in both arms. I will address this later.

01:01:04 In contrast to HFrEF, in the HFpEF stratum on the right, there were substantially more wins in the control group than in the shunt group, both for the hard heart-failure-related outcomes and the KCCQ difference. As a result, the win ratio was 0.61 in the HFpEF stratum, strongly favoring the control group. Most importantly, the pre-specified interaction p-value between these two strata for the primary effectiveness win ratio outcome was 0.0146, demonstrating that these two groups responded differently to the shunt and their results are not poolable.

01:01:42 The issue that then arises is how to examine the outcomes from a randomized trial that demonstrates that the results from the pre-specified randomized strata cannot be pooled. The classic interpretation, when the primary endpoint is not met as in RELIEVE-HF, is that subsequent analyses are hypothesis-generating. There is regulatory precedence, however, for device approvals when the primary endpoint is missed. Therefore, the issue that we would like you to consider is whether the remaining data are sufficiently strong and sufficiently robust, consistent and convincing that the outcomes are not likely due to chance but do indeed represent a

meaningful advance for high-risk heart failure patients in great need of a safe, effective therapy to improve their lives.

01:02:28 In this regard, RELIEVE-HF did not pre-specify the analysis to undertake if the two stratified randomized LVEF strata responded so differently to the shunt that the data cannot be pooled, essentially invalidating the ITT analysis. Indeed, we are not aware of any prior study protocol that has specified exactly what to do in this uncommon situation. However, we all share the desire not to overlook a truly safe beneficial treatment, especially for high-risk patients with a great unmet clinical need.

01:03:01 In this instance, that group is patients with HFrEF enrolled in RELIEVE-HF, most of whom were NYHA Class III, and in whom event rates remain very high despite maximal GDMT. Thus, we will show you the totality of the effectiveness data from RELIEVE-HF, both pre-specified and post-hoc analysis, emphasizing the outcomes in the randomized HFrEF stratum.

01:03:24 First, we will start with the Global Statistical Test or GST. This method formally pools this total study evidence in a trial across the endpoints in both LVEF strata, both from the primary and secondary outcomes. You can think of the GST as a within study meta-analysis to assess the totality of the evidence and consistency of all pre-specified outcomes within each randomized strata. Because patients with heart failure often have multiple adverse events, it's important to include both first and recurrent events when applicable. The null hypothesis corresponding to a GST analysis is that the treatment doesn't affect heart failure outcomes as a whole, and the alternative hypothesis is that the treatment affects heart failure outcomes. Importantly, a GST analysis allows each event type to contribute only once, so overlapping information isn't double counted.

01:04:21 The primary endpoint in each of the pre-specified secondary endpoints that include the clinical components of the primary endpoint listed as S1 through S7 are shown here. Treatment effects with the shunt were consistent across endpoints, with

strongly positive outcomes after shunt treatment in HFrEF and negative outcomes after shunt treatment in HFpEF. Nearly every interaction was highly statistically significant. Only KCCQ appeared neutral in both strata, an issue I will come back to later. This consistency across endpoints for the hard heart-failure-related clinical outcomes shows that the observed interaction in the primary efficacy analysis was not a chance finding but reflects a true treatment effect.

01:05:06 Now, when we look at the totality of the evidence as reflected in the Global Statistical Test shown on the bottom row, we see that the interaction between HFrEF and HFpEF remains highly statistically significant. Importantly, for patients with heart failure and reduced ejection fraction, the T-score is significant, with a p-value of 0.04. This shows that the totality of the evidence supports improvement of outcomes with the Ventura interatrial shunt in patients with HFrEF.

01:05:37 The question then arises whether this finding may be due to chance, i.e., a false positive finding. To assess this issue, we performed a permutation analysis based on the observed results from RELIEVE-HF that demonstrated that the risk of a type I error for this GST analysis was only slightly above 0.05, meaning that the results are not likely to be due to a false positive finding. More detail on this is provided in figure 24 of the briefing document.

01:06:08 Now, let's explore the data in more detail. Of course, the trial was originally powered for the win ratio analysis in the entire ITT population. That is both LVEF strata pooled. Thus, inherently less power is present when examining the HFrEF and HFpEF strata by the win ratio separately. This limitation can be overcome by recognizing that high-risk heart failure patients often experience multiple adverse events which, if accounted for, can increase study power. In this regard, a limitation of the win ratio analysis is that it only counts a single win, loss or type per patient pair, even if multiple events occur. In this regard, it is like a time-to-first-event

analysis, albeit one that is hierarchically ordered to rank the components of the primary endpoint.

01:06:57 But, like a time-to-first-event analysis, it conceals multiple events, all of those that occur other than the one ranked highest as well as recurrent events at the same level. It thus underestimates the total burden of disease. The fully characterized, the full impact of the shunt, we had pre-specified examining all adverse heart-failure-related outcomes from the primary endpoint, including first and recurrent events with a Nelson Aalen cumulative hazard rate analysis as a secondary pre-specified endpoint. This analysis methodology accurately reflects the overall burden of the disease state and the full effect of the shunt in patients with advanced heart failure.

01:07:38 To demonstrate the importance of examining the comprehensive effects of the shunt on all outcomes, this table shows the number of events excluded from the HFrEF win ratio analysis in the RELIEVE-HF trial. The first two tiers of the win ratio are death and transplant or LVAD implantation, the so-called terminal events that only occur once and thus are fully accounted for in the win ratio. What's not fully accounted for by the win ratio are the events such as heart failure hospitalizations and outpatient worsening heart failure events that either occurred in patients before one of these terminal events and thus were not counted because the terminal events occurred higher in the hierarchy, or that occurred multiple times, but were only counted once.

01:08:23 The top portion of the table shows just how many heart failure hospitalization events were excluded from the win ratio analysis. In total, 50 of 119 heart failure hospitalizations or 42% of all the heart failure hospitalizations were ignored, that is, hidden by the win ratio method. Specifically, 10 of 41 or 24.4% of heart failure hospitalization events in the shunt group and 40 of 78 or 51.3% of heart failure hospitalization events in the control group were not included in this analysis. The win ratio result at this level suggests a comparable number of events in each group,

when in reality the control group experienced twice as many heart failure hospitalizations as with shunt treatment.

01:09:13 Now, focusing on the bottom portion of the table, note that the win ratio analysis excluded 5 of 21 or 23.8% of the outpatient worsening heart failure events from the shunt group and 10 of 30 or 33.3% of the outpatient worsening heart failure events from the control group. Note that for both heart failure hospitalizations and outpatient worsening heart failure events, more events were excluded from the control group than the treatment group.

01:09:41 In summary, the win ratio analysis excluded 65 out of 170 or 38.2% of all heart failure hospitalizations and outpatient worsening heart failure events. As such, it underestimates the total burden of heart failure that HFrEF patients experience. In addition, it concealed more events in control patients, 46.3%, than in shunt-treated patients, 24.2%. The win ratio thus inherently biases against the device that prevents recurrent events such as interatrial shunting in HFrEF.

01:10:18 The best way to appreciate the full effect of shunt treatment in the patients with HFrEF in the RELIEVE-HF trial is with a comprehensive analysis of all events. This slide shows the pre-specified analysis assessing the treatment effect on the four clinical event types from the win ratio combined. That is all-cause mortality, heart transplantation or LVAD implant, all heart failure hospitalizations and all outpatient worsening heart failure events, including first and recurrent events expressed as increasing cumulative Nelson Aalen hazard rates during follow-up. Results for HFrEF are shown on the left and HFpEF are shown on the right.

01:10:58 In HFrEF, the risk of heart-failure-related events was decreased from an average two events per patient during the two-year follow-up to slightly fewer than one event per patient during the two-year follow-up period, a 51% reduction with shunt treatment compared with control. The Nelson Aalen hazard rate ratio was 0.49 with an upper

95% confidence interval bound of 0.65, far below 1.0, providing high confidence in this finding. The p-value was less than 0.0001.

01:11:33 In contrast, in HFpEF patients on the right, the risk of heart failure events was increased with shunt treatment by 69% compared with control. Note that patients at all four groups had multiple events. For example, 134 events occurred in 54 control HFrEF patients while only 76 events occurred in 45 shunt-treated HFrEF patients, which is why a recurrent events analysis is much more powerful than a single events analysis, such as the win ratio or time-to-first event, to appreciate the full effect of shunt treatment on the total burden of disease and heart failure.

01:12:09 Also note that by looking only at the two black control group curves, you appreciate that the HFrEF control group patients exhibited a three times higher event rate compared with the HFpEF control patients, demonstrating the marked unmet clinical need in HFrEF. On average every year, one event was occurring in each HFrEF patient in the control arm despite optimal guideline-directed medical therapy. The interaction p-value for these diametrically opposed outcomes in HFrEF versus HFpEF was less than 0.0001. Again, emphasizing the markedly different treatment effects in the HFrEF and HFpEF strata and that these two groups are not poolable.

01:12:55 In summary, HFrEF patients exhibit the greatest risk of heart failure events despite excellent background guideline-directed medical therapy and cardiac rhythm management and HFrEF patients with shunt treatment demonstrated a marked reduction in hard heart-failure-related clinical outcomes.

01:13:13 To further examine whether these discordant results in patients with HFpEF and HFrEF were likely real, we examine the continuous relationship between LVEF seen here on the x-axis and all heart failure events in shunt-treated versus control group patients expressed as a log-transformed rate ratio on the y-axis using the LWYY approach, which is similar to a Cox proportional hazards regression, but for recurrent events. Compared with other curve fitting techniques, this method does not require

bending or categorizing the continuous covariate. While the 95% confidence intervals are wide, as would be expected, a monotonic relationship is seen between baseline LVEF and the risk of events during two-year follow-up, such that the lower the LVEF, the greater the benefit with shunt treatment.

01:14:03 Note that the crossover from likely improved to worsened outcomes with shunt treatment is noted in an LVEF of 42%, close to the 40% value that was pre-specified to define HFrEF, the cutoff that's used in nearly all device and drug trials.

01:14:21 Lastly, the progressive monotonic relationship demonstrated in this figure is additional evidence that the diametrically opposite treatment effects that were observed in HFrEF and HFpEF with shunt treatment are unlikely to be due to play of chance.

01:14:36 An LVEF difference of 5% is accepted as the degree of variability that may be present between readers or on repeated measurements for 2D echo LVEF assessments. To determine whether variability and measurement of LVEF might affect the outcomes with shunt treatment, we therefore examine the two-year relative risk reductions of all heart-failure-related events in patients with LVEF, between 40% to 43%, 40% to 44%, and 40% to 45%.

01:15:07 As seen here, while caution and interpretation is warranted because the groups are small, heart failure event rates were reduced by shunt treatment up to an LVEF of 43%. With higher LVEFs, the effect was attenuated but still tended to be improved even when patients with an LVEF up to 45% were included. This demonstrates a 5% safety cushion above the 40% upper LVEF cutoff that's been requested in the indication labeling.

01:15:37 Focusing now on the HFrEF strata. This slide reports the pre-specified Nelson Aalen hazard rate ratios and 95% confidence intervals for each clinical event component individually in the HFrEF strata. The first group again shows the 51% reduction in

all heart-failure-related events with shunt treatment. For all-cause death, there was a 52% reduction in events with shunt treatment. For heart transplantation or LVAD implantation, there was an 85% reduction in events with shunt treatment. For all heart failure hospitalizations, there was a 54% reduction in events with shunt treatment. And for all outpatient worsening heart failure events, there was a 36% reduction in events with shunt treatment.

01:16:21 Most importantly, the right-hand column shows the number of patients needed to treat with shunt treatment to prevent on average one event during two years of follow-up. Given the high ongoing event rate in control group patients who are symptomatic on optimal GDMT, the absolute benefits of the shunt are large. Based on the difference in expected event counts over two years, on average, each shunt-treated patient would have one heart-failure-related event prevented in two years compared with remaining on best GDMT only. For death, 6.4 patients had to be treated to prevent one death within two years, and treating only 1.6 patients was needed to achieve a reduction of one heart failure hospitalization on average in this period.

01:17:11 In summary, there were concordant improvements in all four heart-failure-related event types with shunt treatment among patients with HFrEF and the absolute benefits were large. This concordance in this blinded trial provides additional confidence supporting the overall improvement in outcomes seen in shunted HFrEF patients.

01:17:29 Hospitalizations for heart failure were the most frequent event that occurred during the two-year follow-up period in patients with HFrEF. Note that in the control group the risk of heart failure hospitalization steadily accumulated during the follow-up period, perhaps even increasing in risk between one- and two-year follow-up. In contrast, the risk of heart failure hospitalizations after shunt treatment stabilized over time. Thus, the hazard curves continued to diverge at the end of the two-year period.

Shunt treatment decreased the risk of heart failure hospitalizations by 54% during follow-up compared with control, from an average of 1.13 events per patient to 0.52 events per patient, p-value of 0.0002.

01:18:15 This slide shows the adjudicated causes of death in patients with HFrEF. There were numerically fewer all-cause deaths in the shunt-treated group compared with the control group, 13 versus 20 respectively. Deaths were adjudicated to a primary cardiovascular cause, a primary non-cardiovascular cause, or an unknown primary cause. In many studies of cardiovascular devices, an unknown cause of death is conservatively classified as, or grouped with, a cardiovascular cause of death. Thus, there were 12 versus 14 cardiovascular or unknown deaths in the shunt-treated and control groups respectively, a difference of two fewer deaths with shunt treatment. There was one non-cardiovascular death in the shunt group compared with six non-cardiovascular deaths in the control group, a difference of five fewer deaths with shunt treatment. These numbers are small and therefore the causes of death should be interpreted with caution. Nonetheless, one might ask why there appears to be a greater shunt effect in reducing non-cardiovascular deaths than cardiovascular deaths.

01:19:19 It is well known that non-cardiac diseases can trigger or worsen heart failure and that mortality rates are increased in heart failure patients who present with non-cardiac disorders, especially cancer and infections. Thus, greater residual heart failure in control group patients, in other words, less cardiac reserve to adapt to the stress of a major non-cardiac illness, may have contributed to the higher mortality rates when these non-cardiac conditions occurred. Bottom line, it can be challenging to adjudicate the principal cause of death in heart failure patients with multiple comorbidities. For this reason, all-cause death is widely accepted as the parameter that is least prone to bias or misclassification and in this regard there were seven fewer all-cause deaths in the shunt-treated group compared with the control group.

01:20:08 In RELIEVE-HF, all-cause death, cardiac transplantation and left ventricular assist device implantation were mutually exclusive terminal events, the most severe events that led to patients being removed from the trial. Given their life-changing impact on patients, demonstrating a significant reduction in these events by a heart failure therapy is especially meaningful. As seen in the standard time-to-first-event analysis among the randomized HFrEF cohort, all-cause death, heart transplantation or LVAD implantation were reduced to two years with shunt treatment, from 33.4% in the control group to 15.6% with the shunt, a significant 48% reduction. Only 5.6 patients would need to be treated with the shunt to prevent one death, heart transplant or LVAD within two years. Note also that the curves were continuing to diverge at two years, again suggesting an increasing benefit with shunt treatment with even longer term follow-up.

01:21:09 As seen on this slide, the effect of shunt treatment in HFrEF was consistent across the spectrum of all single heart-failure-related events and composite event types. No matter which cardiovascular events were considered alone or in combination, the concordance of outcomes across event types in patients with HFrEF treated with their interatrial shunt is striking, making it further unlikely that these results are due to play of chance.

01:21:35 Finally, while most of our recurrent event analysis were pre-specified to be performed with the Nelson Aalen estimator, the results for all heart failure hospitalizations, all heart-failure-related events and all clinical events, including all-cause hospitalizations, were consistently reduced with shunt treatment compared with control when analyzed with a variety of different recurrent events analysis methods that are often used in evaluating heart failure therapies.

01:22:01 One question that might be raised is whether the number of HFrEF patients that were randomized is enough to provide confidence in these results. There is regulatory precedence for device approvals based on studies involving even smaller numbers of

patients than the 206 randomized HFrEF patients in RELIEVE-HF, especially in high-risk groups with an unmet clinical need in whom the event rate is high. In RELIEVE-HF, among these 206 total randomized HFrEF patients, the number of events in this high-risk population was large, with 210 heart-failure-related events and 363 total clinical events including all hospitalizations, supporting the robustness of the trial findings in the randomized HFrEF stratum.

01:22:47 Finally, FDA will present to you a sensitivity analysis where they selectively remove only control group patients with the highest number of heart failure events in the HFrEF cohort. Such an analysis is suboptimal because arm-specific truncation, one, breaks the equality created by randomization, and two, artificially erases treatment benefit by deleting the very patients in whom shunt treatment most favorably improves outcomes compared with control. In every study, a positive finding can be eliminated by such selective removal of the most positive results.

01:23:23 In contrast, on this slide we provide a less biased symmetric trimming analysis in which equal numbers of HFrEF patients with the highest number of heart failure events from each group were sequentially removed, assessed with a negative binomial analysis of recurrent events. The two forest plots show the rate ratios and 95% confidence boundaries for all heart failure events in blue on the left, defined as the composite of all-cause death, transplant or LVAD, all heart failure hospitalizations and all worsening heart failure events, and all heart failure hospitalizations as a single event type in green on the right.

01:24:02 We start in the top row examining all 206 HFrEF patients and then sequentially trim pairs of shunt control group patients one pair at a time, starting with the patients with the most events and working downwards towards patients with the fewer events. For all heart failure events in blue, the upper 95% confidence boundary remained less than 1.0 until 23 pairs of patients were removed from the shunt and control groups. These 46 patients experienced 72% of all heart failure events. After their

elimination, only 28% of all heart failure events were left for comparison. At this level of removal, remaining control group patients had two or fewer heart failure events while shunt patients had one or less heart failure events.

01:24:49 Similarly, for all heart failure hospitalizations in green, the upper 95% confidence boundary remained less than 1.0 until 13 pairs of patients were removed from the shunt and control groups. These 26 patients experienced 55% of all heart failure hospitalizations. After their elimination, only 45% of all heart failure hospitalizations were left for comparison. At this level of removal, remaining control group patients had three or fewer heart failure hospitalizations while shunt group patients had two or less heart failure hospitalization events.

01:25:26 In summary, the symmetric trimming analysis removes patients in a balanced manner from both treatment arms and therefore preserves the randomized structure of the trial. Moreover, these results demonstrate beyond reasonable uncertainty that the shunt treatment effect is highly robust, persisting until the majority of the recurrent event burden has been removed, meaning that a beneficial shunt treatment effect is seen across the full spectrum of patients, from those having the most events to those having very few events.

01:25:58 Now, in contrast to the clear differences between patients with HFrEF and HFpEF in the response to the atrial shunt in the heart-failure-related clinical outcomes, surprisingly no differences were seen in patient-reported quality of life as measured by the change in KCCQ. KCCQ in this trial was measured at baseline and at 1, 3, 6, 12, 18 and 24 months after randomization. On this slide, changes in KCCQ from baseline during follow-up are shown in the randomized HFrEF strata on the left and the HFpEF strata on the right. As you can see, the KCCQ increased from baseline to follow-up by approximately 10 points in all patient groups regardless of whether they had HFrEF or HFpEF, and regardless of whether they were treated with the atrial shunt or a blinded sham procedure. Specifically, in the HFrEF strata, there was

no between-group incremental improvement in KCCQ in shunt-treated patients, even though the shunt reduced the risk of heart failure hospitalizations by more than 50% as well as the terminal events of death, heart transplantation or LVAD implantation.

01:27:08 Perhaps even more strikingly among patients with HFpEF, both randomized groups, including those treated with the shunt, reported that they were feeling better by KCCQ assessment despite the fact that there was a doubling of the rates of heart failure hospitalization and a tripling of mortality with shunt treatment. Thus, there was a very strong placebo effect in this blinded device trial that lasted at least two years. These results, demonstrating a striking discordance between the hard cardiovascular adverse outcomes and the directional changes in KCCQ, were surprising to us and prompted a detailed literature search that found that such findings were indeed not unique to RELIEVE-HF, but were in fact present in nearly all prior trials of blinded heart failure interventions.

01:28:00 Prior to RELIEVE-HF, there had been few blinded device trials. This slide shows the results from five recent large, representative, double-blind, placebo-controlled drug trials in patients with HFrEF and HFpEF that were powered to show reductions in clinical outcomes and also reported KCCQ findings. These blinded trials in thousands of patients demonstrated highly significant and marked reductions in cardiovascular death and heart failure hospitalizations with each of the agents tested in these trials, as seen in the green shading. Now, prior unblinded trials had shown that such improvements in death and heart failure hospitalizations are associated with between-group differences in KCCQ during follow-up of 15 or more points, with five points considered the minimal clinically important difference. However, the between-group changes in KCCQ from baseline to follow-up in these blinded trials, shown in red, were minimal, only 1.3 to 2.8 points, disproportionate in magnitude to the robust improvements in cardiovascular outcomes that were reported.

01:29:08 Now, here are the data from the blinded RELIEVE-HF trial in the randomized reduced and preserved LVEF strata. This similarly demonstrates this marked discordance, with even greater effects of the shunt on clinical cardiovascular outcomes than the pharmacologic agents, but again, minimal changes in KCCQ regardless as to whether the effects were markedly positive or negative in this blinded trial. Thus, we have identified that between-group changes in KCCQ do not strongly reflect nor correlate with major drug and device effects in blinded HF trials. This was not known to us or to anyone, to my knowledge, prior to RELIEVE-HF.

01:29:51 Regardless, please note that despite the fact that only minimal changes in KCCQ were observed in these pharmacotherapy trials, there is widespread consensus, of course, that these heart failure interventions in these studies substantially benefit patients with heart failure, as reflected by their Class I indications in all guidelines and widespread use. Thus, in blinded trials, minimal changes in KCCQ do not preclude proof of utility as long as clear improvements and heart-failure-related events are demonstrated.

01:30:23 Furthermore, as a completers analysis, the group means do not take into account the patients who died. This slide shows the change in KCCQ in the proportion of patients who improved in green, had no change in blue, were worsened in red, and had death or heart transplant or LVAD implantation in black. In this responder's analysis, at 12 months on the left, the rates of KCCQ improvement were similar with shunt versus control; all the fewer patients tended to worsen who were treated with the shunt as shown in the brackets. By 24 months, on the right, not only was there a marked decrease in the proportion of patients that worsened with shunt treatment compared with control, 34% versus 55% respectively, but the proportion of patients that improved, that's seen in the green bars was also greater with shunt treatment, 53% versus 34% respectively, p-value of 0.01.

01:31:22 Moreover, KCCQ assessment is limited in that it only assesses symptomatology over the prior two-week period. In contrast, New York Heart Association functional classification assesses heart-failure-related symptoms over an extended period of time. As seen in this slide, the proportion of patients that improved by at least one NYHA class at 12 months, in the two shades of green, tended to be greater and fewer patients tended to be worse after shunt treatment compared with control. By 24 months, on the right, these differences were marked, with substantially greater functional improvement in shunt-treated patients than control, 58% versus 26% respectively, with a corresponding decrease in the proportion of patients that worsened with shunt treatment compared with control, 25% versus 47%, p-value of 0.002.

01:32:17 To summarize, the Ventura atrial shunt was demonstrated to be safe in all heart failure patients and especially in patients with HFrEF. The primary safety endpoint of the trial was met by a large margin. Indeed, in 348 shunt-treated patients, zero device- or procedure-related major adverse cardiovascular and neurologic events occurred at either 30 days or through two-year follow-up. Periprocedural complications occurred rarely, adverse events that might be attributed to an atrial shunt were infrequent and occurred at similar or lower rates compared with control. Indeed, in this blinded trial, among patients with HFrEF, site-reported serious adverse events were reduced by more than 40% in patients treated with the Ventura atrial shunt with similar reductions in both cardiovascular and non-cardiovascular SAEs.

01:33:10 Regarding effectiveness, diametrically opposite effects were observed in the pre-specified randomized HFrEF and HFpEF strata. HFrEF patients demonstrated a marked reduction in heart-failure-related events after Ventura atrial shunt treatment, while HFpEF patients demonstrated worse outcomes. The interaction test for this finding was statistically significant, signifying that the response to the shunt in these

two populations are distinct and the results from these two strata are not poolable. A comprehensive analysis of the totality of the data from RELIEVE-HF demonstrated that HFrEF patients have substantial and concordant reductions in the rates of all pre-specified heart-failure-related events that comprise the primary and secondary endpoints representing those outcomes that are most clinically meaningful to patients in this high-risk group who remain symptomatic despite best GDMT.

01:34:07 The GST analysis of the totality of the data demonstrated that these findings are statistically significant in HFrEF with minimal inflation of type I error, meaning that there is minimal risk that these are false positive findings. Thus, the benefit-to-risk profile in New York Heart Association Class III patients with HFrEF strongly favors the interatrial shunt, especially in the absence of any major safety concerns.

01:34:36 The last question that remains is whether there is a biologic and mechanistic plausibility for the discordant results that were observed in the HFrEF and HFpEF strata and RELIEVE-HF. For this analysis, I'll turn the presentation over to Dr. Zile. Thank you.

01:34:51 Dr. Zile: Good morning. My name is Michael Zile. I'm the Charles Ezra Daniel Professor of Medicine at the Medical University of South Carolina.

01:35:00 Using echocardiographic data from the RELIEVE-HF study, our goal was to determine whether and to what extent differences in cardiac structure and function in patients with HFrEF versus those with HFpEF provide a biologically plausible explanation for the differences in clinical responses to shunt placement in these two heart failure groups. Previous studies have suggested that changes in specific cardiac structural determinants can affect rates of mortality and morbidity. In particular, these studies have suggested that when a therapy creates favorable left ventricular structural remodeling, such as reverse remodeling, as evidenced by a decrease in LV and diastolic volume, that this is associated with a reduction in morbidity and mortality. In addition, changes in right ventricular structure and function, which in

turn result in changes in pulmonary artery pressure, also affect morbidity and mortality rates.

01:36:03 I will review these concepts schematically first and then show you data from RELIEVE-HF and then additional data from other published studies. Cardiac structure and function were measured at baseline and 12 months in the two EF groups using echocardiographic studies. This consort diagram displays the sample sizes in each EF group and in each treatment group. The detailed statistical analysis methods used in this echo study are included in your panel pack. This schematic depicts the differences in left ventricular structure and function in patients with HFrEF on the left and HFpEF on the right that may affect the response to shunt placement. At baseline, patients with HFrEF are characterized by an enlarged left ventricle and increased left ventricular compliance. Patients with HFpEF are characterized by normal LV size and a noncompliant LV. We hypothesized that, after shunt placement, patients with HFrEF may undergo favorable LV reverse remodeling as evidenced by a decrease in LV and diastolic volume. In contrast, patients with HFpEF may be unable to undergo favorable LV remodeling and instead will be characterized by no change in LV and diastolic volume.

01:37:28 This slide shows the change from baseline to 12 months in LV and diastolic volume on the left and LV and systolic volume on the right in patients with HFrEF versus those with HFpEF. The gray bars represent changes from baseline to 12 months in the control groups for each EF stratum. The blue bars in HFrEF and corresponding red bars in HFpEF represent changes from baseline in the shunt groups. The green bars represent the difference between control and shunt groups. That is the difference of differences. After shunt placement, there was a decrease in LV and diastolic and in systolic volume in HFrEF, indicating favorable remodeling. In contrast, there were no changes in the HFpEF group. Notably, the differences between the response to shunt placement in the two EF groups are themselves significant.

01:38:27 These structural changes are consistent with the observed reductions in heart failure events in the RELIEVE-HF trial in the HFrEF patients treated with a shunt. Favorable LV remodeling has been associated with reduced morbidity and mortality in patients with HFrEF in a previously published meta-analysis, as shown in this slide. Kramer and Udelson performed a meta-analysis of 40 randomized control trials in approximately 5,000 patients that looked at the relationship between changes in LV and diastolic volume from baseline to after drug or device implementation and the odds ratio of concurrent mortality. The blue symbols represent patients with evidence of reverse remodeling, that is, a reduction in LV and diastolic volume. This reduction was associated with reduction in mortality.

01:39:20 Now, let me overlay data from RELIEVE-HF on this graph. The green circles represent the mean change in LV and diastolic volume and mortality in RELIEVE-HF HFrEF patients treated with a shunt. These RELIEVE-HF data are concordant with the data from the meta-analysis.

01:39:43 A second determinant of mortality and morbidity after shunt placement is change in right heart structure and function. At baseline, patients with HFrEF have an enlarged right ventricle and increased RV compliance, while patients with HFpEF have a normal sized RV and a noncompliant right ventricle. We hypothesized that, after shunt placement in HFrEF patients, a compliant right heart may be able to accept an increase in redistributed blood volume from the left atrium into the right atrium without resulting in changes in right heart size or increased PA pressure. By contrast, after shunt placement in HFpEF patients a less compliant right heart may not be able to accept an increase in redistributed blood and thus result in an increased right heart size and increased PA pressure.

01:40:37 This slide shows the changes in right heart structure in response to shunt placement. Changes in right ventricular structure are shown on the left panel measured as right ventricular end diastolic area index. Changes in right atrial structure are shown on

the right panel measured as right atrial area index. In patients with HFrEF, there were no changes in RV or RA area in response to shunt placement. In contrast, in HFpEF there was an increase in both RV and RA area in response to shunt placement, which indicates unfavorable right heart remodeling.

01:41:21 This slide shows the effect of shunt placement on RV systolic function as measured by RV fractional area change on the left and tricuspid annular plane systolic excursion, or TAPSE, on the right. There were no statistically significant differences in these measurements of RV systolic function in response to shunt placement in either HFrEF or HFpEF. However, there was an apparent trend toward improved RV systolic function with shunt treatment in HFrEF patients but not HFpEF patients. These differences in right heart response to shunt placement between HFrEF and HFpEF shown on the last two slides in aggregate resulted in significantly different changes and pulmonary artery systolic pressure shown on the next slide.

01:42:10 In HFrEF on the left, there was a net decrease in PA systolic pressure in patients treated with a shunt compared to control. There was a 2.2 millimeter of mercury decrease in PA systolic pressure which did not reach statistical significance, but nonetheless may have clinical relevance. In HFpEF on the right, there was a net increase in PA systolic pressure in patients treated with the shunt compared to control, there was a 4.7 millimeter of mercury increase in PA systolic pressure, which was statistically different from control. These changes in PA systolic pressure are consistent with the observed significant changes in heart failure events that occurred in RELIEVE-HF patients treated with a shunt.

01:42:56 Decreased PA systolic pressure has also been associated with reduced morbidity and mortality in patients with heart failure in a previously published meta-analysis shown in this slide. The data shown here were derived from four randomized clinical trials examining changes in pressure using an implantable hemodynamic monitor in patients with chronic heart failure. Please focus on the highlighted data showing data

for change in PA systolic pressure from baseline to six months and its subsequent effect on all-cause mortality. As little as a three-millimeter of mercury decrease in PA systolic pressure was associated with a 14% reduction in mortality. This is quite similar to data presented from the RELIEVE-HF HFrEF group. In contrast, as little as a three-millimeter increase in PA systolic pressure was associated with a 24% increase in mortality. This is quite similar to the data presented from the RELIEVE-HF HFpEF group. This relationship between changes in PA systolic pressure and heart failure outcomes is also present for the risk of heart failure hospitalization events.

01:44:11 In conclusion, the echocardiographic data seen in this presentation provide biologically plausible mechanisms for the differences in response to shunt placement in HFrEF versus HFpEF. At baseline, there are critical differences in cardiac structure and function. After shunt placement, right heart compliance determined the ability to accommodate the left atrial to right atrial shunted volume. Changes in LV remodeling and PA pressures predict subsequent morbidity and mortality. In RELIEVE-HF, HFrEF patients treated with an interatrial shunt had improved morbidity and mortality related to structural and functional characteristics.

01:44:55 I'll now turn the presentation over to Dr. Lindenfeld.

01:45:00 Dr. Lindenfeld: Thank you very much, Dr. Zile. I'm JoAnn Lindenfeld and I'm a Professor of Medicine and Cardiology at Vanderbilt University Medical Center and the Director of Research for VUMC's Heart Failure and Transplant Section, overseeing studies on novel treatments, devices and transplantation. I've had the pleasure and honor of sitting where you currently sit. I served on this Committee for four years and was a member of the Cardio-Renal Advisory Panel for eight years, so I appreciate the time and effort that you have given to review these data. I would like to share my perspective on the benefits and risks of the V-Wave shunt and why I believe the data warrant your recommendation for approval.

01:45:37 When I began to evaluate these data, I wanted to refresh my memory on the FDA's benefit-risk guidance for devices, and like us clinicians, the FDA takes a very practical approach in evaluating benefit-risk.

01:45:48 When looking at benefit, they ask if there is any evidence of clinical benefit and what is the extent of uncertainty for the benefit. When looking at risks, they ask: "Are the known or probable risks more than minimal?" and "What is the extent of uncertainty for the risks?" And finally, when looking at the benefit-risk ratio, they ask: "Do the benefits outweigh the risks?" and "Do they outweigh the risks when considering postmarket actions?"

01:46:14 This is FDA guidance for any device, not just Breakthrough Devices. Looking at the benefit determination a bit closer, it is important to demonstrate that benefits should be considered based on the assessment of the totality of the data, that is, benefit demonstrated from any one or more of the primary and secondary data sets and further stating that benefits should be considered based on the assessment of data, whether or not the results are statistically significant.

01:46:42 This is guidance from the FDA on factors to consider when making a benefit-risk determination, and I certainly agree with their recommendations. This is what guides me in choosing therapy for my patients and I think this trial supports a positive benefit-risk ratio for the shunt in the treatment of HFrEF patients.

01:46:59 Certainly, in heart failure patients there is an unmet need. We have 6 million people currently in the United States with heart failure and that is estimated to grow to more than 11 million by 2050. Half of all of these patients have HFrEF and we know that they have a very high residual risk despite all available treatments. As you can see on the left from the EMPEROR-Reduced trial, a recent trial of SGLT2 inhibitors in HFrEF patients, the two-year residual risk of heart failure hospitalization and cardiovascular mortality is 47% even in the EMPA flows on treated group. But these were primary New York Heart Association Class II patients. The data in HFrEF

patients for RELIEVE-HF on the right show similar but worse outcomes in the sham-controlled group compared to the shunt group. These patients were almost all New York Heart Association Class III, so they were at higher risk than those in the EMPEROR-Reduced trial. You can see that they had a very high residual risk of heart failure hospitalizations and mortality.

01:48:02 This point is further supported by data from this study collating all of the data on guideline-directed medical therapy on survival in HFrEF patients. You can see here that half of all 50-year-old patients with HFrEF on ideal guideline-directed medical therapy will die within 12 years. In contrast, the expected 10-year-survival in healthy 50-year-olds is 90 to 95%. The mortality rate has markedly improved with the four pillars of GDMT, but the survival probability is still unacceptable. This is not what I want for my patients.

01:48:37 Going back through the FDA guidance document, the first question we ask is: "Was the study well-designed and executed?" We believe that RELIEVE-HF was well-designed and executed as a robust, double-blind, sham-controlled study. As we showed you, patients were on optimal guideline-directed medical therapy, randomization was stratified by LVEF strata, follow-up was nearly 99% for the primary analysis, and there were few major protocol deviations.

01:49:06 Next: "Can I safely treat my patients with this device?" We saw extremely good safety results with almost no safety concerns with this device in terms of procedure-related, device-related and long-term outcomes. Speaking as a heart failure clinician, I feel confident in the safety of this device for my patients.

01:49:27 "Will my patients benefit from this device?" We have seen that the benefit reduction in all heart failure events for the HFrEF patients was outstanding, as shown in the upper left panel. On the upper-right-hand side, you can see the difference between the shunt group and the control group in HFrEF patients. These are hard endpoints of death, LVAD or transplant, heart failure hospitalizations and worsening heart failure,

which matter greatly to patients. On the bottom, you see the consistency of these hard endpoints in our HFrEF patients. No matter which single or composite group of endpoints we looked at, there was a marked reduction in adverse outcomes with shunt treatment in HFrEF patients.

01:50:08 And there is a plausible biological mechanism to explain these differences in treatment effect. We have shown that HFrEF and HFpEF patients respond differently to shunting due to differences in left ventricular and right ventricular structure and function. As Dr. Zile showed you, shunt-treated HFrEF patients had improved left ventricular remodeling measured by LV and diastolic and systolic volume index without deleterious effects on the right heart. In contrast, in HFpEF patients, there was no LV reverse remodeling and consistently increased RV and diastolic area index, right atrial area index and pulmonary artery systolic pressure occurred.

01:50:49 The proposed indication is supported by the data and in the best interest of these patients with a high risk of heart failure hospitalization and mortality, those with New York Heart Association Class III, despite guideline-directed medical therapy and left ventricular ejection fraction of less than or equal 40%, to reduce the risk of heart failure hospitalization.

01:51:08 I believe the totality of evidence supports approval. We have shown you a significant unmet need in HFrEF patients. We have a well-executed randomized sham-controlled trial with an excellent safety profile and clinically meaningful improvements in all important hard clinical outcomes. We have also shown you a biologically plausible mechanism for the results. Thus, we believe that the Ventura interatrial shunt has demonstrated a highly favorable risk-benefit profile in patients with HFrEF worthy of approval. As a heart failure clinician, this is a device that I would like to have available for my HFrEF patients who remain highly symptomatic despite guideline-directed medical therapy.

01:51:49 Thank you very much for considering these data and my perspectives. Dr. Abraham will return to manage the question and answer portion of this presentation.

01:51:58 Dr. Abraham: Thank you, Dr. Lindenfeld. On behalf of V-Wave, I would like to thank the Panel and the FDA for your attention. We would be happy to answer all of your questions.

Questions to V-Wave

01:52:12 Dr. Lange: Well, thank you. This is Dr. Lange. I would like to thank the sponsor's representatives for their presentation and this is an opportunity for the next approximately 30 minutes for the Panel members to ask clarifying questions to the sponsor. The sponsor will have time over lunch to get the answers to those questions, so after lunch we'll come back and deliberate, but let me open it up to the Panel for clarifying questions and if you have a question, please raise your hand. I'll try to call you in order. I see Dr. Blankenship with the first question. Jim.

01:52:47 Dr. Blankenship: Thank you. The Echo Core Lab in Hershey Medical Center in table 10 of the supplement from the circulation article; it talks about that echo EF was calculated using biplane technique, but I'm curious about what exactly was the technique for determining ejection fraction. You did show us data suggesting that there was some margin that even if-- Higher ejection fractions at 40% may be beneficial, but I'm curious as to what method was used for ejection fraction. Is it reproducible and is it easily performed? Thank you.

01:53:26 Dr. Lange: Right. Okay. So again, a question about the technique for method of determining LVEF and also its reliability. Thank you. I've got Dr. David Yuh, Dr. Wittes, Amit Shanker, and then Chris O'Connor. Doctor Yuh.

01:53:47 Dr. Yuh: Yes. Thank you. Thank you for a very nice presentation. I was curious; this question is directed towards Dr. Zile. Were there any changes, appreciable changes, in LVEF between the patient populations? You mentioned all the other

factors with respect to biologic plausibility, but I was just curious about LVEF, any changes that you've noticed?

01:54:06 Dr. Lange: Okay, and David, specifically with HFrEF or HFpEF or both?

01:54:10 Dr. Yuh: Both.

01:54:11 Dr. Lange: Okay, great. We'll ask them to provide that information. Great. Dr. Wittes.

01:54:24 Dr. Wittes: Yes. So, can I ask two questions?

01:54:26 Dr. Lange: Yes, madam, you may. And David, you have to take your hand down unless you have another question. Go ahead, Janet.

01:54:31 Dr. Wittes: Okay, thanks. So, first thanks to this very, very clear presentation and this-- Clearly the study was done very well. Here are my two first questions. Do you have a distribution of the ejection fractions in the entire population? What I want to have a sense of-- What the spread was, what the distribution was, and how many were close to the 40.

01:55:03 Dr. Lange: And, Janet-- So, you're asking for that across both groups? HFpEF and HFrEF? Okay?

01:55:08 Dr. Wittes: Yes, across both groups.

01:55:09 Dr. Lange: Okay, great. Okay, and your second question.

01:55:14 Dr. Wittes: Well, my second question is I don't understand how you-- The argument for the link between the permutation test and the showing that there was no very small increase in type I error rate. Can you explain the statistics behind that?

01:55:36 Dr. Lange: So again, the difference between the permutation and the statistical significance? Did I get that correct, Janet?

01:55:43 Dr. Wittes: No, why the permutation test gave evidence that there was very little increase in type I error rate.

01:55:52 Dr. Lange: Okay. And by the way, I'm writing these down so at the end we go over all these, so thank you, Janet.

01:56:01 Dr. Wittes: Okay.

01:56:05 Dr. Lange: Great. Great. I've got Dr. Shanker, Dr. O'Connor, Dr. Page, Dr. Vidovich, Dr. Blankenship again, Mitch, and then Ms. Dunn, and then Eric Leifer. So, Amit?

01:56:16 Dr. Shanker: Okay. Thank you very much for this very comprehensive presentation. Looking at slide 83, you state that changes in LV remodeling and PA pressures predict subsequent CV mortality and heart failure morbidity. If you look at slide 81, you show the PA systolic pressure on average, the difference is reduced in controls versus shunts by 2.2 millimeter of mercury. My question is, in looking at table 33 that you submitted to us, and looking at the echocardiographic data, there appears to be a discrepancy that I would like you to clarify a little bit further. The baseline PASP in the HFrEF shunt patients was 31.5 and at 12 months was actually increased at 33.1 millimeters of mercury. So, I'm having some difficulty grappling with what I'm seeing on the table and what I see on this graph, because obviously we know that, as has been pretty eloquently explained during the presentation, PA pressures matter, and [it's] not just going to matter at one or two years, it's going to probably matter at five years as well. Thank you.

01:57:25 Dr. Lange: Okay, so thank you. I think I've got that one right. Chris. Dr. O'Connor.

01:57:31 Dr. O'Connor: Thank you. Really a well-executed trial and very clear presentations. Thank you for that. The-- Dr. Stone mentioned that sometimes it's difficult to discriminate mode of death, as we saw that there was no difference in CVD in the HFrEF group, but there was in all-cause albeit small numbers. Do we--

It's also difficult with non-fatal hospitalizations. Can we see the rates of cardiovascular hospitalization and all-cause hospitalizations in the HFrEF group? And then the second point is was there any asymmetric dropping of GDMT in the HFrEF cohort?

01:58:21 Dr. Lange: Are you talking about specifically changes in medication doses?

01:58:27 Dr. O'Connor: Was there a differential dropping of GDMT, particularly the SGLT2, which was one that was changing rapidly during the trial-

01:58:38 Dr. Lange: -Okay.-

01:58:39 Dr. O'Connor: -that might have dropped-- Might have increased in one arm versus the other arm post-randomization.

01:58:45 Dr. Lange: Great, thanks, Chris. Okay, good. Dr. Page.

01:58:48 Dr. Page: Yeah, thank you. And I do want to compliment the presenters for doing a very nice job. The formal stratification was written into the protocol and clearly there was a difference between HFpEF and HFrEF and therefore the sponsors have analyzed these independently. I think there was a comment at or around slide 48 or before that about losing power by-- Reducing the number by cutting-- By separating the groups, you lose some power. But then there was a comment about sample size actually being determined in-- Prospectively, with the recognition that analyzing between HFpEF and HFrEF would be performed. I'm asking the sponsor whether, as they powered this study and the sample size determined, was that around the single collected all patients enrolled or was sample size actually adjusted around the opportunity to analyze specifically HFrEF separated from HFpEF?

02:00:12 Dr. Lange: Thank you, Dr. Page. Back to-- I'm sorry, Dr. Vidovich.

02:00:18 Dr. Vidovich: So, thank you very much for these very comprehensive presentations. I do have, probably, let's say two questions, one and a half. My biggest one is the safety of the device. There has been very little embolic events, so,

either pulmonary embolisms, cerebrovascular events, and I would like a better explanation or a better understanding of the background oral anticoagulation, which, again, based on my review, appears to have been present in about 60% of patients, looking at the supplemental material in the published trial and the background antiplatelet agents. So, should this device, let's say, be used in clinical practice, how do we incorporate these findings with recommendations for use based on safety? And then, the second minor question is-- It is clear that placebo effect with devices, say, sham knee arthroscopy, can last for very, very long time, but two years seems quite a long time for a placebo effect. So, I would, again, there was some mention in the presentation, but I would like a little bit more discussion and understanding about this.

02:01:34 Dr. Lange: Thank you, Dr. Vidovich.

02:01:35 Dr. Vidovich: Thank you.

02:01:36 Dr. Lange: Dr. Blankenship.

02:01:39 Dr. Blankenship: Thanks again. And I would like to echo the other panelists in thanking sponsors for a very clear presentation. Again, in Dr. Stone's article in circulation from 2024, in the statistical section, says the results in each LVEF strata, although pre-specified, were not powered and are therefore hypothesis-generating. And then in the discussion he says, whereas these analyses referring to ejection fraction groups were pre-specified, they were not powered and should best be considered exploratory. And that seems like it's a little more cautionary than the arguments we've heard from the sponsors and I just wondered how they put those together. Thank you.

02:02:24 Dr. Lange: Okay, thank you. Dr. Krucoff.

02:02:29 Dr. Krucoff: Yeah, thank you. I'll certainly join the chorus that this was a phenomenal presentation, thanking the sponsor and all of the presenters, and clearly

an extraordinarily well-executed trial. I have two quick questions, maybe for-- One for later and one for now or later, but I'm wondering if at one or two years, or beyond the one-year-point, the sponsor has any data that could be shared about the actual performance of the shunt in the patients who received the shunt. So, patency, flow rates, and hopefully the correlation of both of those over one to two years. My second question is really related to the-- While a very well executed trial, what I took away from Dr. Stone's very elegant presentation of all of the sort of stratification of ad hoc analysis to create a totality of data, if I read this right and heard his description right, is really the implication that the trial design, the primary SAP using a win ratio, was a mistake? Because the hierarchical approach of using death as the top, which I-- Most of us would put at the top of the hierarchy, actually masks the burden of heart failure events. Is the-- My kind of moron-level version of that, is it really saying that this should have been an event-driven analysis rather than a patient-driven analysis or am I missing something? So, that's a question at some point that I would appreciate the sponsor addressing. Thanks, Rich.

02:04:26 Dr. Lange: Thanks, Mitch. Writing that down. Ms. Dunn.

02:04:35 Ms. Dunn: Hello. I do have two clarifications, but first I did also want to say that it was a very comprehensive presentation, so thank you. My question is on Dr. Stone's slide, and I would like this drilled down a little bit more. It looks like there were 508 randomized patients, but then I also saw that 348 patients in the study and all were male, just curious [about] the ratio between male and female patients that were in both sectors of the study. I just think that that's important, that we kind of look at that. So, thank you.

02:05:18 Dr. Lange: Okay, thank you, Ms. Dunn. Dr. Leifer.

02:05:25 Dr. Leifer: Well, thank you. Yeah, no, I certainly echo what everybody else has said about this being a very well-done study and a very elegant and detailed presentation. Actually, I think a question that Mitch raised is actually quite relevant.

I mean, I think that unfortunately for the sponsor and that the statistical analysis didn't meet significance using the win ratio and if they had maybe used a particular type of recurrent event analysis, they might've made it on that term. So, I don't really think that death was masking what was going on below. I mean, certainly part of the hierarchy was that number of heart failure hospitalizations was part of the hierarchy. And so, a bit of the analysis when-- That they were talking about, it was sort of the win ratio was masking the number of events. It wasn't quite right. I mean, you were counting number of events and that could be a tiebreaker for a winner or loss. So, speaking a little bit to what Mitch raised and a bit more about whether events are masked or not, you know, looking at the Statistical Analysis Plan that they provided--

02:06:50 Dr. Lange: So, Dr. Leifer, let me ask you a question, because we will talk about this, and your comments and your perspective.

02:06:54 Dr. Leifer: Okay.

02:06:56 Dr. Lange: Do you-- Is there a question you want to pose to the sponsor, you wanted to ask?

02:06:59 Dr. Leifer: Sure. Okay. I apologize. I'm sorry.

02:07:01 Dr. Lange: No, no. No, your comments are well, and we will-- I'm going to solicit them this afternoon.

02:07:07 Dr. Leifer: Okay. I apologize. I'm sorry. No, no. I mean, my specific question to the sponsor is that, if they really felt that they were going to be looking at the two, the HFpEF and the HFrEF, that there was a big potential looking at them separately, I was wondering why they didn't set up some sort of pre-specified, sort of alpha spending gatekeeping procedure that would've allowed them to do it in a rigorous statistical fashion, if they found that the interaction tests between the HFrEF and the

HFrEF-- And the HFpEF groups was different. So, it's really why wasn't that pre-specified?

02:07:51 Dr. Lange: Great question, Dr. Leifer. Thank you. Dr. Tchantchaleishvili.

02:07:58 Dr. Tchantchaleishvili: Thank you very much for this presentation. I wanted to say that HFrEF category is-- In patients with EF of 35%, it's very different from patients with EF of 15%, let's say. So, I was wondering if you had any data of how many patients you had with EF less than 20%, and if you could comment on that.

02:08:20 Dr. Lange: Okay. And so, Vakhtang, do you want just a number of patients or you want that and their outcomes?

02:08:26 Dr. Tchantchaleishvili: If outcomes are available, yes, I would want to--

02:08:29 Dr. Lange: Okay, okay. Terrific. Alright. Dr. Kumbhani.

02:08:45 Dr. Kumbhani: Yeah. Hi. Thanks. Yeah, I want to thank the sponsors for an excellent presentation and a really well-done study. I think a lot of the questions have been covered. I have two, I guess, mechanistic questions for the team. The first is, I know that a baseline PVR of greater than four was an exclusion criteria for this trial. So, I'd like to see data based on changes in PVR in the HFrEF and the HFpEF groups, and specifically any changes in the shunt fraction based on the changes in PVR. And then my second question is, you know, patients with-- Especially patients with HFrEF will frequently have a lot of valvular disease, especially tricuspid and mitral valve disease, and by increasing-- Potentially increasing RV preload, I'd be interested to hear and understand what the changes in MR and TR or mitral and tricuspid regurgitation in the two arms are as well.

02:09:55 Dr. Lange: Great questions. Great questions. Dr. O'Connor.

02:10:00 Dr. O'Connor: Just a quick question back to the statistical assumptions. It looks like there was a belief that there would be greater benefit in the HFpEF cohort versus the HFrEF strata at the beginning of the trial, it looked like there were-- The

assumptions on the sample size calculations were that there would be 30% greater difference in the HFpEF group. So, the question is was that the hypothesis and the reason for stratification is that the investigators believe that the device would improve efficacy to a greater extent in the HFpEF population?

02:10:45 Dr. Lange: Great. Dr. Blankenship.

02:10:50 Dr. Blankenship: Well, thank you for letting me come back one more time. The group included patients with ischemic cardiomyopathy and non-ischemic cardiomyopathy. Dr. Zile did very elegant work about showing a remodeling effect. And my question is that if a large portion of the myocardium is dead from myocardial infarction, it would be less potential for remodeling and therefore possibly less benefit obtained from the shunt. And I wonder if there was any analysis done by type of cardiomyopathy or would that be something for the future?

02:11:26 Dr. Lange: Thank you, Jim. Dr. Leifer again.

02:11:32 Dr. Leifer: Yeah, one other question. I'm sorry to come again, but yeah, [I'm] curious about this Global Statistical Test that they mentioned on slide 51 and understanding the difference between that test and the win ratio.

02:11:48 Dr. Lange: Okay. Great. Dr. Hauptman.

02:11:57 Dr. Hauptman: Thanks, Dr. Lange. And thank you for the presentation. So, a lot is being made of the echocardiographic substudy, which was used to provide biological plausibility for the findings. So, I have a couple of questions, perhaps for Dr. Zile later this morning. To what degree were the echoes actually unblinded? It would seem to me that they were unblinded by definition since the shunt should be pretty obvious on the echo. We also know that RV measurements can be technically challenging and we didn't hear much about interpretability, so I [am] just curious how much missingness was present in measuring RV function, RV size. And sort of along with that, the sponsor on slide 55 shows what they referred to as sort of a

monotonic relationship between EF and heart failure events, but they didn't comment on the fact that the 95% confidence intervals were wide. Or they may have mentioned they were wide, but they crossed the line of unity except for a very, very small number of-- Or a very limited range of EFs. And I'd like them to comment on that.

02:13:21 Dr. Lange: Okay. Paul, [I] just want to make sure I-- With regard to the right heart measurements, you're talking about reliability or specifically--?

02:13:29 Dr. Hauptman: Well, it is mostly about how often were measurements made that were-- Yes, that were reliable. We all know there are patients for whom RV measurements can be challenging based on the windows that are used. And so, was this, you know, were a hundred percent of the patients evaluated on the RV? Or what percent?

02:13:56 Dr. Lange: Got it. Thank you. Thank you, Paul. Dr. Yeh.

02:14:02 Dr. Yeh: One clinical and one statistical question, the clinical being that, since we know that there may be remodeling and that EFs are not stagnant, and then there is this sort of qualitative interaction where there's harm potentially in a more normal EF, how is the sponsor thinking about if a patient were to get this device and have EF improvement above the 40% threshold, and are they venturing into a territory where the device could subsequently be harmful? How should we be thinking about that? The second is-- I'm wondering in the Statistical Analysis Plan for RELIEVE-HF, if there were some intimation that-- Because the interaction test was significant, that the two subgroups were not poolable. But my understanding also is that those tests were considered exploratory. So, is there language in the Statistical Analysis Plan saying that if the interaction test were significant, that the primary pooled effectiveness analysis would somehow be trumped, would not take place? Or is that something that they are sort of stating after the fact? Thank you.

02:15:15 Dr. Lange: Dr. Wittes.

02:15:21 Dr. Wittes: My question relates-- It's very similar to the one you just asked. So, there's a lot of discussion, both in the briefing book and today, that because the interaction test was significant, you have to separate the two, you have to look at them separately. I don't think that's really always true. You can have a significant test, but there's not a crossover. And I think there are plenty of us who would say, "You can still do the test, you should look at both, but you could do the combined test." So, my question is-- It's a formal statistical question. Was the Gale Simon test of crossover-- Was that statistically significant? I think if that were, then I think most people would agree, "Yeah, you have to separate."

02:16:08 Dr. Lange: And so, specifically the Gale Simon test?

02:16:10 Dr. Wittes: Yeah.

02:16:12 Dr. Bram Zuckerman: Just for clarification, Dr. Wittes, when you use the term crossover, you are talking about a qualitative interaction-

02:16:21 Dr. Wittes: -Yeah.-

02:16:21 Dr. Bram Zuckerman: -to help the sponsor prepare a response to your question.

02:16:25 Dr. Wittes: Yes, I am. Benefit in one group, harm in the other.

02:16:29 Dr. Bram Zuckerman: Thank you.

02:16:31 Dr. Lange: Okay. Dr. Kumbhani.

02:16:36 Dr. Kumbhani: Yeah, thank you. I actually was just going to point out that the onset-- New-onset A-fib or atrial flutter was about 5% at 12 months in the device arm. I'd like to understand also-- This is based on what the sponsor had provided, table 35. And so, what was the overall incidence of atrial arrhythmias in both groups and was that comparable?

02:17:10 Dr. Lange: Alright, Dr. Gomes.

02:17:16 Dr. Gomes: Thank the sponsors for an excellent study. I had a question with regard to how they arrived at the size of the shunt when the device was designed. And I also have a question with regard to the reliability of the echocardiographic findings for the right ventricular analysis and for the assessment of the minimal change in PA pressure.

02:17:56 Dr. Lange: Alright, we're coming to a close for this part. I'm going to add something as well. This is-- I'm sorry, Dr. Yancy, and then I'll be the last, I'll close it out. Clyde. I'm sorry, you're on mute, Clyde.

02:18:12 Dr. Yancy: Thank you Dr. Lange. Let me not only also echo the high bar of the presentations we heard, but the high bar of the questions from the co-Panel members. It's really been in very sophisticated conversation and we're exercising appropriate due diligence. One statement that is in part a question and that is to emphasize Dr. Wittes's first comment. I think it's imperative that we have as much certainty as possible that we've excluded the risk of a type I error. The likelihood of deployment for clinical use is significant here and we need to understand whether or not we have a very strong hypothesis or do we have compelling data. My question is that we also should ask the sponsors to compare this to already existing data from the REDUCE LAP-HF trial published in circulation in September 24, whether-- This study was published in circulation, REDUCE LAP was published in Lancet. But the point there is that it was a much larger trial where there was not a signal of harm in HFpEF, and even maybe perhaps a subgroup that might've benefited. So, I think that that ends up being an important comparator because just like we are emphasizing harm in HFpEF and benefit in HFrEF, what do the other data points say about the absence of harm in HFpEF? The point of bringing up the circulation publication was looking at the ejection fractions as published in the paper that defines RELIEVE-HF, that mean EF or reduced ejection fraction heart failure was right at 40%. And so, I do think it's

important to have further illumination of the distribution of the reduced EF parameters. Thanks so much, Dr. Lange.

02:19:54 Dr. Lange: Thank you, Dr. Yancy. I'm going to take the last three then I'm going to close. I'm going to give you each a minute so we can close and have a little bit of time for biologic break. So, Mitch?

02:20:05 Dr. Krucoff: Yeah, just a quick footnote, Rich, that it not get lost in the conversation. I think the question was raised about the echoes and the Echo Core Lab being unable to be blinded. I just want to make sure we get an answer to that part of it.

02:20:22 Dr. Lange: Thank you.

02:20:22: Dr. Lange: Great. Thanks, Mitch. Paul? Dr. Hauptman?

02:20:25 Dr. Hauptman: Yeah, hi. So, this is a quick question and I may have to wait for the FDA presentation. In the FDA document on page 31, table 11, there looked like there was some imbalance between the shunt group and the sham group in terms of CVA and TIA. And yet the sponsor provided data that suggests there was absolutely no difference. And even though the numbers are small, I just want to make sure that we're on the same page with regard to that. And then maybe the sponsor can also delineate how the Clinical Events Committee would decide whether or not a TIA or CVA was at all device-related or not. I think that might be a challenge in many patients.

02:21:09 Dr. Lange: Okay. Great. Dr. Gomes?

02:21:13 Dr. Gomes: No, I'm sorry. Just lowered my hand.

02:21:16 Dr. Lange: Alright, let me close it out. Two questions for the sponsor. One is if you could provide the Qp/Qs data for both groups shunted, the HFrEF and the HFpEF, that would be lovely. I'd like to talk about that. And then finally, there's-- Obviously there are 97 roll-in patients and [it would] be interesting to see the data for those, because they're very similar. Again, we're about to take a break. I want to thank,

again, the sponsor for excellent presentations. Very clear. I appreciate you are all willing to take our questions. Before I close, Dr. Abraham, do you have any questions about the questions that need clarification?

02:21:54 Dr. Abraham: No, I do not. I think they were quite clear. Thank you very much.

02:21:58 Dr. Lange: Great. So, this will give you time between now and we come back from lunch to prepare answers though. So, with that, again, I want to thank the participants. We're going to take a 15-minute break. We're going to reconvene at 9:30 Mountain Time. That's where I'm at. 11:30 Eastern Time, 8:30 Pacific Time. So, we're going to go offline. You'll see a timer and I'll bring us all back in. So, if you'd like to--

02:22:27 Dr. Abraham: Yeah. Dr. Lange, can you hear me?

02:22:29 Dr. Lange: I can.

02:22:30 Dr. Abraham: Oh, yeah. There is one question that we have. What specifically would you like to see in terms of roll-in data or comparison between roll-in and randomized data?

02:22:42 Dr. Lange: Just what you have in there. How did the patients fare with regard to the same endpoints?

02:22:48 Dr. Abraham: Okay.

02:22:48 Dr. Lange: That'd be great. So, thank you.

02:22:49 Dr. Abraham: Great. Thank you.

02:22:50 Dr. Lange: Thanks, Bill. Okay, see you all in about 15 minutes. Please, turn your videos off.

FDA Presentation

00:04:33 Dr. Lange: It is now 11:30. This is Dr. Rick Lange and I would like to call this meeting back to order. FDA will now give their presentation and I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at my specific request. The FDA will also have 90 minutes to present, and FDA, you may now begin your presentation. Thank you.

00:05:07 Mr. Mondine: Good morning, everyone. This is FDA's presentation regarding V-Wave's premarket approval, or PMA, application for the Ventura Interatrial Shunt System. My name is Victor Mondine. I'm a Biomedical Engineer and the Lead Reviewer for this PMA. You'll hear from key members of the Review Team during this presentation, but we appreciate the contributions of the entire FDA Review Team that has worked on this PMA listed here. This is the outline of FDA's presentation. I'll start by providing a summary of relevant clinical regulatory and device background information along with a description of the RELIEVE-HF pivotal trial design.

00:05:56 Mr. Mondine: Heart failure is a complex clinical syndrome with symptoms resulting from structural or functional impairment of ventricular filling or ejection of blood. It is characterized by high mortality and hospitalization rates and a reduced quality of life. Approximately 6.7 million Americans and more than 26 million people worldwide have heart failure. Heart failure rates are increasing. The lifetime risk of heart failure has increased to 24%, meaning approximately one in four people will develop heart failure in their lifetime. Heart failure management requires high levels of healthcare use-- Resource utilization.

00:06:35 Left ventricular ejection fraction, or LVEF, is an important measurement of the heart's pumping function. LVEF is calculated by dividing the amount of blood pumped out during a heartbeat, also known as stroke volume, by the total amount of

blood that filled the chamber before the beat, also known as end diastolic volume. And LVEF is expressed as a percent. LVEF is commonly used to describe heart failure phenotypes and has frequently been used in clinical trials. LVEF describes the following heart failure phenotypes that are used for clinical decision-making. Heart failure with reduced ejection fraction, or HFrEF, describes patients with LVEF less than or equal to 40%, and heart failure with preserved ejection fraction, or HFpEF, describes patients with LVEF greater than 40%.

00:07:25 For HFrEF patients, the Class 1A cardiovascular professional society recommendations, which are based on strong evidence from multiple high quality randomized control trials and meta-analysis, include lifestyle and comorbidity management; sodium glucose; cotransporter-2, or SGLT2, inhibitors; loop diuretics for symptom management; neurohormonal modulators; and implantable cardioverter defibrillator, ICD, or cardiac resynchronization therapy, CRT, in eligible patients.

00:08:01 For HFpEF patients, the Class 1A recommendations include numbers one, two, and three from above, hypertension management and atrial fibrillation management if applicable.

00:08:17 In heart failure patients, there is usually an increased left atrial to right atrial pressure difference, irrespective of LVEF. It is suggested that a relatively small reduction in left ventricular volume could lead to a relatively large reduction in left ventricular pressure. The creation of an interatrial shunt that permits left-to-right shunting could lower left atrial pressure resulting in increased exercise tolerance and easing of pulmonary congestion symptoms, with the reduction in heart failure complications.

00:08:48 There are still many unanswered questions about interatrial shunting. For example, what is the optimal interatrial shunt size that produces effective left atrial decompression but does not result in right heart volume overload, leading to right heart failure and pulmonary hypertension. Additionally, optimal shunt flow rates and cardiac chemodynamics parameters that can predict clinical success or failure are

unknown. Finally, the optimal patient population that could benefit from this procedure has not been established.

00:09:20 The V-Wave Ventura Interatrial Shunt System was designed to achieve interatrial shunting. The V-Wave shunt is a permanent implant designed to shunt blood from the left to right atrium to improve symptoms in patients with advanced chronic heart failure. The shunt, shown here on the left, is constructed on an hourglass-shaped, self-expanding nitinol frame, with expanded polytetrafluoroethylene, or ePTFE, encapsulation. The Ventura delivery system on the right includes a delivery catheter and is used to hold a shunt, track to the target position over a guidewire and release the shunt. The shunt comes in one size, that is 12 millimeters long and 5.1 millimeters in diameter at the inner neck.

00:10:09 V-Wave's proposed indications for use of the Ventura Interatrial Shunt System are as follows: The Ventura shunt is indicated for NYHA Class III heart failure patients who remain symptomatic despite guideline-directed medical therapy, have an LVEF of less than or equal to 40%, and who are judged by a Heart Team to be appropriate for shunt therapy to reduce the risk of hospitalization for heart failure.

00:10:36 A commonly used classification system that you'll hear in this presentation is the New York Heart Association, or NYHA, functional classification. NYHA functional class categorizes heart failure patients based on symptoms. Class I patients have no symptoms of heart failure during normal activity. Class II patients have symptoms with moderate exertion, such as ambulating two blocks or two flights of stairs. Class III patients have symptoms with minimal exertion, such as ambulating one block or one flight of stairs, but no symptoms at rest. And class IV patients have symptoms at rest.

00:11:16 The Ventura Interatrial Shunt System has undergone the non-clinical test listed here. The non-clinical testing of the Ventura shunt is complete and acceptable. V-wave studied their device in the RELIEVE-HF study. The pivotal IDE application for this

was approved March 2nd, 2018. The shunt received a Breakthrough Device designation on August 5th, 2019. V-Wave filed its PMA on June 3rd, 2024. V-Wave submitted a major unsolicited amendment on March 4th, 2025, that included additional follow-up and analysis. Following review of the PMA amendment and other materials made available to the Agency, FDA referred this PMA to the Circulatory System Devices Panel on August 5th, 2025.

00:12:11 I would like to provide an overview of FDA's Breakthrough Devices Program. For the FDA guidance, a breakthrough device has the potential to provide more effective treatment or diagnosis of a life-threatening or irreversibly debilitating disease versus current available options. The program is intended to provide patients with timely access to select devices by expediting their development, assessment and review. The V-Wave Ventura shunt received Breakthrough Device designation for NYHA Class III and ambulatory Class IV heart failure patients with reduced or preserved left ventricular systolic function.

00:12:49 A breakthrough device designation allows for increased Review Team support, enhanced timely interactions with FDA, efficient and flexible clinical study designs, considerations for the appropriate balance of pre- and postmarket data requirements, and priority review of submissions. It's important to note that the Breakthrough Devices Program does not alter or reduce the statutory requirements for premarket approval. The totality of data must still provide a reasonable assurance of safety and effectiveness.

00:13:23 For Breakthrough Devices, FDA may be willing to accept greater uncertainty for premarket submission along with timely postmarket data collection if the uncertainty in the benefit risk profile can be balanced by other factors, including the probable benefit to patients from earlier access to the device versus the probable risk of harm should additional data reveal the device to be ineffective or unsafe.

00:13:50 RELIEVE-HF is the pivotal trial that studied the Ventura shunt device. The trial enrolled symptomatic heart failure patients treated with guideline-directed medical therapy, or GDMT. The trial consisted of two phases. First, a roll-in phase of 97 patients treated with the shunt. Each investigational site could implant the shunt in up to two roll-in subjects. Roll-in patients were followed and analyzed similarly to the randomized cohort, but their data was not included in the randomized portion of the study. And secondly, a one-to-one randomized sham-controlled trial of shunt treatment versus a sham procedure in 508 patients. Study subjects and study personnel involved in endpoint collection were blinded to treatment group.

00:14:39 Patients were assigned to a treatment cohort after meeting eligibility criteria and completing a baseline visit. Patients were then randomized one-to-one to either the shunt group, which would be treated with the V-Wave Ventura shunt, or the control group, which would be treated with a sham procedure. The randomization was stratified by LVEF.

00:15:03 Key inclusion criteria include the following: ischemic or non-ischemic cardiomyopathy with either reduced or preserved LVEF and documented heart failure for greater than or equal to six months prior to the baseline visit; NYHA Class II, Class III or ambulatory Class IV; patients treated with GDMT for heart failure consisting of heart failure drugs with a Class I indication; patients treated with Class I guideline-recommended cardiac rhythm management devices therapy if indicated; and being able to perform a six-minute walk test.

00:15:39 Key exclusion criteria include the following: severe pulmonary hypertension, right ventricular dysfunction, left ventricular and diastolic diameter greater than 8 centimeters, untreated moderately severe or severe aortic or mitral stenosis, and mitral valve repair device implanted less than or equal to three months prior to the baseline visit.

00:16:04 The primary safety endpoint was the proportion of shunt group patients experiencing device- or procedure-related major adverse cardiovascular or neurological events, also known as MACNE, during the first 30 days after randomization. Randomization in this study occurred at the time of the intervention procedure. MACNE was a composite of all-cause death, stroke, systemic embolism, need for open cardiac surgery, or major endovascular surgical repair. The following events were not included in the primary safety endpoint event rate: percutaneous drainage of a pericardial effusion, percutaneous catheter snaring and removal of an embolized but uncomplicated shunt device, and non-surgical treatment of access site complications.

00:16:52 The primary effectiveness endpoint was the hierarchical composite of the following components: all-cause death; cardiac transplantation or left ventricular assist device, LVAD, implantation; all heart failure hospitalizations, that includes emergency room heart failure visits lasting greater than or equal to six hours; all worsening heart failure events treated as an outpatient; change in Kansas City Cardiomyopathy Questionnaire, KCCQ, score of greater than or equal to five points from baseline to 12 months. The primary effectiveness endpoint analysis was performed when the last enrolled patient had been followed from a minimum of 12 months following randomization and included all available data through 24 months of follow-up.

00:17:45 A heart failure hospitalization required a non-elective in-hospital stay for worsening heart failure that was present at the time of admission and considered as the primary cause of hospitalization and that included at least one calendar date change and required intravenous or mechanical heart failure therapies or the significant augmentation of oral heart failure medication. A worsening heart failure event was defined as an unscheduled outpatient medical contact associated with changes in heart failure therapy and requires documented new or worsening symptoms due to heart failure, objective evidence of new or worsening heart failure, treatment specifically for worsening heart failure, and documented response to treatment.

00:18:31 The hierarchically tested secondary effectiveness endpoints included KCCQ score change from baseline to 12 months; rate of heart failure hospitalization, adjusted for all-cause mortality; time to all-cause death, LVAD or transplant or heart failure hospitalization; time to all-cause death or first heart failure hospitalization; cumulative heart failure hospitalizations; time to first heart failure hospitalization; hierarchical composite of all-cause death, LVAD or transplant, heart failure hospitalization and worsening heart failure treated as an outpatient; and finally change in six-minute walk test from baseline to 12 months.

00:19:15 Clinical outcomes were evaluated in multiple subgroups including age, sex, BMI, diabetes, hypertension, ischemic versus non-ischemic cardiomyopathy, LVEF stratified by HFrEF versus HFpEF, baseline NYHA Class III versus Class IV, baseline six-minute walk time, and baseline KCCQ score.

00:19:40 Now, Dr. Chuan Bi will next discuss the RELIEVE-HF Statistical Analysis Plan and important statistical principles.

00:19:49 Dr. Bi: Good morning. My name is Chuan Bi. I'm the Statistical Reviewer for the V-Wave Ventura shunt PMA submission. I will discuss the related statistical topics of the RELIEVE-HF study

00:20:03 As previously presented, the primary safety endpoint was the percentage of treatment group patients experiencing device- or procedure-related MACNE during the first 30 days after randomization. The hypothesis tested whether the true device- or procedure-related MACNE rate was below the predefined performance goal of 11%. The statistical analysis used a one-sided exact binomial test with an alpha level of 0.025. The study was powered at 87% to detect the difference between a 5% expected rate and an 11% performance goal based on the 200 evaluable shunt group patients.

00:20:55 The primary effectiveness endpoint was a composite endpoint with ranked components by clinical importance, consisting of all-cause death, cardiac transplant or LVAD implantation, heart failure hospitalization, worsening heart failure, and KCCQ improvement. The hypothesis tested whether the treatment improved the composite outcome compared with control.

00:21:23 The Finkelstein-Schoenfeld statistic will be used as the test statistic with an alpha of 0.025 one-sided. Effect size will be measured using the win ratio with a 95% confidence interval. The study is powered at 90%, with a total of 400 patients, 200 per treatment arm. The Finkelstein-Schoenfeld method and the related win ratio approach compare all possible patient pairs between treatment and control groups. Each pair is ranked hierarchically by pre-specified clinical outcomes, yielding a win, loss or tie. The overall treatment effect is expressed as the ratio of wins to losses, providing a non-parametric measure of all-- Of treatment benefit across prioritized outcomes.

00:22:22 This table shows the study powering assumptions which were based on the assumed event rates by LVEF stratum. The total sample size of approximately 400 patients was determined through simulation using these assumed rates. When the study was powered, it was assumed that both LVEF subgroups, HFrEF and HFpEF, would benefit from shunting, with a greater magnitude of benefit assumed in the HFpEF subgroup. For example, as highlighted from the table for the first heart failure hospitalization event, HFH1, the assumed improvement was 9.9% for HFpEF compared with 6.8% for HFrEF. Similar relative improvements were assumed for the second and third hospitalization events and for the KCCQ quality of life score.

00:23:27 Now, I'd like to shift to a key concept that underlies all confirmatory clinical studies: the control of type I error rate. Type I error is the incorrect rejection of a true null hypothesis, that is, concluding that a device is effective when it actually is not. In confirmatory clinical trials, control of type I error rate, which is the probability of

making a type I error, is essential to ensure statistical validity and scientific credibility. Therefore, this error rate must be carefully controlled and pre-specified in the protocol or Statistical Analysis Plan, as it defines the scope of confirmatory testing and establishes which analysis can yield statistically valid inferences. Statistical significance cannot be attributed to any post-hoc analysis conducted after observing the results. Therefore, performing unplanned post-hoc analysis and deviating from the pre-specified analysis plan should not be viewed as conclusive statistical evidence. They are generally used for hypothesis generation.

00:24:51 For the study design of RELIEVE-HF, the type I error rate was controlled through the following pre-specified strategy. For the primary endpoints, safety and effectiveness were each tested independently at the one-sided alpha level of 0.025. For the secondary endpoints, a fixed order of testing was planned using the same alpha level where each endpoint will be tested only if all previous endpoints were significant. As previously presented, the initial design was powered for approximately 400 patients. A pre-specified sample size re-estimation plan was included at the interim analysis to allow adjustment while maintaining the type I error rate control, following the method of Cui-Hung-Wang. The interim analysis was conducted under DSMB oversight and the DSMB recommended that the study continue as planned. In accordance with the pre-specified plan, the total sample size was subsequently increased to 508 patients.

00:26:13 As discussed in the previous slide, the RELIEVE-HF study proposed a clear and strict type I error control strategy. Besides the primary endpoint, a COVID-19 impact analysis was also to be explored on potential external influences on study conduct and outcomes. The secondary endpoints were to be formally tested only if the primary effectiveness endpoint was statistically significant using the same alpha level and following a strict hierarchical order. In addition, 15 pre-specified subgroup analysis of the primary safety and effectiveness endpoints, which were to be

analyzed for this descriptive purposes only. Furthermore, 17 additional effectiveness endpoints and nine additional safety endpoints were to be assessed for descriptive exploration. Because the primary effectiveness endpoint was not met, the hierarchical testing sequence was not initiated and any subsequent analysis should be considered exploratory.

00:27:28 This slide provides statistical context for the subgroup and interaction analysis performed in this study. First, it is well understood that, in general, treatment effects may vary across subgroups and in some trials certain interactions are pre-specified and incorporated into planned confirmatory analysis. However, in most cases, including this study, subgroup or interaction analysis are exploratory in nature, where nominally significant interaction test results may reflect true heterogeneity, but they may also rise from chance finding due to, for example, increased variability in the outcome. When there is treatment effect, the goal is to assess whether there is overall consistency across clinically relevant subgroups. In the RELIEVE-HF Statistical Analysis Plan, interaction tests were intended for descriptive purposes only and not to be used as a test statistic for confirmatory hypothesis tests. As such, any observed differences across subgroups should be viewed as exploratory and hypothesis-generating.

00:28:52 In this slide, I will summarize the post-hoc analyses conducted after the primary effectiveness endpoint was not met, along with the corresponding statistical considerations from FDA. First, the sponsor reported a statistically significant difference in treatment effect between the HFrEF and HFpEF subgroups, with a nominal p-value of 0.0146. However, it is important to note that this interaction test was planned for exploratory purposes only and the small interaction p-value reflects only the difference between subgroups rather than treatment benefit, and that difference was heavily driven by the poor outcomes observed in the HFpEF subgroup treated with a shunt.

00:29:46 The sponsor further analyzed each stratum separately and claimed to demonstrate the opposite treatment effects between HFrEF and HFpEF patients. The sponsor subsequently conducted permutation testing and concluded that the type I error inflation was minimal, suggesting that the observed results were unlikely to represent false positives. Meanwhile, multiple changes were made to the endpoints and analytic methods to further explore apparent effectiveness within the HFrEF subgroup.

00:30:24 However, all of these analyses were performed after the primary effectiveness endpoint was not met. Therefore, p-values arising from these post-hoc analyses, such as unplanned within-stratum analysis, or exploratory evaluations of alternative endpoints, like cumulative hospitalizations, cannot be interpreted as demonstrations of statistical significance. No type I error rate control can be attributed to these post-hoc observations and, consequently, their findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory evidence of treatment effect.

00:31:12 Now, Dr. Andrew Farb will present on the clinical study results.

00:31:16 Dr. Farb: Good morning. My name is Andrew Farb. I'm a Cardiologist and the Chief Medical Officer in FDA's Office of Cardiovascular Devices. I'll be discussing the RELIEVE-HF clinical trial results. Here's the outline of my presentation. I'll start by reviewing the RELIEVE-HF trial results for all randomized subjects. Then, the heart failure with reduced ejection fraction subgroup followed by the heart failure with preserved ejection fraction subgroup, and then some pathophysiologic insights into clinical outcomes. I'll close with a review of the RELIEVE-HF trial strains, limitations and benefit-risk considerations.

00:31:59 First, the trial results for all randomized subjects. This cohort represents the primary analysis population chosen by the sponsor. To review, RELIEVE-HF enrolled 605 patients at 100 sites between October, 2018 and October, 2022. There were 56 U.S.

sites, 3 in Canada, 10 in Israel, 27 in Europe, 3 in Australia and 1 in New Zealand. Prior to the Randomized Phase, there were 97 roll-in patients. Then, 580 subjects were randomized in one-to-one fashion to either the shunt group, 250 subjects or to the sham control group, 258 subjects. There were 249 shunt patients available for follow-up at one year, and 157 at two years. A generally similar number of control subjects were available for follow-up, 256 control patients at one year and 140 at two years. A total of three shunt subjects and five controls were drawn for the trial.

00:33:10 Key demographic and baseline characteristics for the ITT population of all randomized subjects are shown on this slide and can be found in FDA's Executive Summary. Greater than 60% of subjects were male, and about 90% were Caucasian. Subjects were otherwise representative of a U.S. heart-failure population with a high proportion of patients with diabetes, hypertension, hyperlipidemia, and coronary artery disease. Subjects were approximately equally divided between ischemic and non-ischemic cardiomyopathy. And greater than 95% were in New York Heart Association Class III. Baseline demographics and clinical characteristics were generally similar between the shunt and control groups.

00:34:01 This table shows baseline heart failure medications and cardiac rhythm devices. Most patients who are on guideline-directed medical therapy for heart failure including beta blockers, RAS inhibitors, MRAs, and diuretics. And medication use was well balanced between treatment groups.

00:34:22 This slide shows baseline transthoracic echo measurements, which were generally balanced between the shunt and control groups. About 40% of the ITT population were in the HFrEF subgroup; that is an LVEF of less than or equal to 40%. And 60% were in the HFpEF subgroup; that is an EF of greater than 40%.

00:34:44 Right heart cath data are shown on this slide. Like other baseline characteristics, hemodynamic parameters were generally similar between the shunt and control groups.

00:34:55 This slide shows device and procedural outcomes and subjects randomized in the shunt group. The shunt was successfully implanted in all 250 randomized shunt group patients. Transesophageal or intracardiac echo evaluation of just implanted shunts showed 96% of shunts had continuous left atrial to right atrial blood flow, and the remaining 4% had intermittent bi-directional flow. Net shunt flow averaged 110 plus or minus 321 ml per minute. And the ratio of systemic to pulmonary flow, the Qp/Qs ratio, averaged 1.25 plus or minus 0.11. There were no cases of shunt migration, embolization or thrombosis.

00:35:43 As you've heard, RELIEVE-HF was a blinded sham-controlled randomized trial. Those blinded to the assigned treatment included study subjects, the Clinical Events Committee, research staff administering the KCCQ, and research staff collecting study endpoint events. Among study staff not blinded were shunt implanters, sonographers and echo readers. An assessment of shunt blinding effectiveness showed that 2% to 8% of randomized patients correctly guessed their treatment group assignment beyond the play of chance. These results suggest that blinding was adequately maintained through one year following the shunt implant or sham index procedure.

00:36:31 Starting with device and procedure safety, this slide shows the primary safety endpoint results. Recall that the primary safety endpoint was the rate of device or procedure-related major adverse cardiovascular or neurological events, or MACNE, at 30 days post-randomization, which was performed at the index procedure and was evaluated in 250 shunt group patients. No shunt patient experienced the primary safety endpoint event through 30 days. The 0% event rate had an upper 97.5% confidence limit of 1.5%, which was lower than the 11% performance goal. Thus, the primary safety endpoint was met with a p-value of less than 0.0001.

00:37:25 Here are secondary safety events that were observed over the course of the trial in the shunt and control groups. Overall, secondary safety endpoint event rates were

low. There were numerically more cerebrovascular and pulmonary embolism events in the shunt group versus controls, but fewer MI events at two years. There were two type 3 BARC bleeding events in the shunt group at 30 days. Moving to effectiveness, as you've heard, the primary effect of this endpoint in RELIEVE-HF was a five-level hierarchical composite of all-cause death, cardiac transplant or LVAD implantation, all heart failure hospitalizations, all outpatient worsening heart failure events, and the KCCQ score change of greater than or equal to 5 points. This hierarchical composite endpoint was analyzed by the Finkelstein-Schoenfeld method and a win ratio was calculated.

00:38:30 Here are the win ratio results for the shunt group-versus the control group for all randomized subjects. The win ratio was 0.86 with a 95% confidence interval from 0.61 to 1.22 and a non-significant p-value equal to 0.20. The 0.86 numerical win ratio directionally favored the control group. Thus, the primary effect of this endpoint was not met. The per-protocol population results were similar to the ITT population. To set the stage for later discussion, it's important to note that the RELIEVE-HF statistical analysis plan specified that if the primary effect of this endpoint was not met, no further hypothesis driven analysis would be performed.

00:39:22 To further illustrate outcomes between the shunt and control groups, a post-hoc cumulative event analysis through two years of the composite of all-cause death, cardiac transplant or LVAD, all heart failure hospitalizations and all outpatient worsening heart failure events was conducted. This slide shows essentially superimposable curves with a 55.7% annualized event rate in the shunt group versus a 56.0% annualized event rate in controls. The hazard rates were also similar between the shunt and control groups, 1.08 versus 1.14 respectively.

00:40:06 Event rates for the individual components of the primary effectiveness endpoint except KCCQ are shown on this slide. All-cause death numerically favored the control group. There were a few heart transplants or LVADs, which favored the

shunt group. All heart failure hospitalizations were generally similar between the shunt and controls, and all worsening outpatient heart failure events favored the shunt group. Notably numerical between group differences were small.

00:40:38 This slide shows the KCCQ score change through two years. There was a similar increase in KCCQ score of approximately 10 points in both the shunt and control groups at one month. The increased score remained essentially unchanged and was similar between treatment groups through two years.

00:40:59 In summary, for the pre-specified primary analysis of the primary effectiveness endpoint for all randomized subjects, the primary effectiveness endpoint was not met, consistent with no signal of shunt benefit. Rates for the composite endpoint components of death, cardiac transplant or LVAD, all heart failure hospitalizations and all worsening outpatient heart failure events were generally similar between treatment groups at all timepoints through two years. All-cause death and heart failure hospitalization numerically favored the control group, while cardiac transplant or LVAD, and all worsening outpatient heart failure event rates favored the shunt group. However, between-treatment group differences were small. Changes in the KCCQ score were similar between the shunt and control groups from just following the index shunt procedure or the sham procedure onward.

00:42:01 To introduce the discussion about the heart failure phenotype subgroup analyses, recall that randomization was stratified by site and by baseline TTE measured left ventricular ejection fraction as determined by the Echo Core Lab. This resulted in two heart failure phenotype subgroups, a HFrEF subgroup consisting of 206 randomized subjects and a HFpEF subgroup consisting of 302 randomized subjects. In accordance with the statistical analysis plan, an analysis of the primary effect of this endpoint for the HFrEF and HFpEF subgroups was to be conducted based on Finkelstein-Schoenfeld estimates used to calculate a win ratio. As shown in the figure, the win ratio in the HFrEF subgroup was 1.40, a result numerically in favor

of the shunt arm, and the HFpEF subgroup win ratio was 0.61 favoring the control group. The interaction p-value was 0.146 indicating discordant results between heart failure phenotype subgroups. It's important to note that while a nominally significant interaction p-value was seen for clinical outcomes between heart failure phenotypes that were based on LVEF, there was no pre-specified hypothesis driven analysis of individual subgroups per the statistical analysis plan.

00:43:35 Subgroup analysis can provide insights into treatment patterns across different populations. These analyses are exploratory and were not powered for formal hypothesis testing. The subgroup analyses examine treatment effect consistency across populations using interaction tests with Z-statistics on the Finkelstein-Schoenfeld statistic.

00:44:02 For interaction test results, most subgroups showed consistent treatment effects with non-significant interaction p-values. For example, the p-value for age was 0.14, sex 0.50, diabetes 0.47 and hypertension 0.59, indicating no meaningful heterogeneity in treatment response across these factors. In contrast, as shown here and on the prior slide, the LVEF interaction test yielded a p-value of 0.10146 indicating a potential differential response between HFrEF and HFpEF subgroups with win ratios of 1.21 and 0.70 respectively. But the baseline eGFR subgroup also showed a nominally significant interacting p-value of 0.006. This eGFR result suggests potential shunt treatment heterogeneity based on better or worse kidney function. Patients with an eGFR below the median had a win ratio of 0.67 suggesting shunt-associated harm, while those above the median eGFR had a win ratio of 1.20 suggesting shunt-associated benefit.

00:45:34 The sponsor focuses on anomaly significant interaction test in patients stratified by LVEF to support shunt benefit in HFrEF patients, but the significant interaction p-value in the baseline eGFR subgroup also warrants attention. The eGFR interaction p-value of 0.006 was even smaller than the p-value for the heart failure phenotype

subgroup. And a scientific explanation for discordant clinical outcomes associated with the shunt as a function of baseline renal function is not apparent.

00:46:12 The take-home message is that these findings remain exploratory and require validation in dedicated studies designed to test subgroup hypotheses.

00:46:24 I'll next discuss the HFrEF subgroup analysis. It's notable that the total number of randomized patients in the HFrEF subgroup was only 206, 101 subjects received the shunt and 105 were sham controls. The next five slides show baseline clinical echo and right heart cath features of HFrEF subgroup subjects. These are included in your panel packs.

00:46:51 Key demographic and baseline clinical characteristics are shown here. About 80% of subjects were male and greater than 90% were Caucasian. There were high rates of hypertension, hyperlipidemia, and coronary artery disease with a majority having ischemic cardiomyopathy. Over 94% were NYHA Class III, median Six-Minute Walk Test distance was longer in the shunt subgroup versus controls by 32 meters. Other baseline characteristics were generally similar between the shunt and control subjects.

00:47:30 This table shows baseline heart failure medications and cardiac rhythm devices, which were well matched for beta-blockers, renin-angiotensin-system inhibitors, MRAs, diuretics, and cardiac rhythm devices. Nearly all patients were on beta-blockers, around 90% were on RAS inhibitors, greater than 70% on MRAs, and greater than 90% on diuretics. Of note, SGLT2 inhibitor use was 48% in shunt subjects and 53% in controls.

00:48:07 Here are the baseline and 12 months heart failure medications that provide a snapshot of drug use over time. Overall in the HFrEF subgroup, heart failure medication use at baseline and at 12 months was similar between shunt and control subjects. This table shows baseline transthoracic echo assessments in the HFrEF

subgroup. The mean LVEF was approximately 30% in both treatment groups. Mitral regurgitation was graded as moderate or greater in 24% of shunt subjects and 18% of control patients. RV function in the shunt group appears to be slightly better than the control group, but the impact of these differences on clinical outcomes is uncertain.

00:48:56 Here are baseline right heart cath data in the HFrEF subgroup. Hemodynamic measurements were generally similar between treatment groups. The primary effectiveness endpoint, the five-level hierarchical composite of death, cardiac transplant or LVED, all heart failure hospitalizations, all outpatient worsening heart failure events, and KCCQ score was evaluated in the HFrEF subgroup using the Finkelstein-Schoenfeld method and calculating a win ratio. The win ratio of 1.40 numerically favored the shunt group, but the wide 95% confidence interval from 0.80 to 2.46 leads to an indeterminate conclusion regarding the shunts' benefit-risk profile and HFrEF patients.

00:49:48 This slide shows the KCCQ score change through two years in the HFrEF subgroup. Similar to the full randomized cohort of all enrolled patients, at one month there was a similar increase in KCCQ scores in both the shunt and control groups. The initially increased score remained essentially unchanged and similar between treatment groups through two years. Thus, shunt subjects did not experience an improved health status or quality of life compared to controls as measured by the KCCQ score. Improvement in KCCQ score is not observed consistently in some heart failure trials that show benefits for traditional clinical endpoints. In other studies, however, KCCQ score increases, and responder analysis aligns with lower rates of traditional heart failure events. Further, based on the shunts' principle of operation, it was anticipated that interatrial shunting that decompresses the left atrium would reduce pulmonary vascular congestion symptoms and improve health status. The absence of a KCCQ score difference in favor of the shunt group versus controls, particularly during long-term follow-up, that is at 12 months and beyond, adds to uncertainty

regarding shunt benefits in HFrEF patients. Here are Six-Minute Walk test changes from baseline to 12 months in the HFrEF subgroup. There were no significant differences between the shunt and control groups. Notably, shunting did not lead to a comparative functional improvement assessed by walking distance. In summary, in the HFrEF subgroup, there is no evidence that the shunt resulted in patients feeling better or functioning better versus controls.

00:51:41 The five-level hierarchical composite primary effectiveness endpoint, the hierarchical event order and the win ratio primary test statistics were chosen by the sponsor in the RELIEVE-HF study design. The sponsor contends that the inclusion of KCCQ score as the fifth level of the win ratio might confound the primary effectiveness endpoint results as the KCCQ score accounted for 27% of win ratio decisions. This figure shows that if the KCCQ score level was excluded, the 1.31 win ratio had a wide 95% confidence interval from 0.87 to 1.97 leading again to an indeterminate conclusion regarding the shunts benefit-risk profile in the HFrEF subgroup. Thus, deleting the KCCQ score from the analysis did not change the indeterminate results.

00:52:44 Looking at mortality more closely, a mortality benefit associated with the shunt was not anticipated in the HFrEF subgroup. At the time of the primary analysis there were 13 deaths or 14.3% in the shunt group versus 20 deaths or 26.8% in controls. The causes of CEC-adjudicated death are shown in the table and text. Notably, the number of cardiovascular deaths was similar in the HFrEF shunt and control patients, 11 versus 12 respectively. There was one non-cardiovascular death in the shunt group, a neurologic death and six non-cardiovascular deaths in controls, malignancy in two, infection in two, trauma one and pulmonary one. Dissimilarity in cardiovascular death rates between treatment groups does not support a cardiovascular mortality benefit associated with shunt treatment.

00:53:45 In the HFrEF subgroup, event rates for the individual components of the primary effectiveness endpoint, except KCCQ score, are shown here. The rates for the individual components of the primary effectiveness endpoint numerically favor the shunt group. However, only all heart failure hospitalizations did not include unity; that is 1.0 in the 95% confidence interval.

00:54:11 Next, let's take a deeper dive into recurrent heart failure events in the HFrEF subgroup. The sponsor noted that for heart failure events, heart failure hospitalizations and worsening outpatient heart failure events, shunt patients had generally fewer first events versus controls, 54 versus 69 first heart failure events, respectively. However, the frequency of recurrent heart failure events was disproportionately greater in control subjects versus some shunt subjects, 74 versus 34 recurrent heart failure events, respectively. In additional post-hoc analysis, the sponsor noted a trend favoring the shunt for time-to-first event method and anomaly significant difference for two recurrent heart failure hospitalization assessment methods that used a joint frailty model and a Nelson-Aalen estimator method.

00:55:12 This slide presents the distribution of heart failure event counts per subject in the HFrEF subgroup comparing shunt subjects and controls. The plot displays overlapping histograms with blue bars representing the control group and orange bars, the shunt group. The x-axis indicates the number of heart failure events per subject and the y-axis shows the proportion of subjects within each category. The table in the upper right shows the subject counts by event frequency for each treatment group. As shown, a majority of HFrEF subjects experienced no heart failure events. 56 shunt group patients versus 51 controls. The proportion of subjects with one or two heart failure events were similar between the shunt and control groups. However, a notable difference emerges among subjects with multiple recurrent events. The control group includes a far higher number of subjects with four or more heart failure events compared to the shunt group. This pattern suggests

that the overall findings from the recurrent-event analysis may be influenced by a small number of control patients experiencing multiple heart failure events.

00:56:35 In this table, we compare the sponsor's original analyses of the hierarchically-tested secondary effectiveness endpoints with the results obtained after removing just four subjects with the most heart failure events from the HFrEF control group. Confidence intervals indicate the variability of each summary statistic. They are provided for descriptive purposes and should not be interpreted as formal statistical inference. In the original analysis, as shown in green, endpoints such as heart failure hospitalization adjusted for all-cause mortality and cumulative heart failure hospitalizations demonstrated nominally significant hazard ratios favoring the shunt group. However, as shown in blue, after removing just the four control subjects with the most heart failure events, these apparent benefits were no longer statistically significant and hazard ratios shift towards unity. This pattern suggests that a small number of influential control patients may have disproportionately affected the observer results. Clinically, this raises the possibility that the initial apparent benefit might not represent a consistent physiological response to the shunt, but rather reflect random variation or alternatively worse baseline status among those few control patients. From a statistical perspective, there is inherent uncertainty that cannot be resolved post hoc. As these analyses were exploratory, we cannot determine conclusively whether the observed differences were due to a true device effect or simply chance variation.

00:58:30 This figure shows the cumulative hazard for heart failure events in the HFrEF population. The left panel includes all subjects. The control group appears to have a higher cumulative hazard than the shunt group suggesting a positive true outcome difference. In contrast, the right panel excludes only the four control subjects with the most heart failure events. Once those subjects are removed, the curves are more convergent and the 95% confidence intervals overlap. This illustrates how sensitive

recurrent-event analysis can be. Because every hospitalization counts as a new event, a few individuals with repeated events can strongly influence a cumulative hazard and apparent between group differences. Overall, this figure reinforces that the previous nominal significance between the HFrEF shunt group and control groups could be dependent on a few patients with an unusually high number of recurrent events.

00:59:37 This table shows the Nelson-Aalen hazard rates for individual and composite event types. In the sponsor's original analysis, several endpoints, especially heart failure hospitalizations and selected composite outcomes, showed apparent differences favoring the shunt group. After removing the same four controlled subjects, those apparent differences narrowed considerably or disappeared. This, again, points to an issue with the recurrent-event analysis in that by focusing on total event counts, results can be heavily influenced by a small group of specific patients. When such small changes in sample composition can alter the directionality of the observed outcomes, it signals statistical and clinical uncertainty. Overall, the data show that the nominally favorable results are not robust.

01:00:34 On this slide, we respond to the sponsor's critique of FDA's sensitivity analysis approach. The sponsor's argument for symmetric study subject trimming as being a more fair method misinterprets the intent of FDA's sensitivity analysis. Our approach is deliberately asymmetric along the lines of a stress test in that we intentionally advantage the control group by removing just four control patients with the most heart failure events to see whether the observed treatment effect depended on these extreme cases. The fact that event rate differences narrow or disappear under these conditions shows how dependent the findings are on a very small number of influential observations. In summary, FDA's sensitivity analysis is an example of how post-hoc modifications can alter study conclusions reinforcing that such

analyses should not be considered confirmatory and raise uncertainty regarding device effectiveness.

01:01:42 This slide summarizes the post-hoc subgroup analyses conducted to compare HFrEF and HFpEF outcomes. Across a wide range of cardiovascular endpoints, HFrEF hazard ratios are consistently less than 1.0, while HFpEF hazard ratios are generally above 1.0. On face value, this pattern suggests potential shunt benefit in HFrEF and potential harm in HFpEF. The nominal interaction p-values shown on the right are often extremely small, which gives the appearance of a differential treatment effect between the subgroups. However, these findings should be interpreted with cautions for several reasons. First, none of these subgroup analyses were pre-specified in the statistical analysis plan. All were performed after the primary results were known. Therefore, the interaction p-values are not confirmatory evidence of true subgroup differences. Second, most endpoints incorporated recurrent events in which recurrent event counts were heavily concentrated in a small percent of patients. Finally, in addition to the Z-Test used by the sponsor to support a heart failure phenotype subgroup difference, the sponsor also performed a Gail-Simon test for qualitative interaction. Unlike the Z-Test, the Gail-Simon test was not statistically significant for the primary effect of this endpoint. The fact that two different interaction tests yielded inconsistent conclusions adds another layer of uncertainty about whether any true subgroup differences exist. In summary, these post-hoc findings are unconfirmed.

01:03:35 Here is FDA's summary of the HFrEF subgroup analyses that included 206 randomized subjects. There was no significant shunt benefit demonstrated in the five-level win ratio analysis or the four-level win ratio analysis that excluded the KCCQ score. There was no signal that the shunt was associated with reduced cardiovascular mortality. There was no shunt-associated KCCQ score positive effect size versus the control group. A post-hoc analysis suggests that the shunt was

associated with a reduced rate of heart failure events. However, analyses showing statistically significant shunt benefits in the HFrEF subgroup were unplanned and post-hoc lacked a pre-specified plan to control type I error and have an unquantifiable type I error rate. The apparent heart failure outcome differences favoring the shunt in the HFrEF subgroup may have been driven by a few high recurrent event rate control subjects. Thus, these results may be considered hypothesis-generating and interpreted with caution.

01:04:51 Turning next to the HFpEF subgroup analyses, the HFpEF subgroup consisted of 302 randomized subjects, 149 randomized to the shunt and 153 sham controls.

01:05:08 The next four slides show baseline, clinical, echo and right heart cath features in the HFpEF subgroup. Key demographic and baseline clinical characteristics of this subgroup are shown here. Females accounted for 48% of the shunt group and 52% of controls, and greater than 90% were Caucasian. There were high rates of hypertension and hyperlipidemia and a majority had coronary artery disease. Over 95% were in New York Heart Association Class III. Median Six-Minute Walk distance was longer in control subjects versus shunt patients by 35 meters. Other baseline characteristics were generally similar between the shunt and control groups. Besides LVEF, the demographics and clinical characteristics of the HFpEF subgroup differed from the HFrEF subgroup mostly in that patients in the HFpEF subgroup were older and more likely to be female.

01:06:16 This table shows baseline heart failure medications and electronic therapies. Around 80% were taking beta-blockers, an agent of limited effectiveness in HFpEF. A higher proportion of control subjects were on MRAs, and less than 40% of HFpEF subjects used SGLT2 inhibitors. Greater than 90% of subjects were taking diuretics.

01:06:43 Here are baseline transthoracic echo assessments. The mean LVEF was approximately 56% in the shunt group and 54% in controls. Echo parameters were generally similar between shunt and control subjects with a somewhat high

proportion of shunt subjects having moderate or greater mitral and tricuspid regurgitation.

01:07:07 This table shows baseline right heart cath data. The pulmonary vascular resistance in the shunt group was 2.4 plus or minus 1.0 Wood units, and 2.0 plus or minus 1.1 Wood units in controls. There were small right ventricular function differences that favored the control group, but these are of uncertain clinical significance.

01:07:33 The primary effectiveness endpoint, the five-level hierarchical composite of death, cardiac transplant or LVAD, heart failure hospitalizations, outpatient worsening heart failure events and KCCQ score was evaluated using the Finkelstein-Schoenfeld method and calculating a win ratio. The win ratio was 0.61 with a 95% confidence interval from 0.39 to 0.98. These results favor the control group and raise a possibility that the shunt is harmful in HFpEF patients.

01:08:09 Event rates for the individual components of the primary effectiveness endpoint, except KCCQ, through two years in the HFpEF subgroup are shown here. Rates for all events, all deaths, all heart failure hospitalizations and all outpatient heart failure events favor the control group-versus the shunt group. The lower bound of the 95% confidence interval for the relative risk or hazard ratio of all events, all death and all heart failure hospitalizations was greater than 1.0.

01:08:43 A HFpEF subgroup mortality analysis showed 22 deaths or 16.4% in the shunt group-versus 7 deaths or 5.2% in controls. And of these, cardiovascular deaths were numerically greater in shunt versus control patients. An additional HFpEF post-hoc analysis evaluated the four-level hierarchical composite that excluded the KCCQ level. The win ratio in favor of the control group was 0.65 with a 95% confidence interval from 0.45 to 0.93. These results are similar to the five-level win ratio analysis that included the KCCQ score, consistent with the possibility that the shunt is harmful in HFpEF patients.

01:09:37 Next, I'll touch on the sponsor's pathophysiologic insights into the shunt's performance in the HFrEF and HFpEF subgroups that attempt to explain discordant outcomes between heart failure phenotypes. A pre-specified analysis comparing the HFrEF and HFpEF subgroups suggested that the shunt was associated with benefit in HFrEF and harm in HFpEF. These observations contradict the sponsor's expectation that the shunt would be beneficial in all heart failure subjects independent of phenotype and that the shunts' benefit would be more pronounced in HFpEF patients. To gain insights into these findings, the sponsor conducted a post-hoc exploratory analysis of between-group differences in transthoracic echo changes from baseline to 12 months. 508 randomized patients underwent a baseline echo at a median of 1.1 months prior to randomization. Of these, 428 patients had a 12 month TTE, 80 echoes at 12 months were not performed, 18 patients died or had a heart transplant or LVAD, and 62 patient echoes or 12.2% were soon to be missing at random. There were greater than 17,000 echo measurements corresponding to 17 measurements per study, per patient. Of these, 15,495 parameters or 89.7% were analyzed by the Echo Core Lab, and 1,777 parameters or 10.3% were imputed.

01:11:18 The sponsor reported 16 selected longitudinal echo parameters shown in the panel. Among the within heart failure phenotype group evaluations, they highlighted that in the HFrEF subgroup reversed left ventricular remodeling was observed in shunt subjects and there was a smaller increase in estimated pulmonary artery systolic pressure in shunt versus controlled subjects. In the HFpEF subgroup, there were increased right ventricular, right atrial and an inferior vena cava sizes, and increased pulmonary artery systolic pressures in shunt subjects versus controls. In interpreting these findings, one should consider that they are post-hoc exploratory analyses. There are missing data and test-to-test variability in TTE assessments. The clinical significance of numerical differences, considering sample sizes and 95% confidence intervals, among selected cardiac morphologic and hemodynamic parameters

between shunt subjects and their respective controls within two heart failure phenotypes is unclear.

01:12:32 In the next slides, I'll offer some comments on the RELIEVE-HF trial strains and limitations along with benefit-risk considerations. For the RELIEVE-HF pivotal trial, study strengths include that the trial was a well-executed randomized study, enrollment included predominantly NYHA Class III heart failure patients that were symptomatic despite a reasonable regimen of guideline-directed medical therapy and cardiac rhythm device therapies if indicated. And the primary safety endpoint was met. However, multiple limitations should be considered. The primary pre-specified effectiveness five-level composite endpoint was not met for the total randomized patient cohort of HFrEF and HFpEF subjects. There is uncertainty regarding analyses suggesting shunt benefit in the HFrEF subgroup of 206 randomized subjects, including the five-level win ratio composite effectiveness endpoint was not met; excluding KCCQ, a four-level win ratio composite effectiveness endpoint was not met; there was no cardiovascular mortality benefit associated with shunt use; and there was no KCCQ score improvement in shunt subjects versus controls. Based on the shunt's mechanism of action, an improved health status and quality of life associated with a device intended to reduce pulmonary vascular congestion symptoms via LA decompression was expected but not seen.

01:14:19 Although comparing results between heart failure phenotypes was pre-specified, RELIEVE-HF was neither powered nor pre-specified to test shunt effectiveness in the HFrEF versus HFpEF subgroups. A potential shunt benefit in the HFrEF subgroup was based on post-hoc analyses for which FDA contends that it's not possible to estimate a subgroup analysis type I error rate. And observed heart failure outcome differences favoring the shunt in the HFrEF subgroup may have been driven by a few control subjects with a high rate of recurrent events.

01:15:01 Caution is needed in drawing conclusions from post-hoc subgroup analyses, including additional post-hoc endpoints in the absence of a pre-specified statistical analysis plan to control type I error. There are notable relevant clinical trials that should be considered. For example, the PRAISE trials of amlodipine in chronic heart failure and the TACT trials of chelation therapies in prior MI patients. In the PRAISE 1 trial, enrollment was stratified by ischemic versus non-ischemic cardiomyopathy. The overall results were negative for an amlodipine benefit, but a markedly positive outcome associated with amlodipine was seen in the non-ischemic cardiomyopathy subgroup. In PRAISE 2, enrollment was limited to non-ischemic cardiomyopathy subjects and no amlodipine benefit was observed. In the TACT 1 trial, a large chelation benefit was seen in the diabetic subgroup. In TACT 2, that limited enrollment to diabetic subjects, no chelation benefit was seen. In both the PRAISE 1 and TACT 1 publications, the authors provided mechanistic postulates to support subgroup results observed in the initial trials, but they concluded the subgroup results were hypothesis-generating that required confirmatory studies.

01:16:35 Continuing with RELIEVE-HF limitations, there was a signal of possible increased mortality and heart failure event risks in HFpEF patients, and there is limited understanding of the relationships among anatomic and hemodynamic changes associated with implanting an interatrial shunt, shunt flow metrics, and clinical outcomes in heart failure patients.

01:17:00 With regard to clinical decision-making, there are challenges applying the RELIEVE-HF outcomes to patient selection. The sponsor claims shunt benefit in one heart failure phenotype, HFrEF with an LVEF of less than or equal to 40%; and possible harm in another heart failure cohort, HFpEF with an LVEF of greater than 40%. These results pose clinical decision-making challenges because LVEF is a continuous variable. LVEF can change over time in response to therapeutic interventions or disease progression. LVEF is associated with error in the

measurement and variability that can result in changes that cross the 40% EF threshold. For example, the absolute intra-patient repeat LVEF measurement variability using the same method within short periods is greater than 7% in either direction. And finally, LVEF measurement accuracy is operator-dependent, relies on image quality, and is affected by heart rate and rhythm, for example, in the presence of atrial fibrillation.

01:18:14 This figure helps illustrate the challenges. The solid red lines represent event rate differences between the shunt and control group patients in the HFrRF subgroup, that is, shunt events minus control events. The dotted red lines are 95% confidence intervals. Negative values below the horizontal green line favors shunt subjects, and positive values above the horizontal green line favors control subjects; and an increasing beneficial effect of shunt treatment is seen as the LVEF declines. These data suggest that, broadly speaking, below an LVEF of approximately 40%, the event rate difference between the shunt group and the control group favors the shunt group; that is, benefits associated with the shunt. Above an LVEF of approximately 4%, the event rate difference between the shunt group and the controls favors the control group; that is, harm associated with the shunt. However, the 95% confidence intervals around the event rate difference show uncertainty regarding the 40% LVEF cutoff boundary for defining shunt associated benefits versus harms. In the left figure, the upper 95% confidence interval curve crosses the green line of unity consistent with shunt associated harm for total heart failure hospitalizations for LVEFs greater than 30%. Similarly, in the right figure, the upper 95% confidence interval curve crosses the green line of unity consistent with shunt associated harm for the composite of death, heart transplant or LVAD, heart failure hospitalizations and worsening outpatient heart failure events for LVEFs greater than 30%. For LVEFs less than 30%, the upper 95% conference interval curves run very close to the line of unity of no difference between the shunt group and the control group.

These findings present challenges in determining a favorable benefit-risk profile in clinical decision-making for individual patients.

01:20:36 The sponsor conducted a sensitivity analysis using LVEF boundaries for LVEFs greater than 40% to less than or equal to 47% to support a safety margin for the LVEF cutoff or less than or equal to 40% for the HFrEF population. The results of this sensitivity analysis suggest that the shunt appears to provide a favorable heart failure event risk ratio for an LVEF of greater than 40% and less than or equal to 43%. However, it should be noted that the sample sizes are small and there are a few events. Further, the upper bound of the 95% confidence interval for other LVEF intervals greater than 40% or equal to 44%, greater than 40% to less than or equal to 45%, and greater than 40% to less than or equal to 47% exceeds 1.0. Taken together, these data increase the uncertainty of the proposed LVEF safety margin results.

01:21:46 In summary, a 40% LVEF cutoff directs clinical decision-making toward or against shunt use. LVEF measurement factors create challenges in determining a favorable benefit-risk profile for clinical decision-making in individual patients. Victor Mondine will now present FDA's concluding remarks.

01:22:08 Mr. Mondine: Thank you, Dr. Farb. I will now summarize the proposed post-approval study and FDA conclusions. The sponsor plans continued follow-up of all patients implanted with the shunt in the RELIEVE-HF study through five years. Additionally, the sponsor proposes enrolling a single-arm post-approval study, or PAS, that includes a pre-specified performance goal for clinical outcomes. Finally, the sponsor proposes enrolling all U.S. patients not included in the PAS into a registry to gather real-world data. We note that postmarket data cannot be used as a substitute for necessary premarket data that establishes a reasonable assurance of safety and effectiveness. That is to say, post-approval studies are designed for the continued assurance of safety and effectiveness and not to a priori demonstrate safety and effectiveness. In conclusion, the RELIEVE-HF study was a well-executed

sham-controlled randomized trial of interatrial shunting in heart failure patients in which randomization was stratified by LVEF. The event rate for the primary safety endpoint of MACNE within 30 days was 0%, which met the pre-specified performance goal.

01:23:21 The primary effectiveness endpoint was a win ratio of the hierarchical composite of all-cause deaths, LVAD or transplant, heart failure hospitalization, worsening heart failure treated as an outpatient and KCCQ score. The primary effectiveness endpoint was not met. The win ratio was 0.86 with a confidence interval of 0.61 to 1.22 and a p-value of 0.2. The sponsor's post-hoc analysis in the HFrEF subgroup raised uncertainty regarding shunt benefit due to a small sample size and lack of type I error control. Additionally, heart failure event results may have been driven by a small number of control subjects. There was no observed cardiovascular mortality benefit associated with shunt use in HFrEF patients and a possible mortality risk was observed in HFpEF patients. There was also no observed health status or quality of life shunt benefit versus control when this was anticipated based on the device's mechanism of action. Lastly, uncertainty remains as to whether the totality of the data establishes a favorable risk-benefit profile for the shunt for its proposed indication for use.

01:24:35 This completes FDA's closing remarks. We thank the Panel for their time, participation and discussion. It helps us all support public health.

Questions to FDA

01:24:45 Dr. Lange: Great. I'd like to thank the FDA also for an excellent presentation. We're now open for the Panel to ask clarifying questions to the FDA for the next 20 to 25 minutes. So Mitch, we'll start off with you. This is Dr. Krucoff.

01:25:00 Dr. Krucoff: Thank you, Rich. And again, kudos to the FDA team for just a fantastic context for their thoughts on everything we've been talking about today. My one quick question, Dr. Farb, slide number 97-- And I apologize if I missed this, but is

that slide actual patient-level data from RELIEVE Heart Failure or is that slide a hypothetical illustration of the points Dr. Farb was making?

01:25:36 Dr. Lange: All right, we will ask Andy to address that after the presentation. All right, Dr. Yuh.

01:25:45 Dr. Yuh: Thanks, Dr. Lange, and thanks to the FDA for a comprehensive presentation. So, an important question that I believe Dr. Krucoff raised in the prior session was the decision to use a win ratio versus a recurrent-event analysis, particularly with an area where there's a very large disease burden over time before some terminal event. I was just curious, to what extent did the FDA participate in the decision to follow that statistical pathway? It's my understanding, with the Breakthrough Device pathway, that that is a potential mechanism for expediting review is to have a joint data-development pathway. I was just curious if that was in effect in this case.

01:26:33 Dr. Lange: Okay, thank you. We'll answer that. Dr. Shanker, number three.

01:26:39 Dr. Shanker: So, I wanted to really just congratulate the FDA team for doing an excellent job with their due diligence in spite of all the other external moving parts that have happened over the past year and kudos to your team. Regarding slide 71 to 74, it was for me remarkable to see that excluding four subjects had such an impact on the analysis, emphasizing of course the challenges with post-hoc analysis and also a low sample size. So, thank you for pointing that out. My question is regarding imaging and why the FDA felt it was okay just to get echocardiographic parameters at one year and not at two years, and why there wasn't any consideration for multimodality imaging to corroborate some of the finding anatomic and hemodynamic findings. Thank you.

01:27:40 Dr. Lange: Great. Thank you, Dr. Shanker. Dr. Wittes.

01:27:44 Dr. Wittes: Thank you. So, first of all, we can remove the question about the Gail-Simon test from the sponsor because it was answered by the FDA. Thank you so much for looking at that and answering that. I do have a question about the Cui-Hung-Wang test, which wasn't really discussed by either presentation or wasn't discussed in detail in either briefing book that I could find. What it does is to downlight the data from the second phase of the study. And the second phase is the patients recruited after the decision to increase the sample size. And I wonder whether you looked at what that down-weighting was; how much of the results were influenced by the tests; and whether if you'd only used the first 400 patients recruited, what the results would've been.

01:28:45 Dr. Lange: Right. Dr. Yeh.

01:28:49 Dr. Bram Zuckerman: Excuse me, Dr. Lange, I'm not sure the FDA will be able to answer that question during the lunch break. Perhaps Dr. Wittes could also ask the sponsor to look at that important question.

01:29:01 Dr. Lange: Okay. So, Dr. Abraham, I'm going to punt that to you all, to the sponsor again and at the end I'll come back to make sure you understood the question directed toward the FDA. But thank you, Bram. Dr. Yeh.

01:29:16 Dr. Yeh: Thanks. I'll ask the reciprocal question I asked the sponsor for the FDA, which is: It's pretty clear that the FDA views the subgroup analyses on ejection fraction as no different than any of the other proposed subgroup analyses, and I want to understand from the FDA standpoint to what extent they value both the stratification of it, the sort of primacy of that subgroup analysis over the others, or [if] they're truly viewing it as essentially exactly the same as all the other potential exploratory subgroup analysis? And if so, why? Thanks.

01:29:55 Dr. Lange: Thank you. Dr. Leifer.

01:29:58 Dr. Leifer: Yes, thank you for the excellent presentation by the FDA. And this actually might be a statistics question which can't be answered within 90 minutes, but I'll just ask it anyway. I was very interested in the analysis, with deleting the last four patients of the control group. I guess there is-- The fifth patient was in the shunt group. It would've been interesting just to see if that one patient was kept back in. And then finally, also this sort of long tail distribution on slide 70. I think some of the p-values that were computed by the sponsor were based on the Lin-Wei-Yang-Ying test. And I'm curious, with the long tail, relatively few patients having a lot of events-- I wonder what sort of type I error inflation could be associated with that particular type of setup. Again, that's probably not a question you can get in 90 minutes, but it's just kind of interesting to think about. Well, in terms of thinking about the small p-values that the sponsor showed.

01:31:05 Dr. Lange: Thank you, Eric. And if the sponsor or the FDA doesn't address it, we'll ask our statisticians to weigh in on that. Thank you, Eric. Dr. O'Connor.

01:31:15 Dr. O'Connor: Yeah, again, excellent presentation. Question for Dr. Farb. I'm intrigued by, on slide 55, the interaction that was noted with renal function. Is there a subset of patients who have HFrEF and reduced renal function that would confer increased risk?

01:31:46 Dr. Lange: All right. Again, if the FDA does not have access to that individual data, if the sponsor could provide that information, that would be very helpful. Thank you, Chris. Dr. Vidovich.

01:32:01 Dr. Vidovich: Again, fabulous presentation by the FDA. Thank you for adding additional clarification and thought-provoking points with removing four patients. My question is actually the Qp/Qs data. Do we know where this comes from at what stage of the procedure this was done? This is the first time I'm actually hearing this. I was looking at this. Could we get some more clarification? And then again, to Dr. O'Connor's question, is it fully plausible that increase in renal flow

from this might've contributed to this or not? And again, these are interesting questions. I don't know who could answer this either the sponsor or the FDA, but again, if you could clarify, that would be helpful.

01:32:51 Dr. Lange: Dr. Vidovich, great question. And I'm going to add to that, if you don't mind-- I'm wondering if the Qp/Qs or the shunt volume was different between the HFrEF and HFpEF patients.

01:33:05 Dr. Vidovich: It's quite plausible, right?

01:33:06 Dr. Lange: Yes. So, if we could get that information, that'd be very helpful.

01:33:10 Dr. Neubrander: Dr. Lange?

01:33:11 Dr. Lange: Yes.

01:33:11 Dr. Neubrander: This is Rachel Neubrander. I just want to note that likely is a question the sponsor is going to be more able to answer than we are.

01:33:20 Dr. Lange: Terrific. Okay. So, Dr. Abraham, again, we'll come to the end and make sure you got both of those questions. Great. Any other clarifying questions to the FDA? Dr. Yancy? I'm sorry I missed you. Go ahead, sir. You're on mute, Clyde. I'm sorry.

01:33:42 Dr. Yancy: Thanks, Dr. Lange. Just one very short question. What is the precedent and past regulatory reviews by the FDA for the selective removal of patients? This was done to hear from the control group. It does depict an important set of observations, but how has this been deployed in the past?

01:34:01 Dr. Lange: Okay. Thank you. Thank you, Clyde. Dr. Blankenship.

01:34:05 Dr. Blankenship: One more question about that analysis of four patients removed. Presumably the FDA took the strongest case they could find about the idea of removing a few patients altering the result. Did they look at what would happen if

you removed one patient or two patients, or three patients, or four patients or five patients and decided that removing four patients proved the point most effectively?

01:34:40 Dr. Lange: Okay. Just for the record, I want to note the FDA did not remove any patients or remove patient data, but no patients were removed by the FDA. No animals were harmed in this particular study. Great. Other clarifying questions? All right. If not, Dr. Abraham, the three questions that were directed towards the sponsor, do you need any clarification on the clarifying questions?

01:35:16 Dr. Abraham: No, I don't believe so. Thank you.

01:35:18 Dr. Lange: Okay, terrific. We're actually 15 minutes ahead of time and that's okay. What I'm going to do is we want to give adequate time for the FDA and sponsor to provide answers to our queries. We would normally reconvene at 2:00 p.m.. I'm going to ask we reconvene at 1:45 p.m.. That's still the same amount of time. And I would ask both the FDA and the sponsor to make sure that our answers are succinct because I'm sure we'll generate more questions. I want to make sure there's plenty of time that the Panel can get all their questions answered and have plenty of time for deliberation to provide the necessary information to the FDA. So with that, again, I want to thank both the sponsor and the FDA for excellent presentations. I look forward to this afternoon. Let's join back at 1:45 p.m.. For the Panel members, go ahead and mute. Make sure you turn your video off. We'll have a timer on and I'll see you all in 45 minutes. Thank you.

Open Public Hearing

00:05:34 Dr. Lange: This is Rick Lange. It's now 1:46 Eastern Time and I would like to resume the Panel meeting. We'll proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. Kendra Brooks will read the Open Public Hearing Disclosure Process Statement. Thank you, Kendra.

00:05:59 Ms. Brooks: 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 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 any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this 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.

00:07:16 Dr. Lange: Thank you, Ms. Brooks. The FDA has received eight requests to speak prior to the final date published in the Federal register. Our first five speakers have opted to pre-record. These videos will now begin and then I'll call on Speaker 6, 7 and 8 following that. Let's hear the pre-recorded opinions.

00:07:36 Ms. Rivera: Hello, and thank you for giving me the opportunity to speak today. I have no financial disclosures. My name is Salina Rivera. I'm 48 years old and I live in San Antonio, Texas with my husband. I'm a mother to a 21-year-old son, and a stepmother to my two sons who are 23 and 26. I'm a former Elementary School Teacher, now a Health and Life Coach, and I'm in the process of publishing my first book. I'm also a proud member of the Lions Club where we serve our local community and I work as a patient advocate for those living with heart failure.

00:08:11 When I was 29 years old, back in 2006, I was diagnosed with the advanced stages of heart failure. I was told I had less than a month to live and would likely not survive

waiting for a heart transplant. For 17 months, I lived completely dependent on that mechanical pump because instead of giving up, I chose hope. I joined a clinical trial for the HeartMate II LVAD, the left ventricular assist device. That device became my lifeline. It kept me alive when my own heart couldn't. And through these 17 months, my heart was able to rest, which helped it recover enough to function on its own and the LVAD was removed. Thanks to the LVAD, I was given 16 more years with my native heart; 16 beautiful years that I never would've had without that trial. There were many years of watching my son grow up, remarrying, gaining two more sons, and this past year celebrating our 15th wedding anniversary. I was living a life that once seemed impossible.

00:09:26 Then in 2022, everything changed again. I developed a severe staph infection and my heart began to fail again. This time my only option was a heart transplant. Once again, I went into cardiogenic shock and I had to rely on another device, the Impella 5.5 pump to keep me alive while waiting for a heart transplant. About a month later, I received the gift of life, a new heart from my donor. Her heart beats inside of me today and her family has become part of mine.

00:10:02 Ms. Rivera: I've lived with heart failure for almost half my life. I know what it's like to fight for every breath, to feel exhaustion and to live with the constant uncertainty of what tomorrow might bring. But I also know the power of medical innovation because it gave me more time. It gave my son a chance to grow up with his mother. It gave me a chance to find love again and have a family. And these memories we will cherish forever. When I learned about this new shunt treatment for heart failure, I couldn't help but think “I wish this had been available when I needed it.” If there had been a way to reduce pressure on my own heart and slow the progression of my disease, I might have avoided the LVAD, the infection and even the transplant. If I had this option then, I would have said yes in a heartbeat.

00:11:00 Ms. Rivera: I'm deeply grateful for the devices that saved me and my new heart, but I also live every day knowing the risk associated with having someone else's heart. That's why I believe so strongly that patients deserve every safe, effective innovation that can improve their lives like the shunt. So, I please ask you to remember my story and remember the thousands of patients who are still waiting, still hoping for another chance at life because technology gives us more than time. It gives us hope and it gives us back our futures. Thank you so much for your time, your compassion, and for the work you do to save the lives like mine.

00:11:49 Ms. Monroe: Hi, I'm Rhonda Monroe, and thank you for the opportunity to share my testimony today. I'm the Founder and CEO of BOOST, Better Outcomes Optimal Scientific Therapies, and I'm also the U.S. Lead for Heart Life Foundation. My review and analysis are informed by two decades of patient-advocacy experience acquired through grassroots advocacy and community education, health system experience as a Board Director and Fiduciary of two community hospitals for over six years where we built the first community cath lab. I have heart disease nonprofit leadership experience, medical society advocacy, legislative advocacy, think-tank engagement, and professional patient advocacy.

00:12:45 However, it's my personal experience as a HFrEF patient that has moved me to join you today. At 36, I suffered a massive heart attack five days after giving birth to my third child. A delayed diagnosis for an entire week led to five coronary artery dissections in my left main, LAD, circumflex, right coronary and a diagonal. I had an emergency quadruple bypass. The next morning in recovery I had another heart attack, and a third in the following month. A few months later, my bypass graft failed and I was diagnosed with heart failure. I had aneurysms all throughout my heart and my apex became aneurysmal. My ejection fraction was 21% and my prognosis was poor. In fact, I was told to get my affairs in order and prepare for my untimely demise. Instead, I called a press conference from my hospital bed. Then I

researched, advocated for and received unconventional cutting-edge therapies because I was unwilling to leave my newborn, kindergartner and fourth grader without a mother. You could say my advocacy career began advocating for myself. Today I gratefully stand in the gap for the multitude of existing patients and the estimated 300,000 patients diagnosed with New York Heart Association Class III heart failure each year, very few of whom will go on to receive a heart transplant.

00:14:26 The United Network for Organ Sharing reported only 4,100, slightly over 4,100 transplants in 2022. There's a great need but little remedy for this patient population who is on GDMT for drugs and devices yet remain symptomatic. I believe V-Wave offers hope for this group and here's why. Safety is not a concern and that's great from a patient perspective. Second, the heart team patient selection approach offers balanced group expertise which is preferred over a single refer. Third, protocolized physician training will ensure all patients receive skilled care. A control commercial market rollout provides additional guardrails that benefits patients by allowing for careful selection of qualified sites. And finally, the five-year patient follow-up will provide information on any adverse events and a robust set of data that can be analyzed.

00:15:38 In my heart failure journey, innovative therapy gave me an opportunity with my children, the oldest of whom has an accounting degree, the middle who recently graduated with a Master's in Applied Data Analytics, and my baby who will graduate from Duke University in the spring. I've also had the privilege of engaging in clinical research to improve patient engagement, patient diversity, and develop patient-facing materials. My life has been rich and meaningful beyond my poor prognosis. Personal fortitude and media engagement opened a pathway to an alternative treatment option for me. Patients shouldn't have to resort to such desperate measures. A favorable reply for V-Wave will provide patients with a choice. And to be honest, that's all we really want: a chance and a choice. Thank you for listening.

00:16:41 Dr. Reed: Well, thank you for the opportunity to comment. My name is Dr. Grant Reed. I'm an Interventional Cardiologist at Cleveland Clinic. I have no relevant financial disclosures. I have a Master's of Science degree in Clinical Research and believe I am uniquely suited to comment on this issue because I have an expertise in high-quality observational studies and clinical trials. I also have first-hand experience deploying the V-Wave Ventura Shunt in an early feasibility study with the device, so I can testify to its ease of use and safety.

00:17:12 I specifically want to address the subgroup findings from the RELIEVE-HF trial in patients with reduced left ventricular ejection fraction and an EF of less or equal to 40%. In this pre-specified analysis, patients treated with the Ventura Shunt had an annualized adverse cardiovascular event rate of 49.0% compared to 88.6% with placebo. This is a relative risk of 0.55 and 95% confidence interval of 0.42 to 0.73, with a p-value of less than 0.0001. This represents a 45% relative risk reduction, and as such, this is not a borderline signal. The statistical probability that this occurred by chance is less than 0.01%. This indicates a clinically robust signal for the benefit of shunt therapy in patients with reduced ejection fraction. The magnitude of benefit is striking and is biologically plausible. Interatrial shunt therapy reduces left atrial pressure, improving pulmonary vascular congestion in patients with HFrEF. This mechanism is supported by prior observational studies, by benchtop studies and by pilot studies in space. And these all report similar hazard ratios for reduction in hospitalization due to heart failure. The consistency of these findings across multiple data sets reinforces that this is highly unlikely to be an isolated result due to chance. Based on the results of RELIEVE-HF and REDUCE LAP II, we now understand that patients with HFpEF in isolated diastolic dysfunction may not benefit from shunt therapy, while patients with HFrEF may be a distinct population whose physiology may be better suited to handle the flow across the septum due to these devices, and thus, benefit from reduction in pulmonary vascular congestion.

00:18:58 While the overall RELIEVE-HF trial was neutral due to the outcomes within the HFpEF population group, this HFrEF subgroup analysis was pre-specified, adequately powered and lined with mechanistic expectations. Requiring another full confirmatory trial may delay access to therapy, which could significantly reduce morbidity mortality in this heart failure population who have few remaining treatment options. Patients with HFrEF indeed do face progressive disease in high event rates even despite optimal guidelines directly medical therapy. And every year of delay means thousands of preventable hospitalizations and perhaps even deaths. These patients do not have the luxury of time. The effect size observed here is so strong that I believe it negates the need for another lengthy randomized trial before approval. Instead, a reasonable regulatory pathway would be approval of the Ventura Interatrial shunt for HFrEF patients with robust post-approval registry study to monitor real-world safety and effectiveness. This pathway has recently been followed with success with other device therapies and could be followed here as well. In summary, the evidence of benefit in HFrEF is compelling, statistically strong and clinically urgent. We have a therapy that can meaningfully change outcomes for this high-risk patient population. And I believe it is reasonable for the FDA to consider approval with postmarket surveillance rather than requiring another lengthy confirmatory trial so that patients can access this therapy without unnecessary delay. Thanks.

00:20:29 Dr. Feitel: Hi, my name is Dr. Scott Feitell. I am the Director of Heart Failure in the Cardiac Intensive Care Unit at Rochester Regional Health. I have no financial disclosures relevant to this trial. Our site happened to be one of the larger enrollers in the RELIEVE-HF clinical trial looking at interatrial shunting for the management of heart failure. Our experience with the device was actually outstanding. We were high enrollers mostly because of our belief in the therapy and the value it brings to this population. Interatrial shunting has a longstanding history, as described as far back as the 1900s. One of my little favorite Cliff Notes of history is Lutembacher

syndrome. It's basically having an ASD in the setting of severe mitral stenosis back in that day from rheumatic fever. And there was a signal there that patients that had smaller ASDs actually derived benefit from them in the setting of severe MS in the pre-surgical era.

00:21:25 So, as you look through the history of how this unfolded through the sixties and seventies and to the modern era, there's always been this idea that if you can make a shunt at just the right size, unload the left atrium and decongest it, patients will feel better. And I think particularly with the systolic heart failure patients in our patient population, we saw that. It's really important not only to look at the clinical context from the trial, but as to what we do in the real world. Many of these patients have Class III heart failure symptoms. They're significantly symptomatic, they're greatly limited. And this trial was really well designed. Every patient had to go before a Steering Committee. I myself had to present many of these patients. And they really made sure that patients were on appropriate guideline-directed medical therapy. So, these were patients that were on maxim-tolerated therapy looking for options that-- They may not be candidates for a transplant or an LVAD at this point. They're not quite sick, but they're clearly not well enough that they can get by with their daily activities without limitations. And so, if you look at the landscape that currently exists for heart failure in this space, we don't have a lot of therapies right now. So, once we maximize GDMT for these patients, we're greatly unlimiting our options. And I think this is an area where interatrial shunting provides a huge boon for these patients. It gives them an opportunity to derive benefit from a therapy that, again, we have nothing else in this disease state space. There are therapies like cardiac contractility modulation, embarrassingly, that currently are FDA-approved and yet they also do not have survival benefit behind them. There's a huge grey zone again between Class I and II symptoms where you can do most of your activities okay; Class IV symptoms where you need LVAD or a transplant. I think this therapy really fits the bill. And if you look at the clinical data from the trial from RELIEVE-HF,

these patients did derive benefit, and reduced hospitalizations and improved quality of life significantly. And with that, I fully endorse the therapy and I hope it gets approval for future patients to derive benefit.

00:23:19 Dr. Hemmati: Good afternoon. My name is Dr. Houman Hemmati. I'm a Board-Certified Physician, President of Heart Failure Advocates of America, and a longtime Clinical Researcher in Biopharma. I'm here today as an advocate and as a son of a heart-failure patient. I want to be clear, I have not been compensated by Johnson & Johnson or V-Wave. I trained at Stanford, UCLA, Hopkins, Harvard and MIT, and I've spent time caring for patients with severe heart failure in intensive care settings at Stanford Hospital when I was there for internal medicine training.

00:23:51 But no experience shaped me more profoundly than caring for my father who lived for years with advanced heart failure, with reduced ejection fraction and ultimately died after repeated ICU admissions. I cannot remember the last time I saw him sleep flat in the bed. I spent night after night in ICUs watching him grasp for air, watching machines do the work his heart and lungs could not do. But despite maximal medical therapy, nothing meaningfully improved his quality of life. It simply prolonged his suffering.

00:24:18 And when I first learned about the V-Wave Ventura Shunt while I was in clinical trials, I was hopeful especially for patients like my father who truly have no other options. And when the results emerged, I became convinced this is the therapy that represents exactly the type of innovation Congress intended the FDA to accelerate under the 21st Century's Cures Act for Life-Threatening Diseases. Here is the core fact in the pre-specified heart failure with reduced ejection fraction population, the RELIEVE-Heart Failure trial demonstrated a large, consistent and statistically robust reduction in heart failure events, including hospitalizations in serious clinical outcomes with a 100% success and zero device-related major adverse events. This was not a post-hoc discovery. The heart failure reduced ejection fraction analysis

was explicitly pre-specified in the protocol with stratified randomization by ejection fraction and planned interaction testing. This makes the findings valid, reliable, and fully aligned with FDA standards.

00:25:20 And I want to emphasize what these patients actually looked like. Every participant in this study was already on maximal tolerated guideline-directed medical therapy, and those decisions were confirmed by an independent Eligibility Committee. They represent the very sickest New York Heart Association Class III heart failure with reduced ejection fraction patients and the real-world patients who are at the end of their road. And many experienced a 90% approximately annual likelihood of death, transplant, LVAD or hospitalization. This is a terminal condition with no therapies left to offer.

00:25:56 So, for the FDA to require a new five-year clinical trial before approval would mean that most of these patients will be dead before the therapy ever becomes available. That is not an abstract concern. It is exactly what happened to my own dad. We must acknowledge the ethical dimension here. There is no meaningful safety signal. There is a clear pre-specified, biologically plausible benefit. And these patients have no alternatives except worsening disability, repeated hospitalizations and death.

00:26:25 The FDA has repeatedly approved devices with weaker evidence and far less favorable safety profiles because the risk-benefit calculus justified it. The Ventura Shunt has an extraordinary safety profile, arguably unprecedented for an implantable cardiac device and a compelling signal of benefit precisely in the population most in need. Requiring another trial first is not only scientifically unnecessary, it is ethically indefensible and inconsistent with the FDA's patient-centered public health mission and its obligations under the 21st Century Cures Act. A postmarketing confirmatory study is absolutely appropriate, but denying current patients access while awaiting another five-year trial is in fact a decision that more patients must die without the chance of benefit from a therapy that's already demonstrating real clinical potential.

00:27:14 On behalf of families like mine and the more than one million Americans living with advanced heart failure with reduced ejection fraction, I urge this Committee to vote in favor of approval of the V-Wave Ventura Shunt and allow patients finally to have access to a safe, innovative therapy when nothing else remains. Thank you.

00:27:35 Dr. Lange: Let's proceed with Speaker 6.

00:27:39 Dr. Abrams: Yes, hi. Can I be heard okay?

00:27:41 Dr. Lange: We can hear you, Michael. Thank you.

00:27:42 Dr. Abrams: Very good.

00:27:43 Dr. Lange: Please, introduce yourself.

00:27:44 Dr. Abrams: Thank you. I'm Dr. Michael Abrams, a Senior Health Researcher with a nonprofit consumer advocacy organization, Public Citizen. I have no financial conflicts of interest related to today's topic. The V-Wave Ventura Interatrial Shunt System is being evaluated by this Committee for potential FDA approval as a treatment for symptomatic heart failure that is non-responsive to guideline therapy and where the left ventricular ejection fraction is less than 40%. Because this device is implanted, of course, into the heart via catheterization, it's a Class III device thus requiring the sponsor to demonstrate the highest level of safety and effectiveness evidenced before approval is granted.

00:28:29 The FDA briefing document for today's meeting is largely critical of the sponsor's premarket application, or PMA. The PMA is mostly based upon the sponsor's updated analysis of its RELIEVE-HF trial, a randomized controlled trial involving 508 heart failure patients assigned one-to-one to either the shunt installation or a sham procedure. The trial was designed to test the expectation that the V-Wave would offer relief to all heart failure patients regardless of their ejection fraction. That pre-specified primary therapeutic goal was not achieved. However, post-hoc analyses, which split the sample into those with ejection fraction less than 40% (low

ejection fraction) compared to others, revealed that the shunt was beneficial for the low-ejection-fraction subgroup alone. Based on these results, the sponsor is now seeking the imprimatur, the seal of approval on their device from the FDA. FDA reviewers appropriately have concerns about such analysis driving an approval decision at this point.

00:29:43 Here are some of those concerns. The subgroup testing was to be performed only if the full heart failure group effectiveness endpoint was met. Accordingly, false positive results, or so-called type I errors, are a great concern here. And the subgroup analysis should be "interpreted with caution" and considered as "hypothesis-generating and for descriptive purposes only."

00:30:15 To underscore this fundamental statistical principle, the FDA cited a 2016 paper by Pocock and Stone, which says that "We find it hard to think of an example in which an apparent benefit in a subgroup in a trial with a negative primary outcome has led to a confirmation in a subsequent trial." The FDA and its briefing materials further described at least three cardiovascular trial series (the PRAISE, the TACT, and the Paragon) that first demonstrated significant subgroup effects. But later, they had to reject those effects because they were not confirmed by a second trial. The FDA review also noted that the low ejection fraction subgroup analyses did not show significant V-Wave benefits on the primary outcome variable just on a subset-- Or the composition of that variable. For example, the FDA review said this, "It is important to note that the low ejection fraction subgroup as shunt subjects did not experience an improved health status or quality of life status compared to control subjects."

00:31:28 Finally, it should be noted that the post-hoc analysis upon which this application is built showed that shunt recipients with preserved ejection fraction, that is greater than 40%, experienced significantly more harm than their match controls based on the sponsor's primary analytic strategy. This unanticipated result exposes the

plausible risks associated with this device. One other caution described by the FDA is that the ejection fraction measurement, which is a percentile, is subject to error and changes over time due to factors other than treatment, such as natural evolution of the disease. Accordingly, it is uncertain that a single ejection fraction threshold, like 40%, can reliably indicate whether a shunt treatment should be used or otherwise.

00:32:15 Regarding adverse effects of the V-Wave Shunt, the FDA noted that major adverse events, such as all-cause death and stroke, were not evident in the one month after shunt installation. However, within two years, there was some signal regarding cerebrovascular and pulmonary risks apparent with this shunt use.

00:32:36 These and related points lead to the following conclusion: The benefit-to-risk profile of the V-Wave Interatrial Shunt for heart failure with reduced ejection fraction remains speculative. Public Citizen, thus, urges the Committee to recommend that the FDA reject this PMA. Further FDA-consideration of the PMA should be contingent on the sponsor conducting a new and appropriately powered clinical trial. Thank you very much.

00:33:06 Dr. Lange: Thank you, Dr. Abrams. Speaker 7?

00:33:19 Dr. Diana Zuckerman: Thank you. I'm Dr. Diana Zuckerman, President of the National Center for Health Research. Our nonprofit public health research center focuses on the safety and effectiveness of medical products. And we do not accept funding from any entities with a financial interest in our work. So, the center has no conflicts of interest, but my father worked for J&J his entire career and I inherited J&J stock from him. However, J&J won't be happy with my testimony today. My expertise is as a former faculty member and researcher at Yale and Harvard, and as an expert in FDA policy in the U.S. Congress, the White House, and at several nonprofit organizations.

00:34:03 As a Breakthrough Device, the FDA gave priority review to this shunt because it's a novel technology with the potential to provide more effective treatment for certain patients. I'm sure you noticed the two pages of exclusion criteria to participate in this study. It was studied on a relatively small proportion of ambulatory Class IV heart failure patients with reduced or preserved left ventricular systolic function.

00:34:35 The FDA points out that Breakthrough Devices must meet the same standards as other medical devices to get on the market. A reasonable assurance of safety and effectiveness. FDA may accept greater uncertainty if appropriate, such as if a device treats a life-threatening disease when no alternative treatments are available. However, in this case, the device was not more effective than a sham control in the overall study. Should a device that is no better than placebo be approved since its short-term safety is no worse than placebo? That makes no sense because it certainly adds to the cost of medical treatment, and when used by physicians who are less experienced, then those participating in this clinical trial will have to assume the risks could increase as well. And if it is approved, it could legally be used for any heart failure patient. In fact, device companies have been pressuring Congress to require Medicare to pay for any Breakthrough Devices on the market. And for that reason, your work is especially important today.

00:35:51 I'm here to discuss the scientific evidence and the statistical issues because that's my expertise. But I have a personal stake as well because both my parents and all four of my grandparents died of cardiovascular disease. And my mother lived for years with heart failure. So, the fact that the control patients sometimes did better than the shunt patients really concerns me. I agree that the study design is very impressive. The primary effectiveness endpoint was a composite including all-cause death, and cardiac transplantation or LVAD implantation, as well as several other variables, including KCCQ score of quality of life. But keep in mind that secondary endpoints were to be tested only if the primary endpoint was statistically significant.

00:36:53 And to quote the FDA, the primary effectiveness endpoint was not met and there was no signal of shunt benefit in the primary effectiveness endpoint results. Rates for the composite endpoint components of death, cardiac transplantation and LVAD, heart failure hospitalization, and worsening outpatient heart failure events were generally similar between the shunt and control groups. And at all time points through two years changes in quality of life scores were similar between the shunt and control groups. All-cause death and heart failure hospitalization rates actually favored the control group; while cardiac transplantation, LVAD and worsening outpatient heart failure events favored the shunt group. But those differences were all small. The calculations of the individual components and the method of calculating composite rates were not pre-specified and that's why we can't draw conclusions regarding statistical significance.

00:38:07 The company did its best to figure out who was most likely to benefit from the shunt. Those analyses are important for the company to help them either improve the shunt or specify an indication that shows a benefit compared to the control group. However, as the FDA pointed out, those post-hoc analyses should be considered exploratory or hypotheses-generating and they should not, under any circumstances, be used to justify FDA approval given the failure to meet the primary endpoint on cardiovascular events.

00:38:46 We all know that post-hoc analyses have major shortcomings including type I errors and lack of control for multiple comparisons. And when they're conducted on subgroups and have inconsistent results, it is impossible to draw conclusions. So as FDA pointed out, even four patients in the control group can change the results because of the smaller subgroups being analyzed. And that's why it is absolutely essential this shunt should be studied in larger groups of specific types of patients before it can be considered for approval.

00:39:24 Just briefly, I want to say the win ratio data are problematic as well. As noted in articles published last year in circulation and elsewhere, the win ratio has important limitations. Number one, it's unclear how to prioritize component events. Is a heart attack worse than a stroke? Is one early hospitalization worse than two later hospitalizations? And number two, combining short-term symptoms with major outcomes later in the trial as a single metric may conflate short and long-term efficacy. In conclusion, for all components of the composite endpoint, the sponsor expected that event rates would favor the shunt group, so it was notable that it didn't. And the similarity in cardiovascular death rates between true groups does not support a mortality benefit associated with shunt use. Thank you very much.

00:40:30 Dr. Lange: Thank you, Dr. Zuckerman. And now we'll move on to our last speaker. Speaker 8.

00:40:39 Dr. Packer: All right. Thank you so much, Dr. Lange. Members of the Committee, I've spent the last 40 or more years doing randomized clinical trials in heart failure and I have spent my entire career looking at subgroups. I'm representing myself today. No one's paying for my time. More than a year ago, V-Wave asked for my opinion on their data as a one-time consultation. By my request, my agreement included a clause indicating I could present my independent views on their data to regulatory agencies, but I will not be expressing any opinion about their data or their device. I am going to be talking about the reliability of subgroup analyses in heart failure trials.

00:41:38 Now, subgroup analyses are inherently underpowered. They're based on a baseline variable to assess the potential influence of the variable on the direction of magnitude of the observed treatment effect. If you perform countless analyses, you will almost always find some subgroup that appears to show an influence to the baseline variable. But how would you make the judgment that a subgroup finding was real? And when I say “real,” I mean replicable, that you would see the same

subgroup effect consistently if the trial were carried out again and again. Now, there are those who believe that there are certain features that make it very unlikely for a subgroup to be replicable, secondary, exploratory, post-hoc outcomes, those that are based on very few events, those that are difficult to explain clinically or those that are based on the variable that is associated with exceptional variability in its assessment, such as ejection fraction. But there are also those who believe that it is possible to identify subgroups that are likely to be replicated. Those based on the primary endpoint, those that are pre-specified, those based on a stratification variable, those that are biologically plausible, those that have a statistically significant interaction p-value. It sounds pretty nice, but none of these are useful in determining whether a subgroup finding is replicable. Almost always subgroup interactions cannot be replicated.

00:43:37 I want to give you my personal experience with probably the most striking example of this. This is the results of the PRAISE 1 studies, a trial of amlodipine versus placebo in chronic heart failure. Now, you can see the design here: 1,153 patients were randomized. There was a pre-specified stratification procedure. Patients were stratified, either ischemic or non-ischemic cardiomyopathy, and then each strata was then randomized to either placebo or amlodipine. And so, we have now a stratification variable and a pre-specified subgroup analysis based on that stratification variable.

00:44:29 Here's the overall results on all-cause mortality. Oh no, it sort of looks like it goes in the right direction: 16% reduction risk, p-value 0.07. And now, let's take a look at the pre-specified subgroup analysis based on the stratification variable. Now, on the left you see the effect on ischemic patients, on the right in patients without ischemic cardiomyopathy. On the left, hazard ratio 1.02, not statistically significant; on the right, in non-ischemic patients, hazard ratio of 0.54, highly statistically significant.

And now, if you look at the interaction p-value, it's 0.004. Gosh, this is as good as a subgroup gets in a clinical trial.

00:45:32 And did we have a mechanism to explain this? Well, physicians can always think of a mechanism, always. We thought patients with non-ischemic cardiomyopathy had coronary microvascular vasospasm, as in Takotsubo cardiomyopathy, and that amlodipine would block this mechanism. We had several substudies on different variables that support it. But imaging or biomarker substudies performed in the same trial are problematic, since any play of chance that causes an apparent effect on events in a subgroup would cluster with the surrogate. Essentially in the same trial, patients who do well have surrogates that well, but they do not inform on the likelihood of replication. So, we needed to replicate this amazing subgroup finding in PRAISE 1. Significant interaction p-value, very small p-value; hazard ratio of 0.54%. The two trials, PRAISE 1 and its successor trial, PRAISE 2, used the same protocol, the same definition of non-ischemic cardiomyopathy, the same dose of amlodipine; relied on the original group of investigators; recruited patients with the same baseline characteristics receiving the same background therapy. PRAISE 2 was entirely carried out to confirm the subgroup finding of PRAISE 1.

00:47:26 And here's what we found. No confirmation. In the non-ischemic cardiomyopathy group-- This is the subgroup in PRAISE 1 that had a hazard ratio of 0.54. In PRAISE 2, looking only at those patients, the hazard ratio was 1.09. We could not replicate this subgroup under almost identical conditions as the first trial. So, even under conditions of pre-specification and stratification, even when there are highly significant interaction p-values, even when the endpoints are of exceptional clinical significance, like all-cause mortality, treatment subgroup effects seen in trials of interventions in patients with chronic heart failure are rarely replicated. And therefore, if you want to know if a subgroup finding is real, you actually have to do another trial in order to test that hypothesis.

00:48:35 But we particularly worry about the actionability of subgroups showing a qualitative interaction, where one group seems to benefit and the complementary subgroup seems to be harmed, especially when the decision between the two is determined by a variable that is not measured with precision in clinical practice. I thank you so much for your attention and I would be very happy to take any questions that members of the Committee might have. Thank you again.

00:49:12 Dr. Lange: Thank you, Dr. Packer, for participating. In fact, I'd like to thank all the Open Public speakers for their participation. And with that, I will close this particular section of the meeting and proceed with today's agenda.

Panel Deliberation

00:49:29 Dr. Lange: It is 2:30 p.m., we'll proceed with the Panel Deliberations. Although this portion is open to public observers, public attendees may not participate except by the specific request of the Panel Chair, and that's me. Additionally, we request that all persons who are asked to speak identify themselves each time. It will also help the transcriptionist identify the speakers. Over the next hour, we will allow the sponsor and the FDA to address the questions that were posed by the Panel members. And I'll ask if the sponsor and the FDA are prepared at this particular time. Dr. Abraham?

00:50:22 Dr. Abraham: Can you hear me? Hello?

00:50:24 Dr. Lange: Hi. Dr. Abraham, can you hear me?

00:50:27 Dr. Abraham: I can hear you. Can you hear me?

00:50:29 Dr. Lange: I can hear you as well.

00:50:31 Dr. Abraham: Oh, great. We're ready. Thank you.

00:50:33 Dr. Lange: All right, I'm happy to-- I've listed all of the questions. I'm happy to just march down them with the person who asked them. Is that okay with you, Dr. Abraham?

00:50:44 Dr. Abraham: That sounds fine. Thank you.

00:50:46 Dr. Lange: Terrific. Dr. Blankenship first asked about the technique for measuring the LVEF and the reliability. We might also fold it into questions about measurements of the right heart as well, which were asked by a different Panel member.

00:50:58 Dr. Abraham: Right. So, the Echocardiographic Core Laboratory, which was housed at Penn State University and led by Michael Pfeiffer, used the modified Simpson's method for assessment measurement of LV ejection fraction. They have an internal quality-control/quality-assurance process to look at both inter-observer as well as intra-observer variability. And the Bland-Altman Plots from the Echocardiographic Core Lab from the RELIEVE-HF study QC process are shown on this slide. You can see inter-observer variability for LVEF on the left hand side of the slide, and intra-observer variability on the right hand side of the slide. And I guess I would characterize this as being both excellent and within the known range of variability for LVEF, which is plus or minus 5 LVEF units or percentage points.

00:52:06 Dr. Lange: Dr. Blankenship, does this answer your question?

00:52:13 Dr. Blankenship: Yes, it does.

00:52:14 Dr. Lange: Thank you.

00:52:15 Dr. Blankenship: Thank you very much.

00:52:16 Dr. Lange: Thank you. Thank you, Dr. Abraham. Dr. Yuh asked if there was appreciable change in the LVEF with regard to the HFrEF and the HFpEF patients.

00:52:30 Dr. Abraham: Yes. So, there was no change in LV ejection fraction in the HFpEF patients. That data is not shown, but shown on this slide, which is from Table 38 in the briefing document, you can see the changes in LV ejection fraction in the HFrEF cohort stratified by randomized assignment to shunt or control. There was about a 2.2 LVEF unit improvement in ejection fraction in the shunt group, and 1.3 improvement in LVEF in the control group.

00:53:10 Dr. Lange: Right. Dr. Yuh, does that answer your question satisfactorily?

00:53:15 Dr. Yuh: It does. Thank you.

00:53:16 Dr. Lange: Thank you. Okay. Thank you very much. Question number three was by Dr. Wittes. She wanted to know more about the distribution of ejection fractions, across the entire population, and specifically how many were close to the cutoff of 40.

00:53:32 Dr. Abraham: Yes, so let's put the slide up and you can see the distribution of LVEF values at baseline, which reasonably reflects the epidemiology of heart failure, while perhaps a little bit less clear from this particular crude graph, which we put together quickly. We do know in heart failure that there tends to be a bit of a bimodal distribution reflective of peaks within the HFrEF and the HFpEF populations. And I can't tell you the exact number, we can infer it from this slide, the number of patients around the LVEF cutoff between HFrEF and HFpEF of 40%.

00:54:20 Dr. Lange: Those two parts. Dr. Wittes, does this address the question you had regarding that?

00:54:25 Dr. Wittes: Yes, it does. The bimodality is pretty striking.

00:54:28 Dr. Lange: Yes. Yes, it is.

00:54:29 Dr. Abraham: Thank you.

00:54:29 Dr. Lange: She also asked about the permutations and why it was described as giving little evidence of a type I error.

00:54:37 Dr. Abraham: And I'm going to ask our consulting statistician, Dr. Hendrix, to address that question.

00:54:44 Dr. Lange: Thank you.

00:54:47 Ms. Hendrix: Suzanne Hendrix, Statistical Consultant. So, when we did the permutation test, it was based on the idea that when you're looking for a type I error control issue, often what you'll do is simulate the null scenario. And in this case, we mixed up the treatment arms to simulate a null scenario and then look at how often significance is found under that null scenario. This is often done for a single test, and in our case, we realized that we had a series of decisions that we had looked at and we needed to do it for this series of decisions. So, we did the same process and we looked at the possibility of getting significance in three different ways. So, on the left of the slide here, it shows that we could have had significance on the overall test, which is the ITT population, and then we could have significance on the interaction, which could lead us to either a HFrEF or a HFpEF, whichever is the better of those two groups. And so, we wanted to incorporate all of these separate decisions into our permutation testing to estimate what the type I error would be with that series of decisions being made.

00:55:58 The analysis shown here includes the primary outcome and seven secondary outcomes. The interaction test was shown at the top with Yes or No, and then it leads down on the left. If the ITT is significant and positive, we get a 2.5% one-sided significance level, and that's our type I error that turns into a two-sided type I error of 0.05. And then on the right hand side, [there] is what happens when the interaction test is significant, as significant as ours, how often that happens. And then when the best stratum is selected, and in this case there's a false positive rate of 0.08 one-sided. When you look over to the middle then, where we estimate the type I

error we add in the 0.052, which is what we had in our 10,000 or 100,000 simulations two-sided, and then the additional inflation due to the interaction testing on the right with the 0.002.

00:56:53 Now, here we show the interaction test as the top decision and then the pooled ITT as second. But if we switch those two and first look at the pooled ITT and then look at the interaction test also, it comes out with the same estimated inflation of type I error. So, we believe that this accounts for our best estimate of what we think the type I error inflation could be with this additional testing of the interaction and then the better of the two subgroups.

00:57:24 Dr. Lange: Dr. Wittes, does this-- I mean, I'm satisfied, but this answers the question about how they got there?

00:57:30 Dr. Wittes: Yes, it answered the question of how they got there. I'm not sure it satisfies my-- I think I would've had other questions, but now I know what they did. Thank you.

00:57:39 Dr. Lange: Perfect. And in fact, this is a foreign language-- I'm going to ask you to interpret it later during our discussion.

00:57:45 Dr. Wittes: Okay.

00:57:46 Dr. Lange: Okay. So, thank you very much. We had a question regarding echo discrepancy in Table 33, and a question about changes in LVEF and changes in pulmonary artery regarding mortality in slides 83 and 81. So, Dr. Abraham? And I believe that came from Dr. Shanker if I'm correct.

00:58:18 Dr. Abraham: Yes. So, there's no discrepancy here, but let me just resolve the issue and I'll share with you the figure shown by Dr. Zile in our core presentation. The observation that there was a slight increase in PA systolic pressure in the HFrEF patients treated with a shunt shown by the blue bar here is correct. But what we're looking at is the between-group difference, the difference between control and shunt

patients. Because in many patients heart failure is a progressive disease. And we see in the control patients that they have a rise, a progressive rise in PA systolic pressure. That rise is less in the shunt-treated patients, so that the between-group difference is -2.2 millimeters of mercury. And then similarly, when we look at the HFpEF patients, we'll see that there's no change in the HFpEF controls, but there is a worsening, a rise in PA systolic pressure such that the between group difference is nearly 5 millimeters of mercury. So, the table shown in the briefing document, the figures shown here-- The data are consistent.

00:59:38 Dr. Lange: Dr. Shanker, does that answer the question that you had posed?

00:59:42 Dr. Shanker: It does, and thank you for the clarification. But there still was an increase in the shunt group, correct? At 12 months.

00:59:49 Dr. Abraham: Yes, but you have to-- In a controlled trial, you have to adjust it for what's seen in the control group. So again, I think it's the between-group difference rather than the within-group difference that really makes the difference here and fits with the prognostic information that Dr. Zile shared with you as well. Those data are all based on between-group differences as well.

01:00:12 Dr. Shanker: But there was an increase, right?

01:00:14 Dr. Lange: Yes, but you're right, Dr. Shanker, and this will be a part of our Panel Deliberations. Thank you. Thanks for the answer by the way, Dr. And thanks, Dr. Shanker, because I'll ask you to pursue that.

01:00:25 Dr. Shanker: Thank you.

01:00:27 Dr. Lange: Dr. O'Connor asked about rates of all-cause hospitalization versus cardiovascular hospitalizations in the HFrEF group, and also about a change in GDMT, particularly with SGLT2. So--

01:00:46 Dr. Abraham: Yes. Okay. Let's have a slide up to address the first question. This slide shows heart failure hospitalizations, hospitalization for cardiovascular

causes and all-cause hospitalizations here. And you'll see that in all instances, the hazard ratio falls to the left of the line of unity, the confidence intervals are narrow and none of the upper limits of the confidence intervals cross the line of unity.

01:01:25 Dr. Lange: And then regarding differences in SGLT2?

01:01:30 Dr. Abraham: Yes, so we'll show HFrEF subgroup medications at baseline and at 12 months. It's a very busy table, I apologize for that. It comes from the briefing document, from the FDA's briefing document. But I think it's fair to say that there really are no substantive changes in medications from baseline through 12 months of follow-up. If one looks specifically at the SGLT2 inhibitors, the utilization at baseline was about 50% utilization, at follow-up was about 60%. So, there was some increased penetration in the use of SGLT2 inhibitors during the course of the study. But any numerical differences here, I think, are unlikely to be clinically meaningful.

01:02:28 Dr. Lange: And we're going to look at slide 60 with the FDA. A little bit different. It will talk about differences in SGLT2 inhibitors between shunt and control patients. A marked difference. By the way, the other question was-- These are medications. It doesn't talk about doses or changes in medications and how those are handled. Are you able to address that, Dr. Abraham?

01:02:51 Dr. Abraham: I am not. First of all, for SGLT2 inhibitors, it's a one-size-fits-all dosing, so we don't need to worry about dose changes or titration with that class of agents. In regard to the other agents, we have not had a chance to analyze dose changes. But on preliminary, look at that, which we did earlier in the analysis of these data-preparing publications, it looks like there are very small changes in doses throughout the course of the study. You may recall that we had a centralized Eligibility Committee that only accepted patients who had been tried on higher doses and had demonstrated intolerance to them. So at baseline, these patients were on best-tolerated GDMT.

01:03:46 Dr. Lange: Dr. O'Connor, to the best of his ability, does that at least partially satisfy?

01:03:51 Dr. O'Connor: Yes, it does. Thank you.

01:03:57 Dr. Lange: Thank you, Chris. Dr. Page asked about the sample size determination prospectively, in other words there. And so, if you want to talk about that.

01:04:06 Dr. Abraham: Yes, I'm going to ask Dr. Stone to address that question.

01:04:13 Dr. Stone: Thank you and good afternoon, everybody. The trial was powered for the entire ITT group; that is the combination of patients with reduced and preserved ejection fraction. And you might ask why we did that. Well, we actually went into the trial believing that it was most likely that the shunt would be effective in both patients with HFrEF and HFpEF. As you recall, at the time we designed RELIEVE-HF, there was one other major sponsor, and there was a lot of excitement about HFpEF in particular because there are so few therapeutic alternatives. And of course, as you know, the REDUCE LAP-HF II trial was done just in HFpEF patients. We also thought that it would work very likely in HFrEF patients, so we extended the population to include both, and you've seen those sample size assumptions. However, we were aware of this fact of the difference between cardiac structure and function. And so, we therefore pre-specified this primary stratified grouping according to LVEF and interaction testing to make sure that the results were consistent. Finally, what I would say is that we did not adjust the sample size based on any information that we had on outcomes in HFrEF versus HFpEF, and that it did take more than four years to randomize these 508 patients in this very rigorous trial, especially given how high risk they were.

01:05:42 Dr. Lange: So, Gregg, expand because one of the future questions was what made the decision-- If it wasn't based upon any results, what made the decision to go from 400 to 500 patients?

01:05:52 Dr. Stone: Yes, it's a great question. And I mean, I'll give a first answer. Bill may want to expound. But basically we just wanted to collect more data to look at different subgroups, not only HFrEF and HFpEF, although I think that did drive it because we saw-- We did have the numbers of patients that we were enrolling in those two subgroups, and we did want to get more data in HFrEF patients as well as less frequent subgroups as well. The trial was going well, it had kind of reached its peak enrollment, and so we did decide to expand 100 more patients just to collect more data. And that decision was taken in discussion with FDA, who agreed.

01:06:31 Dr. Lange: Dr. Page?

01:06:34 Dr. Wittes: Can I interrupt and ask a question?

01:06:36 Dr. Lange: Yes, sure. Sure, Dr. Wittes. And then I'll come back to Rick Page. Go ahead.

01:06:41 Dr. Wittes: But that's not what you said in the briefing document. The briefing document talked about the Cui-Hung-Wang paper, which is very different from just saying, "I want an extra 500." Can you explain what that difference was?

01:07:00 Dr. Abraham: Sorry, Dr. Wittes, I think I missed part of your question. Could you restate it, please?

01:07:12 Dr. Wittes: Yes. In your paper and in the briefing document, you talk about the increase in sample size was because of the use of the Cui-Hung-Wang paper, which is very different, and that has really important implications for how the analysis is run. That's very different from the answer you just gave, that said you wanted more people, so you added another hundred.

01:07:44 Dr. Abraham: Let me-- I think there are two things here that we're talking about. First of all, the Cui-- How do you say it? Cui--

01:07:55 Dr. Lange: "Cui" is fine.

01:07:56 Dr. Abraham: "Cui" is fine. That involved-- And that actually involved down weighting of the patients who were included in the interim analysis. That was done at the request of the FDA during the design phase of the study. So, the first 200 patients, not 400 patients, the first 200 patients that were included in the interim analysis were down weighted in the final analysis. The reason for adding the additional hundred patients was in part due to what Dr. Stone stated. And in addition to that, due to the concern that heart failure hospitalization rates were demonstrated to be lower during the COVID-19 pandemic, Dr. Lindenfeld, who could speak to this, her institution at Vanderbilt published data on this as did others around the world. But there was a marked reduction in heart failure hospitalizations for the first part of the COVID-19 pandemic. And we were making these decisions under that sort of influence. So, we thought that we would hedge our bets by adding an additional hundred patients. One, to just have more data overall and for the exploration of subgroups, but also because of this concern about event rates due to COVID-19.

01:09:24 Dr. Lange: So, Dr. Page, did that answer your question?

01:09:28 Dr. Page: Yes, that answered the question. I still have other concerns, but we can handle that during our discussion.

01:09:29 Dr. Lange: Terrific. And I appreciate it because what we'll try to do is we'll get through all of the answers and then we'll have a chance to discuss this, deliberate it as a Panel. And I can always go back to the sponsor or FDA if we need further clarification. So, thank you.

01:09:45 Dr. Wittes: Great.

01:09:46 Dr. Lange: Dr. Vidovich asked about the post-device placement, anticoagulants, antiplatelet protocol, and also asked to describe a two-year placebo effect, or at least talk about it. Go ahead.

01:10:06 Dr. Abraham: Yes. So, let me take the first question and I'll ask Dr. Stone to respond to the second. In the study, patients who were already treated with oral anticoagulation for a clinical indication continued on oral anticoagulation. Patients who were already prescribed dual antiplatelet therapy for a clinical indication continued on dual antiplatelet therapy. And then, those patients who weren't minimally on dual antiplatelet therapy received dual antiplatelet therapy. And we placed everyone on aspirin and used blinded clopidogrel, so clopidogrel or placebo to maintain the blind in the study. And you can see the distribution of those various approaches to either protocol-mandated dual antiplatelet therapy, open-label dual antiplatelet therapy or chronic oral anticoagulation on the table shown on this slide.

01:11:15 Dr. Lange: Dr. Vidovich, does that address that question?

01:11:18 Dr. Vidovich: I would only add, so was anybody on triple therapy at any point receiving aspirin, P2Y12, and some oral anticoagulant?

01:11:29 Dr. Abraham: Yes. I'm sorry. I can't give you the numbers now. We can try to get that information and get back to you with it. But there were patients that were, for example, on chronic oral anticoagulant therapy and perhaps aspirin or clopidogrel. There may have been patients on all three, but that was a very small number of patients.

01:11:54 Dr. Vidovich: Thank you.

01:11:55 Dr. Lange: And the two-year placebo effect, do you want to--

01:11:58 Dr. Abraham: Yes. Gregg's going to tackle that one.

01:12:03 Dr. Stone: Well, thank you. This was one of the really fascinating things that came out of this study. Prior to this, there were very few studies that actually looked and assessed within a blinded framework with how long the placebo effect actually lasted. And as you saw, we actually measured KCCQ at about six time periods, basically every six months throughout two years. And I think the data from this trial,

which showed very, very good blinding, by the way, are pretty incontrovertible that the placebo effect lasts for at least two years. And I think patients enter into a clinical trial believing they're going to get better. Everybody here knows what the placebo effect is, and especially in desperate heart failure patients. That was a substantial placebo effect that lasted and lasted and lasted particularly striking, particularly in the HFpEF strata where patients did not improve in either of the arms and perhaps even got worse in the shunt arm. But the placebo effect is very strong and appears to be very long lasting.

01:13:07 Dr. Lange: That's sort of a-- It's an observation certainly to explain it, but okay. Dr. Vidovich, is that okay?

01:13:12 Dr. Vidovich: Yes, that's interesting. We can follow this up in our discussion later--

01:13:14 Dr. Lange: We can talk about that.

01:13:15 Dr. Vidovich: Yes.

01:13:17 Dr. Lange: Gregg, the next question was from Dr. Krucoff. It was two parts. One is about patency and flow rate of a shunt at one year and beyond, but he further asked "Was the use of win a mistake?" In other words, because-- Should you have been on an event drawn versus or-- Event-driven or patient-driven analysis?

01:13:42 Dr. Abraham: Okay. And again, I'll take the first question and Gregg will address the second. So, in regard to the performance state of the shunt, it is summarized on this slide. So, let me first put this into context. The roll-in cohort was designed in part in order to perform a very robust shunt patency study. We did not want to do serial TEEs in the randomized cohort. If we did it only in the shunted patients, that would effectively unblind the study or unblind the patient. And we didn't want to subject-control patients to serial TEEs. And of course, TEE is the best way to look at this. The data is not as reliable by transthoracic echocardiography. So,

in the 97-patient-roll-in cohort, you can see the results. There was 100% shunt patency through 12 months. The average flow across the shunt with an average gradient from the left to the right atrium of about 5 millimeters of mercury was just over 1 liter per minute, about 1.1 liters per minute. And the Qp/Qs average, 1.22.

01:15:06 Dr. Lange: Super. Is there any data past 12 months?

01:15:11 Dr. Abraham: No, because we didn't do the TEEs beyond 12 months.

01:15:15 Dr. Lange: Perfect. Mitch, does this address that question?

01:15:17 Dr. Krucoff: So, Rich, yes. Thank you, Bill. I think. So, let me just make sure. Shunt patent by TEE is 0% or 100%, right? It's a dichotomous call.

01:15:29 Dr. Abraham: Yes, so, it was, but what you see here is that there's on average, no decrement in flow, no decrement in gradient or anything here. And these were really widely open, widely patent shunts.

01:15:45 Dr. Krucoff: So, flow when they were first put in targeted at 1.5?

01:15:50 Dr. Abraham: As far as the Qp/Qs?

01:15:53 Dr. Krucoff: Qp/Qs. Yes.

01:15:54 Dr. Abraham: Oh, no. No. We really were aiming for what we had seen in early studies, first in human and pilot studies, we're targeting a Qp/Qs of about 1.2 to 1.3. Certainly it was our goal in the design of the shunt and we will answer this in more detail in response to a subsequent question. But the goal in design and sizing this shunt was to keep the Qp/Qs under 1.5, aiming for something in that 1.2 to 1.3 range.

01:16:30 Dr. Lange: Right. Thank you.

01:16:31 Dr. Krucoff: Okay, thank you. Thank you.

01:16:34 Dr. Abraham: Okay, Gregg's going to take the second of those questions.

01:16:40 Dr. Stone: Well, thanks. Dr. Krucoff, I believe you wanted to know if in hindsight using the win ratio in this trial was a mistake. And I would say, admittedly it's something that we would not have repeated again. And we would not repeat again when we would redo the trial, and for a variety of the reasons. Number one, as you've seen in this trial, you can hide in a high-risk population-- That having a lot of recurrent events. You can hide, you can mask a lot of the events that occur. And in fact, you can mask them in an asymmetric way. And that's actually probably what would be expected in future trials as well, where you are, again, concealing more events in the control arm than in the treatment arm. So, you lose a lot of power when you do that. Number two, of course, the win ratio that we had chosen included the KCCQ. And at that time, almost all studies that had been popularized around KCCQ had correlated it with death and heart failure events. But those were in open-label trials. This was one of the first blinded trials. And as you saw and is now showing you in retrospect with other pharmacotherapy trials, in blinded trials, the KCCQ doesn't seem optimal as a hierarchical tier within the win ratio to detect symptomatic differences between patients.

01:18:02 And then, the last comment I would make is that what we've also learned about the win ratio is it gives you about as much power as a standard time-to-first-event analysis. It's not a recurrent-event analysis. And even if you look at a level such as heart failure hospitalizations, when you're breaking ties with, let's say, three heart failure hospitalizations versus one, you're still only getting one win, loss or tie. So, it's basically like one tick-up mark on a Kaplan-Meier curve. And almost all studies now have shown you have very similar power to time-to-first-event analysis, although it does get to hierarchically rank the order in which you're looking at the events. So, it's very different from a recurrent-events analysis and it doesn't help us with power. So, were we to do it again? Yes, I would definitely recommend a recurrent-events analysis for all high-risk heart failure trials such as this.

01:18:55 Dr. Lange: Super.

01:18:56 Dr. Krucoff: Okay, thanks. Thanks, Gregg. Well, we'll do the--

01:18:58 Dr. Lange: Gregg, while-- Gregg, while you're there-- I'm sorry. Thanks, Mitch. Dr. Blankenship had made a comment or actually read your statement from the 2024 article, I'll allow you to give a one-minute answer where you describe the results as not powered and hypothesis-generating and exploratory. So Gregg, I'll allow you to explain that.

01:19:20 Dr. Stone: Well, thank you. Yes, I mean, I think whenever you go beyond the primary endpoint, I think we all agree a standard statistical principle is that results are hypothesis-generating, and we're not asking anybody to put aside what you believe. So, we've generated a hypothesis and the question is, is the data consistent enough? Is it robust and profound enough? Is it internally explainable with a biologic mechanism, etcetera? And is there minimal inflation of type I error such that this hypothesis that we've generated is convincing? And for all the reasons we've discussed, we do believe that it is.

01:19:57 Dr. Lange: Thanks for that. Thanks for that. Mitch, I didn't mean to cut you off.

01:20:03 Dr. Krucoff: Thanks, Rich. I just wanted-- And I want to thank Gregg because I was actually asking a much simpler question that I had followed that-- The win ratio is a per-patient analytic approach. The burden-- I think the words he used was “The burden of the disease is an event-related approach.” And obviously later, Rich, we can discuss more. The burden approach event-related can be driven by a small number of patients where ultimately, I think from a public health point of view, we want to know how we're doing in all the patients, so we'll come back to that.

01:20:46 Dr. Lange: Okay, great. We'll come-- I want to try to get to the questions. Thank you. Question: “If there really was some concern that HFpEF”-- “If we're going to look at an interaction between HFpEF and HFrEF, and in fact there could be a

difference, why were these not pre-specified in terms of providing a rigorous statistical analysis after that?" That was from Dr. Lifer.

01:21:10 Dr. Stone: Well, thanks. As we mentioned before, we went into the trial thinking that the shunt was going to decrease left atrial pressure, which is the proximate cause of most symptoms and heart failure hospitalizations in both patients with HFpEF and HFrEF. And that's what most people thought at the time. And so, we were, though, aware of the fact that cardiac structure and function were different in these two conditions, and we thought that was an important enough difference that we stratified randomization on that basis and pre-specified interaction testing. So, we did not-- Again, as I mentioned, it took more than four years to enroll this trial. And we, of course, with any subgroup, even a pre-specified randomized separate strata, would be underpowered for our principal test for each of those groups. And neither we nor to our knowledge any other study has ever pre-specified what to do in this very unusual situation where you get such a markedly positive interaction. So, we tried to respond to that with a very unbiased way of looking at the totality of the data, first with the global statistical test and to show that there was a minimal 0.002 likely inflation of type I error.

01:22:24 Dr. Lange: Thank you. Ms. Dunn had asked about the gender of HFpEF and HFrEF groups, noticing it seemed like there were a lot of men. So, if you'll provide that data, Bill.

01:22:40 Dr. Abraham: Yes, the data provided on this table for the ITT population, in which 37% of the patients were women, and then stratified by the HFrEF and HFpEF populations. And I would say reasonably reflective of the epidemiology of those disorders, we know that far more women are affected by HFpEF than by HFrEF. You can see that the HFpEF cohort included 50% women and in the HFrEF cohort about 18.5% of the study participants were women.

01:23:22 Dr. Lange: Thank you. Thank you. Ms. Dunn, does this address your question?

01:23:26 Ms. Dunn: Well, I am HFrEF myself. I was just curious when I also saw that 84% of the males-- So that left 16% for female [participants]. When I was looking at the chart, 91% were Caucasian, so that leaves 9% of other ethnicities. Is there a reason why these clinical trials were done in predominantly Caucasian-area hospitals? If you could maybe answer that.

01:23:57 Dr. Abraham: I can. And so, this was a global study and about half of the enrollment occurred in Europe and in Israel where, for better or for worse, unfortunately I guess I would say, enrolled predominantly white men. I will follow that by saying that if one looks at the U.S. enrollment, the representation particularly of underrepresented minorities-- Let's go ahead and put this slide up. And we can see the enrollment of Whites, Blacks, and Hispanics in total. And then in the U.S. and outside of the U.S. In the U.S. it's not bad, 15.5% of the patients were Black, and about 14.5% of the patients were Hispanic in U.S. enrollment. But, of course, that's diluted by the enrollment of predominantly White men outside of the U.S..

01:25:05 Ms. Dunn: Okay, thank you.

01:25:07 Dr. Lange: Thank you very much. Dr. Tchantchaleishvili asked about the number data on patients with an LVEF of 20% or less. And I realize that's a small number.

01:25:20 Dr. Abraham: It is a small number and that's shown here as we go back and look at the distribution by LVEF. So, those with an LVEF of less than or equal to 20% included 14 patients, or about 2.8% of the population. We did have time during the break to look at the outcomes in those patients. Let me bring that data up on the next slide. And you'll see that it is very consistent with the overall findings, where as for example, in heart failure hospitalizations, there are 17 events in the control group and only 2 in the shunt group. If we look at all heart failure events, inclusive not only of heart failure hospitalizations, but death, LVAD/transplant and worsening heart failure events treated as an outpatient, there are 23 events in the control patients and

7 events in the shunt patients with LV ejection fractions less than or equal to 20%. So, I hope that you find this data to be reassuring and responsive to your question.

01:26:33 Dr. Tchantchaleishvili: Thank you.

01:26:34 Dr. Lange: Is that-- Okay. Terrific. Terrific. Dr. Kumbhani had asked whether you have any information regarding shunts with regard to PVR. And also talk about the valve in a heart disease in the patient's HFrEF.

01:26:48 Dr. Abraham: Yes. Dr. Stone will address these questions.

01:27:01 Dr. Stone: Right. So, we only have baseline PVR. That's a value that's generated from right heart catheterization and we did not have follow-up right heart catheterizations within the randomized cohort. Right now, I can address, though, I think the next question or one of the questions coming up [that] relates to both frequency and changes in mitral regurgitation and tricuspid regurgitation. So, let me show you that. Let's put up this slide. So, here is, let me-- There's a lot of data on this slide, so I'll focus you on it. You've got mitral regurgitation for about the first five rows, tricuspid regurgitation for the bottom five rows. And this is looking only at moderate or greater. We excluded patients with severe mitral regurgitation and tricuspid regurgitation. And then you have the baseline data treatment versus control, and then the 12 month data treatment versus control. And as you can see, there was approximately 20% of patients at baseline that had moderate or severe mitral regurgitation and tricuspid regurgitation. And you can see that the balance between the two groups pretty much stayed the same over the 12-month follow-up. This is the ITT group. If you'd like, I can also show you the results specifically in the HFrEF group. Would you--

01:28:24 Dr. Lange: Dr. Kumbhani, is this sufficient or would you like to see it in the HFrEF group as well?

01:28:30 Dr. Kumbhani: Yes, thank you, Dr. I'd love to see it in the HFrEF group if you have it available.

01:28:34 Dr. Stone: Yes. And here it is. Here it is in the HFrEF group. You could see, again, at baseline, moderate or greater mitral regurgitation perhaps trended slightly more in the treatment group than the control group. And then at 12 months, you can see there was slightly less mitral regurgitation in both groups. So, 14% versus 10% moderate or greater, almost no increase to severe mitral regurgitation or tricuspid regurgitation. And a similar pattern with tricuspid regurgitation. So, the severe valve disease tended to get a little bit less in both groups with very similar outcomes in each.

01:29:13 Dr. Lange: Right. Dr. Hauptman, do you have a question about this?

01:29:16 Dr. Hauptman: Yes, if I can. Thanks, Dr. Lange. So, Dr. Stone, I think you just mentioned that you excluded patients with severe MR, did I understand that correctly as an exclusion criterion?

01:29:27 Dr. Stone: Yes. If they had severe mitral regurgitation, we recommended that they would have TEER therapy first or surgery or whatever else to treat the severe mitral regurgitation.

01:29:39 Dr. Hauptman: So, the majority of the patients had moderate or less?

01:29:43 Dr. Stone: Well, here you can see, for example, there were 24% and 18% of treatment in control group patients at baseline that had moderate or greater. But you can see it's the moderate, which is 2 plus, is what most of it is moderate to severe, which is 3 plus was 2% in 3% of patients and no patients had severe MR.

01:30:04 Dr. Hauptman: So, the reason why this may be relevant is I don't recall seeing anything in your proposed labeling that would suggest that clinicians should exclude patients with severe or maybe even moderate to severe MR, out of concern that with the shunt you may find greater increments in right atrial pressure.

01:30:23 Dr. Lange: So, Paul, hold that thought because we'll talk about that when we talk about later if we're going to approve it, what should we modify in the indications? We'll throw that in PVR and other things as well. So great, great comment. Dharam, you wanted to follow up?

01:30:38 Dr. Kumbhani: Yes, thank you, Dr. Stone. Thanks for the data. Can I maybe come back to the comment about the PVR? My comment was based on baseline PVR and-- In the REDUCE LAP II study, that was a very important effect modifier in terms of the baseline PVR and how that affected shunt flow. And that's why I wanted to see if you might have that data available. Hopefully that--

01:31:10 Dr. Abraham: Yes. So, we have looked at this. Remember that in RELIEVE-HF, in contrast to REDUCE LAP-HF II, we did not perform exercise hemodynamics, but we do have resting hemodynamics at baseline. The FDA had specifically asked us to look at baseline PVR above and below 2.0. And remember our upper limit was four, so essentially it's up to 2 and then between 2 and 4. I can bring that slide up now for you and show you the results which suggest that there really is not a major difference between those patients, in outcome, between those shunted patients with a PVR less than 2 Wood units versus those with a PVR greater than or equal to 2 Wood units. Perhaps the hazard ratio is a little bit lower in the lower PVR group, maybe a little bit of attenuation of effect, but certainly no signal for harm here in HFrEF patients. Yes.

01:32:26 Dr. Lange: Dr. Kumbhani, does that address your question?

01:32:28 Dr. Kumbhani: Yes. Thank you.

01:32:29 Dr. Lange: Super. Dr. Leifer, if you don't have a question, I'll have you take your hand down.

01:32:35 Dr. Leifer: I did have a-- I did want to get one clarification. I didn't have a chance to ask it when Dr. Stone-- It was about-- My question [is] about specifically looking

at the HFrEF versus HFpHF subgroups in the statistical analysis plan. When I look at the plan on page 312, it doesn't call out the-- Looking at HFpEF versus HFrEF, it lists about 15 different subgroups here, and I'm just trying to get straight in my head if I'm just missing something in the statistical analysis plan.

01:33:14 Ms. Hendrix: Suzanne Hendrix, Statistical Consultant. So, there are two different places where you can see something about the interaction analysis. The one that everyone notices is the one that's down in the exploratory section that specifically says, “All of these analyses will be considered for descriptive purposes only.” But if you go back up to the primary effectiveness endpoint section, that's where it talks about doing the interaction testing for HFrEF and HFpEF. And when you have significant interactions, and specifically when it's a crossover interaction like the one that we're seeing, that's the case where you split the two groups. So, there's two places earlier on where it does talk about that, but later is when it talks about just the descriptive purposes. And that's all the whole laundry list of 17 separate comparisons.

01:33:59 Dr. Lange: But there's no statistical plan offered when they're cut out, is there? Did I miss that?

01:34:05 Ms. Hendrix: I'm sorry, say that again?

01:34:07 Dr. Lange: Is there a statistical plan for when you break that out like that?

01:34:12 Ms. Hendrix: No. So, there was no alpha spend that was set aside for that, and I've never seen that set aside ahead of time.

01:34:16 Dr. Lange: Okay, thanks.

01:34:17 Ms. Hendrix: Yes, thank you.

01:34:16 Dr. Lange: Okay, thanks. I appreciate that. Chris O'Connor had asked a question about statistical assumptions. Chris, do you want me to follow up with that? He'd

asked whether you believe there was a better benefit in HFpEF than HFrEF, and is that why the populations are not equal? That is related heavily towards HFpEF.

01:34:43 Dr. Abraham: Yes, no, I want to be very clear here. We did not hypothesize that HFpEF patients would do better than HFrEF patients. As a matter of fact, most of our preliminary data prior to RELIEVE-HF, including a pre-clinical model of HFrEF and a pilot study, which enrolled predominantly HFrEF patients, supported the use of the shunt in the HFrEF population. The reason why I think there is some confusion about this is that in powering the study, we use data from implantable hemodynamic monitoring studies that suggested a larger treatment effect in the HFpEF versus the HFrEF subpopulations. But that was simply used for powering. Again, it emphasizes our thinking at the time in regard to the importance of looking at this data based on LVEF strata or subgroups. But it should not be taken to imply that we hypothesized that HFpEF patients would do better than HFrEF patients.

01:35:57 Dr. Lange: Does this address your question, Dr. O'Connor?

01:35:59 Dr. O'Connor: Yes, it does. Thank you.

01:36:00 Dr. Lange: Dr. Zuckerman, I see your hand up regarding the statistical question I posed to them. Go ahead.

01:36:07 Dr. Bram Zuckerman: Yes, this is a problem that we get into with many sponsors that the final SAP needs to be better locked in, and there needs to be more emphasis on type I error controls. So, I do think there may be a divergence of opinion between sponsor and FDA regarding what the final SAP is. At an appropriate time, I would just ask Dr. Lange to let Dr. Chuan Bi characterize FDA's understanding of the statistical analysis plan also.

01:36:53 Dr. Lange: Super. And we will come back to that. Thank you, Dr. Zuckerman. Dr. Blankenship asked about whether there's a difference between ischemic and non-ischemic cardiomyopathy in terms of outcomes.

01:37:07 Dr. Abraham: Yes, those outcomes are shown on this slide. And as you can see, looking at the four hard clinical outcomes, there is no difference between ischemic and non-ischemic patients. And if you'd like, I can show you, but it looks exactly the same, although with broader confidence intervals for the primary win ratio outcome as well. So ischemic and non-ischemic patients benefited similarly from shunting.

01:37:42 Dr. Lange: I'm not sure I quite understand that because it looks to me like there you've got over 200 HFrEF patients that were treated. So, can you break that up by treatment, Bill? This is all patients.

01:37:56 Dr. Abraham: So, there are 206 HFrEF patients, and 129 in the ischemic subgroup and 77 in the non-ischemic subgroup.

01:38:09 Dr. Lange: Okay.

01:38:10: Dr. Abraham: And then, we're looking at the Nelson-Aalen hazard ratios here where the point estimates are identical to one another.

01:38:18 Dr. Lange: Thanks for that explanation. I was mistaken. Thanks for identifying what physical analysis you used as well. I appreciate that. Dr. Leifer asked whether you'd like to describe the difference-- I'm not sure we need to spend a lot of time on this, the global statistics test versus the win. I think we're going to spend a lot of time in deliberations talking about that, but I'll give you one minute if you'd like to--

01:38:37 Dr. Abraham: Okay. We're going to ask Dr. Hendrix to talk really fast.

01:38:43 Ms. Hendrix: Thank you. Suzanne Hendricks, Statistical Consultant. This is actually a really important question. And the first slide I want to show is the win ratio. And as we mentioned, the win ratio is excluding 38% of events, twice as many in the active arm compared to the control arm. Second thing I want to show is the-- Here is the primary endpoint secondary 1, 2, 3, 4, 5, 6, 7. And when you put all of these together, what we're doing is we're respecting the pre-specified hierarchy of

primary secondary endpoints and making sure we align with what was specified in the SAP. When you put all of these together and account for the overlapping information, the global statistical test tells you how much evidence you have for a treatment effect in the two groups after accounting for that overlap. Now, the next one, this one shows the third way that we looked at it. And this third way is the recurrent-event analysis that parallels the primary pre-specified win ratio, but allows us to count all recurrent events as well. And now, the last slide where I summarize. Sorry, this is super fast.

01:39:48 Dr. Lange: No, you're fine.

01:39:49 Ms. Hendrix: Okay.

01:39:50 Dr. Lange: We've seen this, so you're doing a great job. Keep going.

01:39:52 Ms. Hendrix: No, so, this piece is new. This piece here, what I want to show you is that the primary endpoint, the win ratio, shows the difference between the two groups, but as I mentioned, it's excluding a lot of data. The second one is the GST with the primary and six secondary outcomes without the KCCQ. And that shows more divergence and statistical significance separating the groups. The top section of this page shows a T-statistic because the GST specifically does not give you a hazard ratio. It only gives you a T-statistic because it combines across several different outcomes, including outcomes that are event-based and outcomes that are not event-based. Now, we also did the Gail-Simon test here using the GST, and we got a p-value on the Gail-Simon with the GST of 0.02. The p-value that we get using the win ratio is 0.12, so it's trending towards significance even for the Gail-Simon. But when you do the GST, that allows us to include all of the primary and secondary endpoints, then we get significance. When we look at the bottom here, now what we're showing is the primary endpoint again, the win ratio again, but now we're comparing it to the recurrent-events analysis. So, we now have three different ways of looking at the totality of evidence, which is what the FDA has asked to be

evaluated today. And the recurrent-events analysis here shows a highly significant interaction p-value, and the p-value from-- Oh, I didn't bring it up from the Gail-Simon test for that, is also less than 0.001.

01:41:28 Dr. Lange: Dr. Wittes, I'm going to be calling on you shortly.

01:41:32 Ms. Hendrix: Okay, thanks.

01:41:32 Dr. Lange: Thank you. Dr. Hauptman, asked again about the echo. How did you address unblinding by the echocardiographers? I mean, obviously they don't know the patient, but they know the treatment and they're reading echo values. So, go ahead.

01:41:53 Dr. Abraham: Right, so the echos-- For the Core Laboratory-- Were submitted to the Core Laboratory-- The transthoracic echocardiograms were submitted to the Core Laboratory without an indication as to whether or not the patients were in the shunt or control arm. Although certainly readers might infer if a shunt was present, if they either visualized a shunt or saw flow across the interatrial septum. So, in that regard, I think it is fair to assume that the Echo Core Lab was unblinded in the assessment of those echos.

01:42:31 Dr. Lange: That's great. And you'd presented measurements regarding LVEF. Do you have any measurements for reliability or inter- and intra-observer variability with the right heart measurements?

01:42:42 Dr. Abraham: Yes, we don't specifically have information on the inter-/intra-observer variability. I'll bring up a slide. It was just literally put together. Go ahead and put up AA 45 please. Where'd that go? There it is. And you can see here the missing echo data for Right Atrial Area, RV End-Diastolic Area. And you'll see that there's very little missing data here.

01:43:23 Dr. Lange: Dr. Hauptman, does this address your questions adequately?

01:43:25 Dr. Hauptman: Yes, it does. Thank you, Dr. Lange.

01:43:28 Dr. Lange: Thank you.

01:43:28 Dr. Abraham: Thank you.

01:43:28 Dr. Lange: Dr. Yeh asked about what happens if the EF improves.

01:43:36 Dr. Abraham: Yes--

01:43:37 Dr. Lange: How do those patients do?

01:43:39 Dr. Abraham: Yes. So, let's bring up the couple of slides that I have. I'd like to show this one first just to familiarize the group or remind the group that there is an entity that we call heart failure with improved ejection fraction. It is defined in the ACC/AHA Heart Failure Guidelines as an improvement in EF from below 40% to above 40%. But I think most importantly, the guidelines tell us that heart failure with an improved ejection fraction is phenotypically distinct from HFpEF, or heart failure with a preserved ejection fraction, and that we should continue to treat heart failure with an improved ejection fraction as we treat heart failure with a reduced ejection fraction. So, we looked into this a bit more deeply. In the RELIEVE-HF study, we found that there were a total of 39 patients who met the ACC/AHA definition for heart failure with improved ejection fraction. So, we looked at their outcomes and compared them to outcomes in patients with HFrEF who did not improve their LVEF, and to HFpEF patients. And what you've seen, and this is known about the heart failure with improved LVEF population, their event rates improved compared to HFrEF with a non improved LVEF. But despite that improvement, there is still an apparent treatment effect here with a hazard rate ratio of 0.64. I understand that there are a few patients in this group and the confidence intervals are broad, but there is no indication that that transition from HFrEF to HFrEF with improved ejection fraction is associated with any harm in these patients.

01:45:43 Dr. Lange: Dr. Yuh, does that adequately address your question?

01:45:49 Dr. Yeh: That's my-- Yes.

01:45:50: Dr. Abraham: Thank you.

01:45:51 Dr. Lange: I'm sorry. Dr. Yeh not Dr. Yuh. Dr. Yeh, I'm sorry, Bobby. Not David. Bobby, does that address your question?

01:45:57 Dr. Yeh: Yes, it does.

01:45:58 Dr. Lange: Okay, thank you. I have a question now about new onset AFib in the various groups. Dr. Kumbhani had asked that question.

01:46:12 Dr. Abraham: Yes, data regarding new onset or incident arrhythmias in the RELIEVE-HF trial was acquired through adverse event reporting. And I can show you the data focusing on atrial fibrillation, but really the table includes all other or most other sorts of incident arrhythmia as well. And you can see that in regard to atrial fibrillation or atrial flutter, the number and percent of events was relatively low and not different between the treatment and control arms. And that can be said for other forms of arrhythmia depicted on the slide such as ventricular tachycardia or ventricular fibrillation.

01:47:01 Dr. Lange: Dr. Kumbhani, does that address your question?

01:47:05 Dr. Kumbhani: Yes. Thank you.

01:47:06 Dr. Lange: Great. Dr. Gomes, you had asked about how they arrived at the size of the shunt. I think they've already described that they tried to keep it as a shunt size about 1.2 to 1.3 to 1. And you also asked about the reliability of RV measurements. And we have LV reliability but not RV. So, we ask this.

01:47:25 Dr. Abraham: Yes, I think I would add one additional point. And that is, within the world of interatrial shunting, shunt sizes ranging from 5 to 10 millimeters are under investigation. And so, we tended to be on the conservative side in terms of shunt size to make sure that we weren't bumping up against the Qp/Qs that was 1.5 or greater. And according to the congenital heart guidelines, for a native ASD of 5

millimeters or smaller, you never do anything with those in terms of intervention to close them.

01:48:11 Dr. Lange: Great, thank you. Dr. Yancy had asked about comparing this to the results of the REDUCE LAP. So, let me turn it over to you.

01:48:22 Dr. Abraham: Yes, I think it's a very important question because there are some similarities, some internal consistency between the observations made in the RELIEVE-HF HFpEF cohort and the REDUCE LAP-HF II patients. So, first of all, I want to point out that on average the RELIEVE-HF HFpEF patients were sicker than the REDUCE LAP-HF II patients, higher prevalence of diabetes, ischemic heart disease, atrial fibrillation, much higher NT-proBNP levels at baseline, lower eGFRs, a higher proportion of New York Heart Association Class III patients. In terms of other measures such as E/e' prime, LA Volume Index, TAPSE, cardiac output and PVR, the RELIEVE-HF HFpEF patients were sicker or more advanced than the REDUCE LAP-HF II patients. However, as many of you know, within the REDUCE LAP-HF II patients, there was defined a non-responder and a responder group in a post-hoc analysis. And if one looks at a comparison of outcomes between RELIEVE-HF HFpEF patients and the REDUCE LAP-HF II non-responder subgroups, you'll see that there is a striking similarity in outcomes. So, in many ways, I think the results of the REDUCE LAP-HF II trial are actually quite supportive of our observations in the HFpEF population of the RELIEVE-HF trial.

01:50:17 Dr. Lange: Dr. Yancy, any comments regarding that?

01:50:21 Dr. Yancy: We can discuss further, but that's adequate. Thank you, Dr. Abraham.

01:50:23 Dr. Abraham: Thank you.

01:50:25 Dr. Lange: Thank you, William. And the last question from Dr. Hauptman was-- It appeared to be a small difference, but resolving the differences of TIA CVAs between the FDA data and the sponsor's data.

01:50:40 Dr. Abraham: Yes, Dr. Stone will address this.

01:50:45 Dr. Stone: So, thanks. I'll show you two slides. First in the entire ITT population and then just in the HFrEF group. So, here's the entire ITT population. Sorry, it's not a beautiful slide, but it's the data. So, if you note cerebrovascular events at two years, there were 11 in the shunt group and 6 in the control group. You'll note that the majority of those-- The next three rows should actually be indented. The next three rows are subgroups of all cerebrovascular events. So, if you actually look at stroke, there was a difference of two strokes, 7 versus 5. If you look at CNS hemorrhage, which is again a concerning event, it was 0 versus 1, 1 in the control group and 0 in the shunt group. The biggest difference was in TIAs, which is 4 versus 1. And those, as you know, are usually 5- to 30-minute events, and it's very hard to know a hundred percent sure whether or not those are cerebrovascular events or not. But these are very, very small numbers. And I would also point out none of these are close to statistically significant. And on the other hand, if you look at myocardial infarctions, documented MIs, there were 5 fewer in the shunt group. So, I think we have to be very careful, of course, interpreting trends from these small numbers.

01:52:06 And then finally, I'll just show you very quickly the HFrEF group because there may actually be a difference in safety as well as effectiveness in HFrEF compared to HFpEF because of differences in cardiac output and flow patterns, etcetera. We don't know that, of course, for sure but these are the data in HFrEF. And here you can see that there were 4 cerebrovascular events versus 3 in the shunt versus control group. So, these patients also had-- 60% of them had atrial fibrillation, we would expect a background stroke rate of probably somewhere between 2% and 4%. So, I think these are not different than what we would've expected going into this trial.

01:52:48 Dr. Lange: Dr. Hauptman, does that address your question?

01:52:51 Dr. Hauptman: It does. Although again, I think the table that was originally shown by the sponsor had zero events, so the tables didn't line up perfectly. So maybe you can explain that.

01:53:03 Dr. Stone: I think what you're thinking about is perhaps the MACNE events, okay? The safety--

01:53:10: Dr. Lange: The 30 days.

01:53:11 Dr. Stone: Right. Which were device- or procedure-related events, and those were adjudicated by a central committee as zero. So, there were no such events that were definitely adjudicated or probably adjudicated to the device. What the data that I just showed you was all cerebrovascular events.

01:53:32 Dr. Hauptman: Understood. I think I did make the point though that-- And having sat on a lot of Clinical Events Committees, I could see how it might be a challenge to really know what the etiology was, unless even a 99% carotid obstruction or something like that, it would be pretty obvious. But because you can get intermittent right to left shunting and so forth, it might be difficult for a CEC to truly be able to know definitively.

01:53:59 Dr. Stone: I agree with you entirely, which is therefore why we looked at all of the data as you see on the slide in front of you in HFrEF.

01:54:06: Dr. Hauptman: Thank you.

01:54:07 Dr. Lange: Thank you. I'm going to go to the FDA, by the way, and there's still some that the sponsor has to answer. Before I do that, Dr. Zuckerman, I see your hand up.

01:54:18 Dr. Bram Zuckerman: Yes. Thank you, Dr. Lange. And I want to thank the sponsor for doing a great job of getting through so many questions in a comprehensive manner. One of the questions that's come up with the win ratio is the fifth component, which is the utility of the KCCQ. The sponsor has suggested that

it's not very useful. I'm wondering, Dr. Lange, if during this period Dr. Farb can briefly comment on the FDA analysis of the KCCQ, because I do think it's a different perspective.

01:54:56 Dr. Lange: Sure. And what I'm going to do, if that's okay with you, is we'll go through the FDA questions, and I want to hear both about statistical analysis that we've talked about, and then from Andy as well. Okay. So, we will do both of those, Dr. Zuckerman.

01:55:16 Dr. Bram Zuckerman: Thank you.

01:55:17 Dr. Lange: Andy, Dr. Krucoff had asked about slide number 97, whether this is hypothetical or this based upon the RELIEVE-HF data. This was the risk-benefit profile challenges.

01:55:31 Dr. Farb: Yes. Dr. Lange, this is based on the RELIEVE-HF data, actual data. This is not hypothetical data or from some other source.

01:55:40 Dr. Lange: Terrific. Terrific. Thank you.

01:55:42 Dr. Farb: Thank you.

01:55:44 Dr. Lange: Dr. Yuh had asked about who decided to use the win ratio. The FDA obviously provides support and advice and works with the sponsor. Was it the FDA or the sponsor that chose the win ratio for this particular study?

01:56:02 Dr. Neubrander: This is Rachel Neubrander. I can start, and maybe Dr. Farb can chime in. We did collaborate with the sponsor on the design of the pivotal study. In this case, the sponsor proposed the win ratio as the primary endpoint in the course of those discussions that we were having with the sponsor. And as noted, this approach has both strengths and limitations, but we felt at the time it was reasonable. Andy, do you want to comment further on the choice of endpoint?

01:56:31 Dr. Farb: Yeah, so ultimately, it's the sponsor's decision to design the trial and choose their primary endpoint. In this case, the win ratio as the primary analysis and the hierarchical order, it seemed a reasonable way to go forward. I think Dr. Yuh also asked about recurrent events and did we consider those. And the recurrent-events versus time-to-first-event is currently a hot topic in heart failure trials. In fact, at a recent heart failure collaboratory meeting, this was the primary discussion on the table. And after that discussion, there was value seen for both approaches with no consensus of one being necessarily superior to the other. Perhaps during your discussions, Dr. O'Connor, who chaired that meeting, would have more insights on that particular question.

01:57:29 Dr. Lange: Okay. Dr. Shanker had noted in slide 71 to 74 how four patients that low sample size had affected or skewed things out. It was a small number of patients. He asked about the echo, specifically. And there was an echo done at 12 months, but not 24, and no other modality imaging. Was that a consideration?

01:57:59 Dr. Farb: So, per the protocol, there is a 24-month echo. We don't have that data. Perhaps the sponsor has those data, but echo was the primary means of imaging those patients. And I think you've heard from the sponsor about not wanting to do follow-up TEEs in the randomized trial cohort.

01:58:27 Dr. Lange: Dr. Shanker, do you have an interest in seeing the 24-hour echo results if they're available?

01:58:35 Dr. Farb: 24 months.

01:58:36 Dr. Lange: 24 months, not 24 years, I'm sorry. I meant, yes, 24 months.

01:58:39 Dr. Shanker: Yeah. 24 years would also be good as well if we had that available through time travel. The reason I think this is important is we're seeing initial possible benefit, right? But with progressive RV loading, that PVR could go up and

you could be essentially paying Peter to rob Paul. So, I think having that data longitudinally, it would be very helpful.

01:59:10 Dr. Lange: Okay, great. All right, I'll give you a second, sponsor, if you've got it, because I've got some more questions for the FDA. Dr. Wittes had already asked about the sample size and the DSMB. They've previously addressed it. Do you need more clarification, Dr. Wittes, at this point?

01:59:25 Dr. Wittes: Well, I must say I don't understand the answer. I don't understand whether the method was used, why it-- How it was used, and then how the effect of-- If it was used, what the effect of the down weighting of the early sample was. And was there a differential, for example, were the less than 40 and the greater than 40, were they-- The allocation, the number of people in that early group, was that different and did they get down weighted in a different way? I don't understand it at all. I think it hasn't been described in a way that I can understand.

02:00:08 Dr. Lange: Okay. Let me turn it back both to the sponsor and then we'll go to the FDA to talk about this. So, if you would address Dr. Wittes question?

02:00:21 Dr. Hendrix: Yes. Suzanne Hendricks, Statistical Consultant. So, what I can explain to you is that when we did the primary analysis, we did do a down weighting of the patients who were included in the interim analysis. We looked at it both with and without the down weighting and it did not make a big difference in terms of the final outcomes. Does that address your question?

02:00:42 Dr. Wittes: Not quite.

02:00:43 Dr. Hendrix: Okay, go ahead.

02:00:44 Dr. Wittes: So at 200, I gather it was at 200 that you decided to increase the sample size.

02:00:50 Dr. Hendrix: Right.

02:00:51 Dr. Wittes: Was that done on the basis of the, I can't pronounce-- The Cui-Hung-Wang analysis or was that just said we're going to add 500, another--?

02:01:02 Dr. Hendrix: No, no. So, the DSMB did the interim analysis. They gave a report back that said it looks like the event counts are low. They increased the sample size on that basis. The way it's worded in the document is a little ambiguous. That method is just a description of the weighting that would be used at the end of the study, and it's actually just weighting the 200 patients with six month data down weighted in the final analysis. So, that reference was meant to only refer to the analysis at the end and how that down weighting was happening.

02:01:34 Dr. Wittes: But the reason for the down weighting in that method is that it's based on the effect size that you observe in the method. And what people seem to be saying is it wasn't based on the effect size. So, I may ask two questions. Was it based on the effect size, in which case you have to do the down weighting? Or was it not based on the effect size, in which case, why did you do the down weighting?

02:02:02 Dr. Hendrix: It was not based on the data that had come in so far. It was based on a pre-specified, specific down weighting that had to do with how much patient data was available at the time of the interim and then how it would be weighted in the final analysis. So, it was all pre-specified and locked down and had nothing to do with the actual results that were observed in this study.

02:02:23 Dr. Wittes: Okay, thank you.

02:02:26 Dr. Lange: FDA, in response to-- Obviously the sponsors have had the opportunity to talk about the interactions and then there's subsequent statistical analysis. I'd like for you to be able to respond.

02:02:42 Dr. Neubrander: Sure. Dr. Chuan Bi is going to comment from the FDA perspective.

02:02:48 Dr. Lange: Thank you. Dr. Bi?

02:02:50 Dr. Bi: Oh, hi. This is Chuan. I'm the Statistical Reviewer at the FDA. So could you go to slide 175? That may be the one. Yeah. This is the original wording from the SAP that the sponsor mentioned regarding the subgroup analysis in addition to the section dedicated to the subgroup analysis plan. So, the second sentence specifically says, "The difference in the primary effectiveness endpoint test statistics between the HFrEF and HFpEF subpopulations will be examined using a Z-test." However, we do not interpret this language as evidence that subgroup analyses via interaction testing were intended to be formally hypothesis-tested or hierarchically-tested for probability prior to the primary effectiveness endpoint. Yeah. So, that appears to be a descriptive comparison rather than a formal statistical gate for the primary analysis.

02:04:06 Dr. Lange: Okay. I see Dr. Wittes shaking her head. She understands.

02:04:09 Dr. Wittes: Yeah.

02:04:11 Dr. Lange: Super. Super.

02:04:12 Dr. Hendrix: Can we comment on the-- Can the sponsor comment as well?

02:04:17 Dr. Lange: Let me finish the FDA questions. I'll come back to you.

02:04:18 Dr. Hendrix: Okay, go ahead. Thank you.

02:04:19 Dr. Lange: Dr. O'Connor mentioned, Andy, slide 55, the difference between HFrEF and eGFR and the interactions. And in fact, is there a group of individual HFrEF with decreased eGFR that have a-- Do they respond differently to therapy than those who have a normal eGFR? Can the sponsor provide that data?

02:04:57 Dr. Abraham: Yes. Let me respond to the question. So in this case, I think we're looking at the ITT population and much of the interaction between eGFR and outcome was driven by the HFpEF population. Let me bring up-- Let's see. Okay, so here is what things look like in the HFrEF population where you no longer see a

significant interaction based on eFGR-- eGFR, estimated GFR in the HFrEF patients. So really that ITT finding was driven by the LVEF-- By the HFpEF subgroup.

02:05:56 Dr. Lange: And do you have that as well?

02:05:59 Dr. Abraham: Let me see if we do have eGFR specifically in the HFpEF subgroup. If we can't lay our hands on it quickly-- Let's see. This is ITT. No, go to HFpEF. Okay. All right. So, here we go. It doesn't show isolated eGFR, here is the subgroup analysis for HFpEF with the other pre-specified subgroups. But if you focus on the third set of data from the bottom, eGFR, you'll see that there was substantial worsening with the eGFR less than the median, and a neutral effect for those patients with HFpEF who had better GFRs than the median.

02:07:17 Dr. Lange: Okay. Thank you. Chris, does that address your question?

02:07:22 Dr. O'Connor: Thank you. Thanks, Bill.

02:07:24 Dr. Abraham: Thanks, Chris.

02:07:25 Dr. Lange: Great. Dr. Vidovich asked about Qp/Qs, when was it estimated. It sounds like it was in the roll-in patients and not in the subsequent patients. Is that correct, Bill?

02:07:43 Dr. Abraham: Okay. Yes. And our observations-- Because I think he also asked about differences between HFrEF and HFpEF.

02:07:53 Dr. Lange: Yes.

02:07:53 Dr. Abraham: So, what we saw was in fact that there was a bit more shunt flow in the HFrEF population, not the HFpEF population. About 13% greater shunt flow in the HFrEF population compared to the HFpEF population. And that was nominally significant in terms of p-value. And there was also a significantly higher Qp/Qs ratio in HFrEF patients versus HFpEF patients of 1.28 versus 1.23, while the p-value was 0.0066. You know, one might question the clinical relevance of 1.28

versus 1.23, but if anything, there was a little bit more shunt flow in HFrEF rather than HFpEF. So, I don't think shunt flow explains the adverse outcomes observed in the HFpEF population.

02:08:55 Dr. Lange: Terrific. Thank you. And I think I have three more things to address. One is Dr. Yancy had talked about the FDA, the precedent for the elective removal of control patients. And Dr. Blankenship, follow that up with "You remove four, what's it look like at the 1, 2, 3, or 4?" So Andy, I'll let you address that and then follow that with your analysis of the KCCQ.

02:09:24 Dr. Farb: Okay. Thank you, Dr. Lange. So, if we can pull up that slide to Dr. Yancy's question. So look, we are very interested in recurrent-event analysis and knowing that recurrent events are important to patients. And so we noted the tail, maybe if you could pull up the other slide, the primary slide that we showed during the presentation. That seemed to be an inflection point where the recurrent analysis really split between the two groups and starting at around four events per subject. So, we thought it would be reasonable to take a look at how strong the evidence was to support shunt benefits in this HFrEF subgroup. And one way to do that would be to take away a certain number of patients which had the most recurrent heart failure events to see if those disproportionately changed the statistical outcomes. And we did that. We thought four was a reasonable number. We also have done other analyses, I think to address the others, maybe Dr. Blankenship's questions about how we-- Instead of picking four, had we done three or two or one. And Dr. Chuan Bi has a slide to show you on that as well. So, I set the stage and I'll let him take it from here.

02:11:01 Dr. Bi: Yeah. So, this figure displays Nelson-Aalen cumulative hazard curves with 95% confidence intervals for the HFrEF patients comparing the shunt group against the control group with the progressive subject removal. So yeah, this is the result. And recall that this stress test was done to illustrate that the recurrent analysis

may be heavily influenced by those subjects who have a high recurrent number of events, with a highly skewed distribution, as few as four of the most extreme subjects which can impact the nominal p-values.

02:11:54 Dr. Lange: Dr. Yancy, does this address your question?

02:11:58 Dr. Yancy: So, would it have been inappropriate to simply do a fragility analysis?

02:12:05 Dr. Bi: We're not certain about that.

02:12:10 Dr. Yancy: I'm just a little concerned about the empiricism of arbitrarily selecting four, whereas looking at a fragility analysis gives you some sense of what's the overall durability of the finding. And that typically is more informative. But this is helpful. Thank you.

02:12:26 Dr. Abraham: Yeah, Dr. Lange, we'd like to respond as well. The first time we saw this analysis with four control subjects selectively removed from the analysis was when we received the draft slides from the FDA. They never brought this up to us previously. And so I think it's fair to ask our statistician, Dr. Hendrix, to respond to this analysis.

02:12:51 Dr. Lange: Yeah. So, Dr. Hendrix, if you'll respond to two things, both this and then I ask you to hold off on your other comments. So, please provide both of those.

02:13:01 Dr. Hendrix: Okay, thank you. Suzanne Hendricks, Statistical Consultant. So, we did several sensitivity analyses for this secondary endpoint, number five, which is the one that we're looking at here. And there was also secondary endpoint number two, which was the frailty model, the joint frailty model. And this one was the one that-- This was the Nelson-Aalen, and it did have that long tail. This is restricted to only the heart failure hospitalizations. And if you look at the analysis that includes all of the events, the recurrent-event analysis, including all events that were part of the primary pre-specified win ratio, then you get significance even with those four patients removed. So, you only lose significance if you look at a single endpoint.

And if you look at that single endpoint only with the Nelson-Aalen, with this specific comparison, we didn't have time to do the analysis excluding five patients, but we did several other sensitivity models including a permutation test. The permutation test P-value, the worst it ever got on the Nelson-Aalen and some of the other sensitivity models we did, the lowest p-value-- Sorry, the highest p-value we ever got was .017 for those sensitivity models. So, when we do pressure test this model, it's actually quite robust. And when you include all events instead of just heart failure hospitalizations, it's also quite robust.

02:14:26 The other question that I wanted to talk about was just the Gail-Simon test and where we ended up with that. So, as I mentioned earlier, the Gail-Simon test had a p-value of .12 for the win ratio. And as we've shown, the win ratio is less sensitive to treatment effects. And that includes also being less sensitive to interaction effects because we're excluding 38% of the events that happen. When we do the Gail Simon test using the global statistical test, which is the totality of the evidence, we get a p-value .0201, and when we do it using the recurrent-event analysis with all of the events that were part of the pre-specified primary win ratio, we get a p-value less than .0001. And so for those reasons, we believe it's inappropriate to pool the groups. And we believe that showing the two groups separately is a more appropriate analysis for interpretation of the totality of evidence.

02:15:22 Dr. Lange: So noted. All right. I believe all the questions that were asked at that time have been addressed. Was there anybody that had asked a question previously that has not been addressed? That means I've got--

02:15:43 Dr. Leifer: Yeah-- Dr. Lange?

02:15:45 Dr. Lange: Yes? I can't tell who's speaking.

02:15:47 Dr. Leifer: It's Eric Leifer.

02:15:48 Dr. Lange: Okay. Dr. Leifer?

02:15:51 Dr. Leifer: Yeah. No, I appreciate-- I know, particularly for Dr. Hendrix, how hard it is to do statistics in real time, so I appreciate all this. I did have a specific question though that I raised before, which I guess hasn't been completely answered because I was still looking--

02:16:08 Dr. Lange: Go ahead, restate it. Please restate it.

02:16:10 Dr. Leifer: Yeah. My question is, there's been a real focus on the interaction test for the HFrEF versus HFpEF. And I know in the statistical analysis plan there were about 15 different interaction tests that they said they were going to do. In the protocol, there were about three sex LVEF and site. And I'm just trying to find if there's some place in the protocol or the SAP that said, "We're really focused on the LVEF strata."

02:16:49 Dr. Hendrix: Yes, there were three places, I believe, where LVEF strata was specifically shown. The first place is when we did the sample size calculation to begin with, it was done separately within those two groups. The second one is that it was the only stratified variable besides site that was used in the study. And then the third is in both the protocol and in the SAP in the section on primary effectiveness endpoint, it's the only interaction that's mentioned in that paragraph. And the way it mentions it in both the protocol and the SAP is that we would do an interaction test to assess for homogeneity. And so that specific text, here we go.

02:17:34 Dr. Lange: Super.

02:17:35 Dr. Hendrix: Here's the slide that shows-- Let's see, did it come up? Here it is. So, in the protocol it says, "The safety and effectiveness of the shunt according to pre-specified LVEF subgroups will be assessed by interaction testing." That was in the section about the primary effectiveness endpoint. And then that next sentence there, "Primary effectiveness endpoint analysis will be performed on a combined HFrEF and HFpEF population." And then immediately after that sentence, which is in the

single paragraph of the study protocol on primary effectiveness endpoint, it says, "The homogeneity of the treatment effect will be examined in an analysis of the interaction between treatment effect and the HFrEF/HFpEF subpopulation." So, none of the other subgroups are talked about in those sections at all. And they're all talked about again together at the very end, and that's the section where it says that they'll be used for descriptive purposes. This one's repeated down there, but none of the others get the priority this one does in the primary effectiveness section. Thanks.

02:18:34 Dr. Lange: Dr. Leifer, if you're saying something, you're muted. Well, we've come to a stopping point right now. We will come back and deliberate as Panel-- I see some hands up. Dr. Zuckerman, Dr. Farb, Dr. Wittes. I'd like to take a 15-minute break at this particular time. Bram, that's a double hand. Go ahead.

02:19:00 Dr. Bram Zuckerman: Yes. Yeah. Did we answer your question, Dr. Lange? You wanted to know the clinical outcomes of the roll-in patients in some more detail from the sponsor?

02:19:13 Dr. Lange: Yep. And I was going to ask for that. Go ahead, Bill.

02:19:16 Dr. Abraham: Yeah, let's bring that up. First of all, emphasize that this was a roll-in cohort, not a randomized cohort. There is no parallel control group for comparison. So, what we've done is a comparison between predicted outcome and observed outcome in the roll-in cohort. And I'll show you that information for the HFrEF population for comparability to what we've presented today in regard to or from the randomized trial. So, we use two well-validated risk prediction scores in heart failure, the MAGGIC score, and the Barcelona BIO-HF score. And you will see that based on the baseline characteristics of the roll-in HFrEF cohort, the predicted mortality ranged from about 20% to 25%, and the observed mortality was 12.5%, so about half of what was predicted. That's about the best we can do with this uncontrolled roll-in data. But I think it provides some confirmatory data, or at least

some reassurance that the shunt performed well in these roll-in HFrEF patients as it did in the randomized cohort.

02:20:48 Dr. Lange: And for those roll-in patients, all we collected was mortality data? We didn't have any of the other data?

02:20:53 Dr. Abraham: No, no. The issue is that the predictive models only predict mortality. So, that's why the comparison here is to mortality. Now, we do have other data from the roll-in cohort. For example, we have data on the KCCQ score, which improved on average in this unblinded single arm roll-in cohort by 15 points. I think it adds to Dr. Stone's concerns about the KCCQ where in unblinded trials, we see about a 15 point improvement in the KCCQ, and it's exactly what we saw in the roll-in cohort. So, the subjective data collected in the roll-in cohort all looked very good.

02:21:39: Dr. Lange: Right. When we come back, I just want to see one slide that shows all of what happened to this group in total.

02:21:45 Dr. Abraham: Okay. We'll see if we can get that together.

02:21:47 Dr. Lange: That'd be great. That'd be great.

02:21:48 Dr. Farb: Dr. Lange, permission to respond on the roll-ins? Or did you want to wait until later?

02:21:54 Dr. Lange: Yeah, let's wait until later.

02:21:56 Dr. Farb: Okay. We have some data from the actual trial that you might be-- The Panel may be interested in.

02:22:01: Dr. Lange: Yeah. And so I'll let the sponsor and you all respond. But let's take a 15-minute break and then when we come back, we'll-- Now that the questions have been answered, we'll begin the deliberations and we'll center that around the FDA questions. At that point, I reserve the right to either call the FDA to respond to anything or the sponsor, and that will obviously be my request, and that's to facilitate

our deliberations around the questions that the FDA poses. So, thank you all. And by the way, I want to thank the sponsor. A lot of data, a lot of questions in a short period of time. You guys did a great job of providing that. I really appreciate that. FDA, you had fewer questions, but still responded just as well. So, thank you all very much and we'll start a 15-minute timer and I'll see you back very shortly.

00:07:19 Dr. Lange: I'm Rick Lange. It's 4:21 p.m. Eastern time and we're soon going to focus our discussion on the FDA questions. But there are three clarifying questions remaining. I'd like to have them answered. Two directed towards you, Andy, Dr. Farb. One is information regarding the roll-in patients you might have, and I'd like for you to discuss KCCQ. Then I'd like Dr. Greg Alexander from the FDA to talk about the frailty testing because there was some question about that. So, Andy?

00:07:51 Dr. Farb: Thank you, Dr. Lang. So, you recall that in roll-in patients, they are in the study as part of the investigational plan. As you know, they have the same enrollment criteria, the same assessments, the same treatments, and the same follow-ups except that they all get the shunt. So, we'll call these the roll-in subgroup. And then I'm going to show a slide of the actual data comparing the roll-in subjects versus the randomized subjects in the HFrEF subgroup. If you could show that slide, Victor. And so here are the curves of-- And this really gets to the key question about selective subgroups and how the results can vary. So, if we look at the green line or the HFrEF roll-in subgroup, and you can see that their cumulative events are the highest, they're higher than the HFrEF control in the randomized trial and much higher than the HFrEF randomized shunt group. And again, this raises levels of uncertainty about what is going on with the HFrEF shunt group.

00:09:10 And we did show some data about how the disproportionate amount of recurrent heart failure events were clustered in a few patients. And we don't see, when we looked at the baseline characteristics, we could not find any explanation for this. They apparently were very similar to the baseline clinical and imaging

characteristics of the HFrEF randomized shunt patients. So, it tells you that shunt subgroups can differ markedly and it does raise some levels of uncertainty. And the table slide also shows a higher rate of death. If you go back to the previous slide, you could see on the first three rows speak to death. And the highest event rate for death is in the roll-in shunt subjects, and higher than the randomized HFrEF shunt subgroup, which is otherwise unexplained.

00:10:18 Dr. Stone: All right. Make the mic live.

00:10:20 Dr. Lange: Paul, you have a quick question about that?

00:10:22 Dr. Hauptman: Very quick question. I want to thank Dr. Farb for showing that. I mean, did you also do the analysis just to kind of drive the point home with the HFpEF roll-in patients?

00:10:31 Dr. Farb: Yes, we can show those data if you go onto the next slide. I think it's-- Once again, the highest risk is in the roll-in subjects and they share the same characteristics as the randomized HFpEF subgroup.

00:10:51 Dr. Stone: So, Dr. Lange, if we could respond, because I think there is an explanation.

00:10:57 Dr. Lange: Go ahead.

00:10:59 Dr. Stone: So, if you could bring up AA-52. So, there were actually key differences between the roll-in shunt-treated patients with HFrEF and the randomized shunt-treated patients with HFrEF. Of course, the roll-in-treated patients were treated earlier. So, first of all, if you look-- And these are some of the key differences, many of the other differences are not significant, but these are some of the ones that really stick out. The patients are actually substantially heavier, slightly more obese. There's much less use of ICDs, there's much less use of ARNIs, there's much less use of SGLT2 inhibitors. These are major differences that can definitely affect prognosis in these patients.

00:11:47 If you look at the echoes, it's particularly striking the ICD use, given that the ejection fraction is actually approximately two percentage of LVEF unit points lower in the roll-in patients. The right ventricular function tended to be worse in the roll-in patients than in the randomized patients. And if you look at the hemodynamics, the right atrial pressure was higher. The pulmonary artery pressures were six millimeters higher, and we showed you how important that prognostic variable is. The pulmonary capillary wedge pressure is four millimeters higher. It's 21 millimeters of mercury in the roll-in patients. And the PVR also tended to be higher. So, the roll-in shunt group patients were a higher risk patient population than the randomized shunt group in our estimation, which is why it's so critical to be cautious in any interpretation without a control group with similar characteristics.

00:12:38 Dr. Lange: Mitch, hand up?

00:12:40 Dr. Krucoff: Yeah, sorry, just a quick question. Was the selection process for roll-in patients the same-- With the same rigor that their randomized trial patients? Was there a Committee review, etcetera, etcetera, were they maximized on GDMT, etcetera?

00:13:02 Dr. Stone: They were supposed to be, but we did not have an Eligibility Committee review every strict criteria the way we did in the randomized phase of the trial. And also, Mitch, as you know, in registries, you often will put in higher-risk patients than you very, very carefully select out the patients in randomized cohorts. And that's I think what you're seeing here, those two factors.

00:13:27 Dr. Lange: All right, thanks. We're going to move on. Thanks, Gregg, for responding on behalf of the sponsor. Andy, they've talked about KCCQ. I want the FDA's opinion or perspective on the KCCQ.

00:13:40 Dr. Farb: Yeah, I'll be very brief, Rick. We've heard-- We've seen the sponsor's points about trials that showed, you know, marked benefits of certain

pharmacological therapies with relatively modest benefits for KCCQ score changes, however, those are means. And if we look at another way of looking at KCCQ changes, and that's in a responder analysis, we see here that for these major heart failure pharma trials, that the responder analysis, which are basically degrees of KCCQ score changes, either points increases expressed as control versus the active treatment, and you can see that there is an alignment between the beneficial hard endpoint events that correspond to the responder analyses that seem to track consistently with the active treatment arm in the pharma trials for these major studies.

00:15:01 Dr. Lange: Thank you. Thank you. And the last thing I'd like to clarify before we go into our Panel discussion is that Dr. Alexander, could you provide some insight into the statistical analysis?

00:15:16 Dr. Alexander: Yes. I just want to-- Gregory Alexander, I'm the Director of the Statistical Programs here at CDRH. I just wanted to make sure there's no misinterpretation about the post-hoc analysis that we performed, which was in the form of a stress test trying to understand the implications of recurrent analysis, recurrent-event analysis. The main difference is that the recurrent analysis looks at the total burden of events in the group. And we wanted to understand how much that burden, that total burden, could be driven by those smaller subset in the skewed distribution that had a majority of the events, which is the reason why we investigated how removing a few of these high burden patients in terms of events could affect nominal statistical significance. And that's what we're trying to illustrate. Now, we did it in a very obvious transparent, unbiased way. However, the problem with post-hoc analysis in general in trying to derive interpretations is that those effects are often hidden while you attempt to extract data in a post-hoc analysis setting. And so this gave us a gauge of just how susceptible such analysis may be in

the recurrent phase versus, say, a time-to-event or win ratio or other more individual specific patient analysis. Just to clarify.

00:16:53 Dr. Lange: Yeah. Dr. Yancy, does that help at all? Terrific. Terrific.

00:16:58 Dr. Stone: And Dr. Lange--

00:16:59 Dr. Yancy: That helps. I'm sure we'll have a conversation later.

00:17:02 Dr. Stone: And Dr. Lange, if the sponsor can respond very quickly--

00:17:06 Dr. Lange: Actually, not. Not to offend. We've had 90 minutes to go through this. There's going to be a difference between both.

00:17:14 Dr. Stone: Okay. I appreciate you. Thank you.

FDA Questions

00:17:15 Dr. Lange: Yeah. But thanks, Gregg, I appreciate it. Now's the time for the Panel to begin to deliberate. So, we'll begin to do that right now. And we're going to center that around the FDA questions. So, Panel members, electronic copies of the questions have been emailed to you and are posted on the FDA website. I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription. And I'm going to turn over to Victor Mondine who will provide us with the first question.

00:17:47 Mr. Mondine: Question 1. The primary safety endpoint was the rate of device- or procedure-related Major Adverse Cardiovascular or Neurological Events (MACNE) (including all-cause death, stroke, systemic embolism, need for open cardiac surgery, or major endovascular surgical repair) at 30 days post-randomization and was evaluated in the 250 shunt group patients. No patient experienced a primary safety endpoint event, and the primary safety endpoint was met. Additional safety events through two years in shunt and control (sham procedure) groups are shown in Table 1. There were numerically more

cerebrovascular and pulmonary embolism events, but fewer myocardial infarction events at two years in the shunt group versus the control group. Please discuss on the clinical significance of the safety events observed in the study.

00:18:36 Dr. Lange: Okay, this question's open for discussion. Mitch? Dr. Krucoff?

00:18:46 Dr. Krucoff: Yeah. Thanks, Rich. So, I will start with what I think the bottom line is that clearly, in the right hands, the safety of deploying these devices is impressive, but I think that begs a number of other questions. First of all, the control here is a non-invasive approach. It's medical management. There was no other than the sham procedure and we have to keep that in mind as we move along. Secondly, anybody who works in and around a cath lab knows that zero is never the right number for complications if you're doing a transseptal puncture, etcetera. I think we've gotten pretty good, but it's not zero. So, I think those are the cosmetic safety issues. And then the deeper ones, I think we've discussed at some length what happens over time, what happens if LV function changes. I'm a little murky still on what happens actually to the device, device patency, but I think those are open-ended issues. The bottom line, though, is I think this is a relatively safe procedure at the end of the day.

00:19:56 Dr. Lange: Thank you, Dr. Krucoff. Dr. O'Connor?

00:19:59 Dr. O'Connor: Yes. Thank you. Chris O'Connor. I wanted to get clarification on deaths that occur within 30 days. I've worked on a number of CECs and attribution to device is difficult. Were there any deaths within 24 hours, 72 hours, one week of the device deployment that were not attributed to the device? And if we believe that in the HFpEF patients that the device can cause adverse hemodynamic effects, if a patient died of heart failure within 30 days, would that be attributed to the device?

00:20:52 Dr. Lange: So, sponsor? And just a quick yes or no, were there any deaths within 30 days?

00:20:59 Dr. Stone: No. No, there were no deaths within 30 days.

00:21:01 Dr. Lange: That's it. Great. Thank you. Very helpful. Thank you very much, Gregg. Dr. Vidovich?

00:21:07 Dr. Vidovich: This is Mladen Vidovich. So, regarding safety, I probably would like to just break it into two parts. One is the implantation safety. I think this is demonstrated. It was really a straightforward procedure, low fluoro time, low contrast use. What-- Another issue of safety I would like to separate is this high use of oral anticoagulation. So, about 60% of patients on oral anticoagulants, 50% for antiplatelets. The best I can tell from the discussion, AFib flutter was 6%. So I'm at a loss. Why is this such a high level of high intensity anticoagulation? I've even heard that some patients were kept on triple therapy. I'm sure this helped with the patency of the device, like the device getting occluded. Although with a Qp/Qs of a liter, it probably had a hefty flow so it wouldn't get occluded. But again, this raises a large issue for me for the safety. If this were to be used clinically in a wide spectrum of patients, would we maintain this high level of anticoagulation as was done in the trial? And then maybe just one last-- Bleeding seems pretty low given such a high level of anticoagulation also throughout the trial. Again, there was no invasive bleeding, but again, I would've expected a little bit higher bleeding rates on this base level of anticoagulation.

00:22:37 Dr. Lange: So, right now-- Table 4 of the FDA presentation briefing document shows about 60% of the people had a history of AFib or flutter. So, I think what you're referring to is new onset.

00:22:47 Dr. Vidovich: Probably new onset. Okay. That is my bad.

00:22:50 Dr. Lange: Just so you're aware. Okay. Thank you. Dr. Shanker?

00:22:54 Dr. Shanker: Yes. Hi. So, I'm fine with the MACNE 30-day data. I do have concerns and I know it's brought up here in our summary about the two-year thromboembolic

risk, 13 patients in the shunt group or a 5.1% incidence of PE or some type of a CVA versus 2.5% or 7 patients in the control group. And in the first-in-man trial that was done with the first generation, there was a 50% occlusion rate in that shunt. And fortunately we're not seeing that, but paradoxically, pun intended, I'm trying to figure out why there's a doubling of the thromboembolic risk in the shunt group.

00:23:42 Dr. Lange: Thank you for that, Dr. Shanker, and I appreciate the paradoxical, by the way. Good job. Jim Blankenship?

00:23:55 Dr. Blankenship: Well, you look at the, say, short-term safety, which obviously is really good. And then longer term safety, I was wondering about the safety of just the transseptal puncture, and the literature reports about a 1% complication rate from that. There was an interesting study by Cheng [sp?] et al., 2023 Pacing and Clinical Electrophysiology. 78 patients undergoing transseptal puncture with AF ablation had MRIs afterwards and there was a 6% incidence of new MRIs. And so there may be some penalty from simply working in the left atrial in the transseptal puncture, perhaps not due to the transseptal puncture itself. So, if there's any excess of stroke, it might reflect that. In this case they were all subclinical, but of course we don't see that as being a reason not to do atrial fibrillation ablations.

00:24:55 The second issue longer term is I was concerned that perhaps having that shunt would lead to the opportunity for paradoxical embolization over the long term. I think it's reassuring to see, I think the data was that 94% of patients who had a shunt had a left or right shunt, so you would not be expected to get paradoxical embolization unless there was Valsalva or something acute, a much smaller proportion, I think 6% would be bidirectional. So, even though we know that you can get paradoxical embolization through an ASD, it seems like that would be a relatively low likelihood in patients with the shunt.

00:25:30 Dr. Lange: Thank you, Jim. Dr. Page, and then Dr. Kumbhani.

00:25:35 Dr. Page: Yeah, thank you. As Mitch started us off, I'm relatively untroubled by the complication rates and feel pretty comfortable with the safety. I do have a question about the roll-in group and what's different about them. One hypothesis might be people, there's a learning curve that in some way that we don't understand. So, I just wonder about that. And I also just want to confirm with the sponsor, they said there were no deaths in 30 days. Did that include the roll-in patients as well?

00:26:12 Dr. Lange: Let me ask the sponsor to respond to that with regard to roll-in. Any deaths within 30 days in the roll-in group?

00:26:18 Dr. Stone: We are checking. We don't believe so, but we are checking.

00:26:22 Dr. Lange: Thanks Gregg. I appreciate that. We have three more comments. Dr. Hauptman, Dr. Kumbhani, and then Dr. Yeh. Dr. Hauptman?

00:26:30 Dr. Hauptman: Thanks. So on the-- Paul Hauptman for the record on the topic of the paradoxical emboli, what we haven't heard is whether or not if a patient does experience that, and this device is used in thousands of patients, I think we can anticipate it will occur, can the device be removed and the ASD or the puncture site closed? And then the second issue in terms of longer term safety, maybe even shorter term safety I had raised before, and that's just about patients who might have-- Who have severe mitral regurgitation and whether or not they might run into problems with right-sided failure if the device is implanted. So, that maybe addresses more a long-term-- I don't really-- I have no concerns about the short-term safety at this point.

00:27:27 Dr. Lange: Right. Thank you. Dr. Kumbhani?

00:27:27 Dr. Kumbhani: Dharam Kumbhani. Yeah, thank you. So, I think the safety profile looks pretty good. These were not directly part of the primary safety analysis or the endpoints that they looked at, but would report in the secondary, but the two that I think are concordant with other procedures that we do in the transseptal space,

one is the risk of pericardial effusion, which they report happened in one patient in the device arm, which again, we've seen this with multiple devices. We see this with the MitraClip as well, so I think that seems reasonable. The other was what Dr. Abraham provided data for, which is when we do ASD closures or PFO closures, we almost always will quote a 2% to 5% risk of atrial arrhythmias. This is borne out in multiple studies and they report a 30-day rate of atrial arrhythmias of 2%. So, I think these are perhaps not part of the MACNE events, but are important procedural safety endpoints. So, that was more of a comment.

00:28:32 Dr. Lange: Thank you, Dr. Kumbhani. And then Dr. Yeh, last comment.

00:28:36 Dr. Yeh: Similar feelings about the acute observed procedural safety. I think for the cerebrovascular events, the event rates are low enough to not to know what to make of them. I think it doesn't completely rule out that there could be some sort of embolic risk, but those would probably be more appropriately studied with the power that you could get in a post-approval study. What I am a little bit concerned about is just the finding of harm. I know we're talking about HFrEF, but the finding of harm in the HFpEF population just raises the possibility that this device has a safety concern among some humans, among some people. And the mechanism for that may be explainable, but given the spectrum that this heart failure exists on this spectrum, that it's not entirely dichotomous. Just to raise the possibility, maybe we'll get into this more when we talk about effectiveness, that when you're comparing to a placebo or a sham, that having a group that does much worse migrates from an effectiveness signal to a safety one. So, I just want to just think about that in the background as we talk a little bit about effectiveness.

00:29:45 Dr. Lange: Right. So, let me summarize what's been said there. Really not very many concerns with the acute implantation and the safety of the procedure. There are some things that weren't captured in MACNE, things like atrial arrhythmias, pericardial effusions, a small percentage, but nevertheless not captured. But there's

more concern about the longer term safety. What happens if the EF goes up; use of long-term anticoagulation or antiplatelet agents, people that otherwise wouldn't have them; thromboembolic risk, either right to left shunting, paradoxical embolus or the presence of a thrombus on the left atrial side. And then finally, is there a harm in HFpEF patients or a subset of patients? And by the way, I'm going to-- When we talk about hemodynamics, I'm not sure there is a good hemodynamic explanation for this, but overall, I think I've captured at least the comments from the Committee members. Does that address the question sufficiently for the FDA, Bram?

00:30:50 Dr. Bram Zuckerman: Yes. There's been excellent discussion and summary. We're ready to go to Question 2.

00:30:56 Dr. Lange: Right. Thank you very much.

00:31:01 Mr. Mondine: Question 2. RELIEVE-HF was designed to demonstrate device effectiveness in a combined cohort of HFpEF and HFrEF patients. The primary effectiveness endpoint was a hierarchical composite of all-cause death, cardiac transplantation or LVAD implantation, heart failure hospitalization, outpatient worsening heart failure events, and KCCQ score change. The primary analysis used the Finkelstein-Schoenfeld method and calculated a win ratio. The primary effectiveness endpoint was not met with a win ratio of 0.86, and 95% confidence interval of 0.62 to 1.22, and a p-value of 0.20. A post-hoc cumulative event analysis of the primary effectiveness endpoint (excluding KCCQ) through two years is shown here in Figure 2. Similar hazard rates were observed, for the shunt group (annualized rate 55.7%) and control group (56.0%). The individual component rates of the primary effectiveness endpoint are shown in Table 2 and Figure 3. Please discuss the clinical significance of the primary effectiveness endpoint results.

00:32:18 Dr. Lange: Dr. Wittes, I'm going to turn it over to you first if you don't mind. And I realize we talked about clinical endpoints. Go ahead.

00:32:29 Dr. Wittes: Okay, so you're talking about the primary endpoint for the ITT population, right?

00:32:37 Dr. Lange: Yes.

00:32:38 Dr. Wittes: So, it seems to me that this clearly shows, if we're thinking just about the ITT, that there's no effect of the shunt on the population, the ITT population.

00:32:53 Dr. Lange: And therefore, I mean, based upon-- Obviously there was an interaction test that was done and you've heard of, so--

00:33:03 Dr. Wittes: So, are we talking--? Are we going into the interaction test now or are we going just to the ITT?

00:33:11 Dr. Lange: I'll tell you, we'll hold that to Question 3. Okay? [Indiscernible - 00:33:14] HFrEF and HFpEF--

00:33:15 Dr. Wittes: Yeah. It seems to me the data we just saw was overall, and this is all we saw, we would say this shunt seems pretty safe, but it doesn't do anything.

00:33:24 Dr. Lange: Okay. Dr. Krucoff?

00:33:29 Dr. Krucoff: Yeah, I think understanding there's more below the surface, but as we've been talking about, I think the primary study based on its prospective design for the primary endpoint did not meet the primary endpoint. I'm not sure that's a-- Unless this question is meant for more than that, I don't think that's a complicated discussion.

00:33:49 Dr. Lange: Right. I think it's meant just to set the stage, but if there is some disagreement about this or an alternative opinion by this Panel, now's the time to present that. If not, this will be a very short discussion on this. Dr. Yancy, I see your hand. Thank you, sir.

00:34:07 Dr. Yancy: This is Clyde Yancy here. I think it is appropriate as a point of emphasis though, as a standard measure of evaluation of randomized controlled trials

when the pre-specified primary endpoint is not met. For the most part, everything thereafter is really truly hypothesis-generating unless it is overwhelmingly strong in all of the analysis. And so we should not just accept this as a primary endpoint that was not met, move on, but understand how that has implication and how we interpret everything else that's preferable to this trial.

00:34:38 Dr. Lange: Very articulate, Dr. Yancy, thank you. Thank you. Any other comments about this? Pretty succinct. The other thing, Bram, the other comment I would make is I think the clinical endpoints that were chosen are meaningful to the patient population, both in terms of hard endpoints and what I'd say quality of life endpoints as well. And I appreciate the fact that the sponsor gets to choose the analysis and work with the FDA to finetune it. Dr. Krucoff, last comment?

00:35:20 Dr. Krucoff: Yeah, Rich, just along as we move into this. Just I would say to me a patient-related primary endpoint, which is how this trial was designed, is most appropriate and it was the right design. And I think we can talk about event-related and other ways of approaching it. I know it's a hot topic, but personally I think as you look at the data, I think the design was actually the right design.

00:35:54 Dr. Lange: Thank you for that.

00:35:55 Dr. Wittes: I'd like to add something. I actually think it was good--

00:35:58 Dr. Lange: I'm sorry. I'm sorry. This is Dr. Wittes for the transcription.

00:36:00 Dr. Wittes: Yes, sorry. This is Janet Wittes. That having the KCCQ having to get at least a five-point spread, I think that was clinically important.

00:36:11 Dr. Lange: Okay. Thank you. All right, so I think what you're hearing from 2 is the individual components, the design, the analysis, and the outcome, which did not support any benefit. I think we're pretty clear. FDA, do you need any other comments about this?

00:36:35 Dr. Bram Zuckerman: No. That was a good discussion. Let's go to Question 3.

00:36:39 Dr. Lange: Okay. Victor?

00:36:43 Mr. Mondine: Question 3. RELIEVE-HF was designed to show that the shunt would be safe and effective in heart failure patients independent of heart failure phenotype. For the statistical analysis plan, the shunt benefit was expected to be more pronounced in the HFpEF (LVEF greater than 40%) subgroup versus the HFrEF (LVEF less than or equal to 40%) subgroup. RELIEVE-HF enrollment was stratified by heart failure phenotype and there was a pre-specified analysis comparing the primary effectiveness endpoint results between the HFrEF and HFpEF subgroups. The heart failure phenotype subgroup analysis results were discordant suggesting shunt benefit in the HFrEF cohort with a win ratio of 1.40, and 95% confidence interval 0.80 to 2.46, and harm in the HFpEF subgroup with a win ratio of 0.61, and 95% confidence interval 0.39 to 0.98. The interaction test analysis showed a nominally significant p-value of 0.0146. Although RELIEVE-HF enrollment was stratified by LVEF and there was an expectation that the treatment effect may differ in degree between the subgroups, the study was designed to evaluate the effect in the total population, not in each LVEF subgroup separately. There was no pre-specified plan to control type I error in the subgroup analysis.

00:38:07 The sponsor performed multiple post-hoc analysis on the HFrEF and HFpEF subgroups to gain insights into the discordant results. In the HFrEF subgroup, there was a 5-level (all-cause death, cardiac transplant or LVAD, heart failure hospitalization, outpatient worsening heart failure, and KCCQ score change) win ratio analysis that showed no statistically significant difference between shunt and control groups. Also a 4-level (excluding KCCQ change) win ratio analysis, which showed no statistically significant difference between shunt and control groups. Also heart failure events (along with heart failure event in combination components of the primary effectiveness composite endpoint, excluding KCCQ) utilizing multiple analytical models favored the shunt group. All-cause death and transplant or LVAD

rates favored the shunt group. Cardiovascular death rates were similar between shunt and control groups. There's also similar KCCQ scores in shunt and control groups.

00:39:04 In the HFpEF subgroup, they performed a 5-level (all-cause death, cardiac transplant/LVAD, heart failure hospitalization, outpatient worsening heart failure, and KCCQ score change) win ratio analysis that favored the control group. Death and heart failure event rates favored the control group as well.

00:39:27 Pathophysiological insights. The sponsor conducted post-hoc exploratory analyses between group differences in transthoracic echocardiographic (TTE) changes at baseline in 12 months. In N equals 508 randomized patients, there was 12.2% missing 12-month follow-up TTEs. Among the 16 TTE parameters assessed, follow-up TTEs showed reverse left ventricular remodeling in HFrEF subgroup shunt subjects. A smaller increase in estimated pulmonary artery systolic pressure in the HFrEF shunt group versus the control group. It increased right ventricular, right atrial and inferior vena cava size and pulmonary artery systolic pressure in HFpEF shunt subjects versus controls.

00:40:13 A) Please discuss the strengths and limitations of the evidence and your level of uncertainty that the shunt is beneficial in HFrEF patients. And B) Please discuss the strengths and limitations of the evidence and your level of uncertainty that this shunt is harmful in HFpEF patients.

00:40:29 Dr. Lange: Now I'm going to divide this into two discussions. I want to talk a little bit about the statistics and the uncertainty. And Dr. Wittes, I'm going to remind you that there are, like myself, there are many interventional cardiologists. You have to use very short words and very short sentences to describe this. Okay? And the other thing I want to talk about is the pathophysiologic mechanism behind it. So, I'm going to start with you, Dr. Wittes and Dr. Leifer as our statisticians to talk about the strength and limitations of the evidence based upon what you know. Janet?

00:41:02 Dr. Wittes: Okay, so this is Janet Wittes. I'm trying to see how to say this. So, what the analysis did was to look at the HFrEF and the HFpEF and to ask the question, "Is there evidence that the effect of the drug-- Of the device is different in the two groups?" And what they did was to do just a plain interaction test. To me, that's not what I would've done because all that says is-- A statistically significant interaction just says there's a difference in effect. But the real important question it seems to me, if you have two groups, two subgroups, is "Should you be treating them differently, those two groups?" And just because the effect is different doesn't mean that you should treat them differently. They may be both effective, but one more effective than the other. And that leads to-- Can lead to an interaction, a significant interaction.

00:42:09 That is why I asked for the Gail-Simon test. What does the Gail-Simon test do? It asks-- Here you have these two subgroups. Is one of them-- Is there evidence that one shows benefit and one shows harm? So it requires-- So you can have a statistically significant interaction, just saying that they're different, but not a statistically significant Gail-Simon test. Now, it's not a very powerful test because you don't usually design a trial, assuming the two strata are going to show different directions. That's very unusual. But here the Gail-Simon test had a p-value of 0.12. So, I interpret that as-- Given my prior that there shouldn't be a difference in direction, and given the assumption in the study that both strata would be-- The device would be effective in both strata, I view that as not very strong evidence that one is positive and one is negative. Right? Is that clear, what I'm saying?

00:43:37 Dr. Lange: Yes. Yes.

00:43:38 Dr. Wittes: Okay. Okay. So that was the Gail-Simon. So my reaction to this is, "Huh, isn't this interesting?" You're seeing harm in HFpEF and you're seeing benefit in HFrEF, but statistically this could happen by chance. And that's what to me, the Gail-Simon test is saying. And therefore, that leads me to say I'm actually more

interested in the ITT because I don't have strong evidence that the two groups are different in direction. Then we have a whole lot of other analyses that can, quotes, confirm that strengthen the evidence, or strengthen the apparent evidence for the HFrEF. But all of those, it seems to me, all of those analyses were done after the sponsor saw the data. So, the argument that the alpha level, the type 1 error is not inflated, I don't understand that argument because part of the inflation seems to me due to the fact that they saw the data and then they designed the analysis.

00:45:08 So, I find that-- and I was struck by Dr. Packer's discussion of PRAISE. My experience in similar cases where-- And it's not been in heart failure, it's been in other series where you see a surprising difference between two straight up, one shows benefit and one shows harm. The company gets all excited, they do another study. And guess what? There's no difference in the group that shows benefits. There's no effect. So, I've seen this several times and PRAISE is an example that Dr. Packer brought. So my interpretation is, yes, this is promising, but it's not convincing enough to me that there's benefit in the HFpEF-- HFrEF.

00:46:10 Dr. Lange: Thank you.

00:46:11 Dr. Wittes: Oh, and then the same argument goes for the HFpEF. If I argue that, "Hey, the fact that my statistical test can't distinguish those differences in benefit for HFrEF, they can't distinguish those benefits for harm in HFpEF either."

00:46:31 Dr. Lange: Thank you, Janet. Thank you. Dr. Leifer, do you want to add something to this discussion?

00:46:38 Dr. Leifer: Just a little bit. I mean, Janet is a very tough act to follow, but I'll do my best. But no, my thinking is directly in alignment with Dr. Wittes. So, I think it was great that she brought up the Gail-Simon test because that looks to see whether one is really-- Where we think one is harmful and one is beneficial. And in terms of the data itself for the win ratio, the HFpEF showed nominal significance for harm,

confidence interval slightly excluded one. Whereas for the HFrEF group, it didn't quite make nominal-- That didn't even make nominal significance for benefit. And so probably if the HFrEF was a bit more-- Perhaps if the HFrEF was a bit more impressive, maybe Gail-Simon would've been significant, but it did not make nominal significance for benefit.

00:47:44 And then I'll just also echo what Dr. Wittes said. I was a little bit troubled by going to-- Doing several other post-hoc analyses, most of them, which really focused on the number of heart failure hospitalizations because that was the one thing that kind of jumped out a bit. And that was where you were able to look at some of the Nelson Aalen rate estimates and get something that looked pretty convincing nominally there. And then also it pivoted into this sort of global statistical test, which I confess, I actually had to Google while we were talking about it. And it's just a way to try to combine all these different endpoints in a way. I mean, the win ratio combines these different endpoints, but I guess the global statistical test combines them in a way that you might get a little more benefit from having that heart failure hospitalization number be a bit higher. But in any case, I'm really quite in alignment with Dr. Wittes.

00:48:52 Dr. Lange: Dr. Zuckerman, I see your hand up.

00:48:54 Dr. Bram Zuckerman: Yeah, this has been an excellent discussion, but I would just like to ask Dr. Wittes about Question 2 so we can elaborate on this a moment. Janet, you pointed out that the interaction test is positive from a purely statistical point of view. That means that the coefficient in front of the interaction term is not zero. But if I heard you correctly, that does not lead to a definite clinical interpretation. Point number 1. Point number 2 is that the sponsor utilizes some methods to try to calculate type 1 error or the false positive rate. But because these methodologies depend on the actual data stream of the trial, meaning the actual

observed data, you don't believe that these type 1 error calculations are useful. Would those be two reasonable summary statements?

00:50:14 Dr. Wittes: Well, not quite because the first statement is yes, what I want to stress is that an interaction test just says, "Is the effect size different? Is there statistical evidence that the effect size is different in the two groups?" Right? And that was significant. So, that says statistically we have evidence that the effect size is different in the two groups, but it doesn't say that therefore you should treat one group and not the other group because you could have just that one group has a strong effect and the other group has a weak effect. So, that's what I was saying. Whereas what we really want to know is whether one is beneficial and one is harmful.

00:51:05 As far as the permutation test to do the type I error rate. I didn't mean to say I didn't believe it. What I didn't do is understand it. So, because I didn't really understand what was being done, how much was related to the particular data in the study, and how much was post-hoc, I just didn't understand. So I can't-- I'd be interested in what Eric thinks, but I wouldn't say I don't believe it. I would just say I don't understand it.

00:51:40 Dr. Leifer: I actually didn't understand it either. I mean, I think that's one of those things that it's hard to really digest in real time because there were sort of several layers. There was about three levels that the sponsor went through in computing it, and it seems like there was some justification there, but it would probably almost be the kind of thing a few statisticians would've to go to the whiteboard to really understand

00:52:10 Dr. Lange: Dr. Yuh and then Dr. Yeh.

00:52:13 Dr. Yuh: Thank you. I must admit that through most of this day I was actually uncertain of how uncertain I was. But several things, three things in particular came out and started to crystallize things for me. First of all, the clustering of adverse events in the control group amongst just a few patients and exposing the weakness of

that methodology struck me. Secondly, the potential harm that this device has in some patients, granted, it may be in the HFpEF group, but there are some characteristics that we may not know about that may predispose this device to harm. And then finally, this procedure is an alteration of normal physiology, not a restoration like a valve replacement or an aneurysm repair. And I worry about the downstream potential for regression to the mean or recurrence or even worse, some downstream negative effect from altering this physiology. And so those three things combined introduce enough uncertainty to me where I really have concerns, especially in the HFrEF patient population.

00:53:28 Dr. Lange: Thank you, David. Dr. Yeh?

00:53:31 Dr. Yeh: Bobby Yeh here. I just want to think a little bit more about the interaction term. And I think Andy had a really great point, which was that the interaction term significance is driven heavily by the harm signal in the HFpEF group. And so it's interesting to think about if we had a more null HFpEF group, the interaction would've been non-significant. The results in the HFrEF group could be identical as what they are, and maybe we wouldn't even be here having these conversations because the interaction term seems to be the entryway toward all of the subsequent conversation. But that interaction term, if anything, is driven more heavily by the harm signal than it is by the benefit signal. So, I just think it's really important to keep that in mind. I know Andy said that and it was sort of an eye opening moment for me when I thought about it when he said it.

00:54:25 Dr. Lange: Right. And before I come to you, Dr. Vakhtang, Clyde, you were to talk a little bit about this and the LAP where the results are quite discordant. Can I pick your brain about that, Clyde?

00:54:43 Dr. Yancy: Absolutely you can. Because when we look at the possibilities of modulating the natural history of HFpEF, the shunt alteration was tested initially in a HFpEF population, and though there wasn't overwhelming evidence of benefit, and a

lot of subsequent deliberations would suggest that maybe it's related to PVR and resistance changes, the signal of frank harm also was not there. And so I think that when we're looking at these two subgroups and we see one with an unusually strong signal of benefit on some of the clinical parameters and one with an unusually worrisome signal of harm, it just brings to bear the questions about the integrity of the subgroup analysis to begin with. And like Bobby, I'm impressed that a lot of this interaction variable might be driven by these signals of harm and its interaction variable that actually launched the rest of this conversation.

00:55:43 And Rick, while I'm speaking, I want to just help us reestablish a context here because a lot of things are moving quickly in heart failure. In 2025, now nearly 2026, the standard of care for both phenotypes, HFrEF and HFpEF continues to advance. And so there is a need, there's no question about that. And there is residual risk, but the appropriate application of best indicated advice and medical therapy as they exist for HFrEF and the emerging evidence-based strategies for HFpEF are fundamentally changing those natural history curves. Implementation is still an issue, but I don't know that we need to be compelled that there is a need that is so pressing that we have to relax our standard from what we believe is safe and effective.

00:56:33 Dr. Lange: Thank you, Clyde. Dr. Tchantchaleishvili.

00:56:39 Dr. Tchantchaleishvili: Thank you. I just want to say that the group with EF less than 40% is not a homogenous group necessarily. And when the EF is really low, things might be different there. So, Dr. Farb's slide 97 showed continuous analysis with a curve and the upper bounds of that curve, 95% competence interval, upper bound of that crossed the zero line at EF of 30, but it appears again to cross it again at EF of 20, which means that, again, it is no longer certain if it's helpful. Now, that may be because they're not enough patients with EF less than 20%, there are only a handful of patients. But it is also plausible that if cardiac output is low

enough, then any degree of shunt will make things worse. So, there might be a patient population with low EF that will not benefit from this and will be harmed.

00:57:36 Dr. Lange: Okay. So, before we talk about pathophysiology for a second, and I don't want to leave that out of the discussion, let me summarize what's been said so far. There's a tremendous amount of uncertainty. This is a post-hoc analysis driven primarily by the number of heart failure hospitalizations in a small subgroup of patients. I quoted this, "They saw the data and then designed the analysis," the comment that Janet made. The data are hypothesis-generating. They're not convincing. The Gail-Simon test does not support a difference between the subgroups. There is an interaction test, but as Dr. Yeh has mentioned, that's driven heavily by harm in the HFpEF group, which was not seen, as Dr. Yancy mentioned, in the LAP study. And then Dr. Yuh had mentioned his degree of uncertainty because again, the clustering events in few patients, the potential harm in some patients and the altering normal physiology. Dr.--I'm sorry, Ms. Fortin, would you like to speak, please?

00:58:43 Ms. O'Sullivan-Fortin: Hi, thanks so much. I just wanted to ask-- Again, I am here not as a superhero of cardiology, but as a representative of patients, groups and advocates. I wanted to ask, there's this rush in this discussion about confidence to get rid of or throw out or exclude the data of those four patients. And I'm just curious, do we know what the demographic information is for those four patients? Because there were comments earlier about kind of a-- There's a set demographic of who availed themselves to this study. And I'm just curious. I would find it incredibly problematic if we were to find out that those four people, that everyone is rushing to cut out of the analysis, were representative of underrepresented groups in this patient population for this study.

00:59:48 Dr. Lange: Yeah. And I don't know if I have the data. I'll ask the FDA if they have that data. It's so granular that we may not be able to present it at this time, Ms. Fortin, but your point-- Your point's well taken. So regarding--

00:59:59 Dr. Neubrander: Dr. Lang? We do have that data.

01:00:02: Dr. Lange: Okay. So for those four patients, can you describe the demographics? Thank you. Wow.

01:00:10 Dr. Farb: Okay, so here are the data for those four patients. This is Andrew Farb from FDA. They're middle aged-- Three of the four, middle aged. One, a little older. All men. And strikingly two had very, very poor LVEFs, 11.5 and 19.1 and another 21; actually three of the four had extremely low LVEFs. All NYHA Class III, and one had at least moderate to severely reduced renal function. And what the scatter plot up top shows the heart failure, the clustering of heart failure events, and with death in two of those patients. I'm sorry, three of those patients.

01:01:07 Dr. Lange: Andy, all those comments are appreciated, except for the part where you said they're a little bit older. You could have left that part out, Andy.

01:01:12 Dr. Farb: Yeah, I was referring to my-- That was for my purposes. Thank you, Dr. Lange.

01:01:18 Dr. Lange: All right. Kathleen, thanks for asking that question.

01:01:20: Ms. O'Sullivan-Fortin: Thank you.

01:01:21: Dr. Lange: Thank you. Dr. Page, and then Dr. Krucoff.

01:01:23 Dr. Page: Yeah, just briefly, two comments. One is I've been on a lot of these panels and I've never had the statistical experts who are sitting on the Panel not understand what I could only describe as statistical gymnastics or acrobatics in terms of the way the data are being approached after the fact that the primary endpoint was not met. So going back to basics, we didn't meet the primary endpoint and therefore

the rest is hypothesis-generating. And it's taken a lot of work to try to make this so an argument can be made. I understand the desire of the-- First of all, the public speakers who I have tremendous respect for really wanting something and to have hope. But as Clyde very nicely summarized, we don't want to give false hope and we don't want to believe that we're addressing a problem if we really don't have data to support that. So, I love the signal, and if it worked in a randomized trial, I'd be very happy with it. But the degree of work to find statistical significance or find a statistical signal is more than really we can bear.

01:02:45 Dr. Lange: If Dr. Krucoff, Hauptman or Shanker have an opinion that hasn't been expressed, please do so. And if not, we will move on a little bit. So Mitch, I'll leave that up to you.

01:02:56 Dr. Krucoff: Yeah, Rich, sorry, but just very briefly, I want to come back to what I think you said before is that nothing we're discussing here is about excluding patients. It's about including patients. And I think the thing, just to stay crystal clear on, is that the original design of this trial was to include all patients in a win analysis comparison. And we have the results of this trial. We're just not using four out of those 400 patients to generate 20 episodes or events in the course of reinventing how to analyze the results of this trial. So I think coming back to the basics, this was exceptionally well done, in my opinion, an exceptionally well designed clinical trial. All the patients are included in this analysis. It is a patient-level analysis, and I think that's what we're discussing. We're just not magnifying any patients to be multiples of 4 or 10 or whatever.

01:04:03 Dr. Lange: Great. Dr. Hauptman and then Dr. Cetnarowski, and then I'll close it.

01:04:06 Dr. Hauptman: Yeah, I don't want to be redundant, but I will say that Dr. Page, Dr. Krucoff said it well. And I would just say that you live by the win ratio, you die by the win ratio. And you win by your primary endpoint and you die by your primary endpoint. And there's been enough concern here expressed that there's no

benefit for CV death. There's no change in the KCCQ, which, you know, is an important measure. No change in Six-Minute Walk Test, also an important measure. So, like Dr. Page said, I would like to believe this works. I mean, if you think about it from a theoretical basis, it really could be a solution. I just don't see it in the current data.

01:04:45 Dr. Lange: Dr. Cetnarowski. Thank you very much, Paul.

01:04:47 Dr. Cetnarowski: Thank you. So, we're struggling with the efficacy or the effectiveness piece and a missed endpoint or a missed post-hoc analysis doesn't necessarily mean that the safety or effectiveness is lacking. I mean, if I look at the Breakthrough definition, Breakthrough definition, Breakthrough Devices look for a possible or probable benefit. I'm wondering if we should be talking about safety and risk mitigation in this particular case, rather than struggle with the analysis question. I think we've come to the conclusion, certainly a consensus, that the safety component is excellent. V-Safe is safe-- V-Wave is safe. If we look at risk mitigation going forward, especially for a population that's at the end of the road for additional therapeutic intervention, if we look at risk mitigation, that can be provided through specified label, limited label as proposed by the sponsor, by post-approval controls, by comprehensive training on the device, by the registry, by post-approval studies with timely enrollment and continual reporting and communication with the FDA. So, I think all the elements of risk mitigation could be in place in addition to the established safety of V-Wave such that we could consider and potentially recommend with modification the approval of the product. So, that's my point, it's should we get away from the difficult discussions of the analysis, which don't necessarily make or break or define a product, and speak to in terms of safety and risk mitigation. Thank you.

01:06:43 Dr. Lange: And we're going to get to that in number four. We're going to talk about the benefit-risk profile. So, we'll get to that, your point was well taken. Last two comments, and then I'm going to close it. Dr. Zuckerman and then Dr. Gomes.

01:06:58 Dr. Bram Zuckerman: So, let me clarify the Breakthrough Device designation, because this has been touched on by several speakers. Even though this device and deservedly so has a Breakthrough Device designation, the standard for approval is a reasonable assurance of safety and effectiveness. And in clinical terms, that means a reasonable benefit-risk profile. Now, per the guidance, as Dr. Cetnarowski was, I think, just alluding to, if there is increased uncertainty for a variety of reasons, potentially the Agency has more flexibility in looking at a pre/postmarket balance. But it is essential that the Advisory Panel understand that there still has to be a reasonable assurance of safety and effectiveness for FDA to move forward with an approval decision. And that is pretty nicely laid out in the guidance.

01:08:20 Dr. Lange: Thank you. Dr. Gomes?

01:08:25 Dr. Gomes: The statistical analysis has really been very sophisticated. However, from my perspective, it seems that the major problem is that the study was not appropriately powered in the first place to do the post-hoc analysis. Thank you.

01:08:46 Dr. Lange: Yeah, thank you. So, Bram, what the FDA is hearing is there is no certainty-- Nobody on the Panel has expressed certainty in the results. Certainty in the benefit. And there's been, obviously for the reasons that I've mentioned, a lot of uncertainty. I'm going to take a-- I'm going to in one minute talk about the pathophysiology for a second, the explanation which is wrong. In other words, there's now a Qp/Qs of 1.2, so there's a one liter left to right shunt. And in the HFrEF patients, there's no increase at all in the RA and RV size. There should be, it has nothing to do with compliance. You have a liter of blood going through the right side, RA, RV, and LA, and they should be larger, and they're not. They are in the

HFpEF group and they should be. And by the way, they wouldn't be if the RV was less compliant. So, it has nothing to do with compliance at all. I have a lot of concern about the EF measurements and the echo measurements and the accuracy of the measurements. So, there's no reverse LV remodeling. The LV shrunk down because you're shunting blood left to right. It didn't remodel. The stroke volume's not any different. The cardiac output's not any different. The EF is not any different. It's just a smaller volume. And so, that's not LV remodeling, that's just unloading. So I don't think the pathophysiology lines up at all. So, I've spoken as an interventionist, so I'll close with that. All right. Andy, does the FDA have any questions at all about did we fully provide adequate opinions on this?

01:10:29 Dr. Bram Zuckerman: Okay, this question is very important. So, does-- From your summary, Dr. Lang, do your comments pertain specifically to Question 3a, Question 3b, or both of them?

01:10:52 Dr. Lange: Both 3a and 3b. And as the group addressed the certainty, and I just-- As somebody said, you see an effect and you try to find a mechanism, Milton Packer said that best. We can always find a mechanism for some people who want to believe it. Well, unfortunately, the mechanism for this doesn't even make sense hemodynamically, and it's not supported by the echo findings. So--

01:11:21 Dr. Bram Zuckerman: And are there any Panel members who would like to voice a disagreement with Dr. Lange's summary of Question 3? I don't see any, Dr. Lange, so thank you for a very good summary.

01:11:45 Dr. Lange: Well, thank you. Let's move to Question 4.

01:11:49 Mr. Mondine: Question 4. Given the totality of the evidence presented regarding the safety and effectiveness of the device, please comment on the benefit-risk profile.

01:12:02 Dr. Lange: Dr. Shanker?

01:12:02 Dr. Shanker: I mean, I think a lot of this has already been stated. There isn't really as much concern about the safety, although except to look into the thromboembolic sequelae that are being observed at two years. In terms of effectiveness, I mean, we've gone through a lot of statistical acrobatics today, and I've actually had to require a little meclizine because of the dizziness. But I do think that we need more longitudinal data. As you kind of alluded to, the physiology doesn't make sense. We need more hemodynamic, echocardiographic data, clinical data at 1, 2, 4, or 5 years. Because the question is, and I stated this before incorrectly, are we robbing Peter to pay Paul? I mean, we're essentially redistributing the pressure to the right side. And at what point does the right side give out and do you start seeing increases in PVR, etcetera and having a paradoxical impact?

01:12:59 Dr. Lange: Thank you, Dr. Shanker. Dr. Vidovich?

01:13:04 Dr. Vidovich: This is Mladen Vidovich. I just wanted to say-- Maybe that's a continuation to question number three and go into-- I think there was a lot of opportunities in this trial to do some hemodynamic investigation and/or echo investigation, which wasn't done, which would've helped us better understand this conundrum we are in with this HFrEF. And I think that's what you mentioned before, it's about the physiology and unloading. I think we could have learned a lot more and could have been in a better situation right now. Again, we don't have it, but again, it could have also helped us understand the benefit of this device, which I don't fully understand.

01:13:42 Dr. Lange: Okay. Dr. Page?

01:13:45 Dr. Page: Yeah. This issue of benefit versus risk I think is something we need to just dwell on for one moment. The risk is low, the risk is really low, almost unbelievably low, but I do believe it. So, too often these days, especially in desperation, people are going to something that they believe might help or feel it ought to be available to them just in case it could help because the risk is relatively

low or they're in a desperate situation. And as I said before, I consider this responsibility to be a great one for all of us here as we're considering this. But there's a cost to providing false hope. There's a cost to displacing other therapies and other efforts to find something that truly works. If this works, there will be a signal if it's studied in a proper randomized way in the right population. But otherwise, the risk is low, but the benefit is unproven.

01:14:49 Dr. Lange: Thank you. Dr. Krucoff?

01:14:52 Dr. Krucoff: Yeah, I'm going to resonate with risk other than-- I'm not going to say the risk is low five times because to me there is no question. This is an implantable device. It requires an invasive procedure to do it. So, from my point of view, that means if the control is essentially noninvasive, best medical option management, the device that's innovative has got to have certainty about being better. It's low-risk for an invasive device, but the control is not an invasive device. The control is noninvasive management. And I think the impetus in that sense, from my point of view, the benefit-risk that an invasive procedure implanted device has got to have a certainty around benefit. And that's my two cents.

01:15:53 Dr. Lange: Thank you, Mitch. Dr. Yancy?

01:15:59 Dr. Yancy: I'll reframe the discussion about benefit-risk into one about equipoise. I think we have to respect the work done to get this clinical database to where we see it. We have to respect the necessity to explore new interventions, particularly for the varying phenotypes of heart failure. I don't want to leave this discussion with the condemnation of this technology, but rather say that we remain in equipoise. We know that there's minimal risk. We're still trying the right patient population, but I think it's important that we maintain that equipoise and understand the necessity to continue to think about this and not taint the future discussions because we're concerned that there's something here that's already been proven. I think this is version 1.0 of this kind of technology, and I do not want to dissuade innovation and

continued study. So, I would rather reframe benefit-risk to say, "I remain with equipoise."

01:16:56 Dr. Lange: Thank you, Dr. Yancy. Dr. Alexander?

01:17:00 Dr. Alexander: Yes. Along those lines, perhaps the Panel can qualify a little bit what they interpret risk of use of this device or marketing this device. I understand that risk has been interpreted now as the implantation risk, 30 days MACNE and so forth. I'm interested in what I think I heard echo before was that there's uncertainty about long-term risk. There's uncertainty about patient selection using ejection fraction as the biomarker given that those groups are heterogeneous. So, I would like the group to maybe expound on if they're only speaking to implantation risk or if they're speaking to overall risk to having this device on market.

01:17:51 Dr. Lange: Okay. And we will follow that up. Dr. Yuh?

01:17:54 Dr. Yuh: Even in spite of the fact that the procedural risk is low, it's still a foreign body, it's still an object that's planted in the heart permanently, in a relatively low flow, turbulent environment. And so the risk of endocarditis, for example, on a right-sided device with potential for transient bacterial seeding, I think is always going to be there with this device. And so that's just one example of an unforeseen risk, but that's in theory present with this device or any device, quite frankly, that's meant to stay in the heart.

01:18:32 Dr. Lange: Thank you, Dr. Yuh. Dr. Yeh?

01:18:35 Dr. Yeh: Bobby Yeh here. Yeah, I agree with that statement, and I think there's uncertainty about the long-term risk. I think that there's enough width of those confidence intervals around the thromboembolic risk, which is the one I think that we would most be concerned about. That one can't definitively rule out or rule in a safety concern there. So, I have some uncertainty. I agree with the short-term risk

being very low, but also the benefit being uncertain and yeah, that's the-- Well, I'll stop there. Go on.

01:19:07 Dr. Lange: Thank you, Bobby. Ms. Dunn? I'm sorry, you're on mute, Ms. Dunn.

01:19:21 Ms. Dunn: There we go. That's much better. I thought I should weigh in on this. This kind of reminds me, and it may not to all of you, of the Amplatzer device, which I am the proud owner of. It is positioned in my septum. I had a cardiac tear, unfortunately, and lead extraction from getting staph infection in my heart during a device switch out. So, for 10 weeks I had a gaping one inch tear in my septum. And if it wasn't for the Amplatzer, which I was an expert witness for the FDA several years after, so I knew that there were some issues with that device, I probably wouldn't be here today. And I'm lucky I made the 10 weeks before I could get it closed and get a device put back in. So, there are risks. The risks were explained to me. Putting the Amplatzer in, there was a lot of tissue that was hanging on. It wasn't a God-given PFO, it was a tear. And thank goodness I had a very good team and they were able to capture all that tissue and close that PFO that I had.

01:20:35 So yeah, there is risk, but from what I'm absorbing here today is that we have a lot of critically ill patients and there is no alternative for them. And this may be something that could extend their life. And my quality of life has been fabulous with all the procedures and things that I've gone through because of the technology. So, I agree. I really am hesitant to halt technology, but we do need to make sure it's safe for patients and that's where I rely on the rest of the Panel. I can only speak from experience that I'm a happy owner of an Amplatzer device, so thank you.

01:21:16 Dr. Lange: Terrific. We've got about 25 minutes left. Last two comments. Dr. Tchantchaleishvili and then Dr. O'Connor,

01:21:28 Dr. Tchantchaleishvili: If a patient who has this shunt ends up going down the path of the LVAD placement, then it would've to be closed first, or if it has to be

closed during the LVAD implantation, then a surgeon is forced to do a full sternotomy and potentially a longer surgery as opposed to minimally invasive thoracotomy procedure. So, that's another potential risk to keep in mind.

01:21:51 Dr. Lange: Thank you. Thank you. Dr. O'Connor, last comment, last word on this.

01:21:56 Dr. O'Connor: Yeah, I would just reiterate what everyone else has said, that there is uncertainty both in the risk and the benefit because we're being asked to comment on data that is of a sample size that is of 200, and current therapies that are being developed for HFrEF patients are requiring trials with robust endpoints and sample size that are in the thousands, 3,000 to 5,000. So, when you take a nearly tenfold reduction in the sample size, the uncertainty in the confidence intervals around risk and benefit are going to be larger. So, there is that uncertainty.

01:22:37 Dr. Lange: Thank you. Thank you, Dr. O'Connor. To summarize the comments that have been made. The benefits are quite uncertain. The implantation risks are considered to be low, but the long-term safety or long-term risks are still currently unknown. And there are concerns about TIAs, stroke, arrhythmias, endocarditis, other devices LVADs, electrophysiology studies, durability, patency, things of that nature as well. And as Dr. O'Connor mentioned, this is a small sample size of patients. We're trying to draw big conclusions from them. Dr. Zuckerman, does this address the question?

01:23:19 Dr. Bram Zuckerman: Completely. Thank you.

01:23:21 Dr. Lange: Okay, let's move to Question number five.

01:23:25 Mr. Mondine: Question 5. The sponsor has proposed the following indication for use statement: The Ventura shunt is indicated for NYHA Class III heart failure patients who remain symptomatic despite guideline-directed medical therapy, have an LVEF of less than or equal to 40%, and who are judged by a Heart Team to be appropriate for shunt therapy, to reduce the risk of hospitalization for heart failure.

A) Please discuss whether the available clinical data support the proposed indication for use. And B) The shunt proposed indications for use is limited to patients with LVEF less than equal to 40%. Please discuss the clinical implications of using LVEF as a patient selecting criterion considering the variability and measurement error in LVEF assessments, the potential for LVEF to change over time with therapy or disease progression, and the challenges this presents for clinical decision making for individual patients.

01:24:18 Dr. Lange: Maybe I'll take a couple of comments and then I'll summarize. Chris, do you want to comment on this?

01:24:31 Dr. O'Connor: Not right now.

01:24:32 Dr. Lange: Okay. Let me address the available clinical data. These are the patients that were included in the study with certain caveats that weren't mentioned. One is they couldn't have severe MR, they couldn't have an elevated PVR, they couldn't have an LVEDD that was greater than eight centimeters. So, there are additional exclusion criteria. Those patients were not included in this trial. And so, I'd say the available data don't support this in its entirety without those caveats. These were also patients that all had hospitalization within the previous year. Dr. Hauptman?

01:25:11 Dr. Hauptman: Paul Hauptman, for the record. And I agree with you completely, Rick. I'd also be just a little bit concerned on B, what at least I saw clinically for primary prevention with ICDs and CRT was EF creep and there were a fair number of patients who I would have said were EFs in the mid-forties who were 39%. And so that is a concern there in clinical practice.

01:25:40 Dr. Lange: And that goes to part B that you're mentioning Paul. Not only that, but just the variability of reading these. And then we still don't know what to do if the EF goes up. Dr. Shanker?

01:25:50 Dr. Shanker: Yeah, I completely agree with Dr. Hauptman. I mean, and I'm sure Dr. Page can attest to this with the CRT studies and CCM, even the sample sizes have been much, much larger to help address that issue.

01:26:12 Dr. Lange: Dr. Krucoff?

01:26:14 Dr. Krucoff: Yeah, I'm just thinking, Rich, given the discussion all through the day, including even from the company, the manufacturer's side, concerns about where you shift from reduced ejection fraction doing good to preserved ejection fraction doing harm, somewhere around this mystical 40% zone, whether this labeling would even address the potential of warning doctors or black boxing, putting the device into HFpEF patients. I don't even know what to recommend, but I think based on the discussion today, if you're going to label the device for less than 40%, there probably should be some kind of warning if there are indeed concerns about what happens if you put this into Class III heart failure patients who are failing medical management but who have ejection fraction of more than 40%.

01:27:18 Dr. Lange: What I've heard so far, I don't see their hands up right now. I'll summarize and other people can add to the summary. One is the patient population that they present does not exclude the patients they excluded, and that should probably be in the indications. And furthermore, there is some concern again about using an absolute EF both with variability of assessment and with certain populations like CRT populations. And then also what do you do, what do you tell the patient when their EF gets normal? Are they now at risk? And so there are some concerns about that and not any data to base that on right now, unfortunately.

01:28:03 Dr. Bram Zuckerman: Right. So, the label would need greater specificity and further work. Thank you.

01:28:13 Dr. Lange: Thank you. Any other comments regarding that before we go to Question number six? Okay, Paul, if you'll take your hand down just so that-- Thanks. Question number six.

01:28:28 Mr. Mondine: Question 6. The sponsor has proposed the following approach to postmarket clinical data collection: continued follow-up of implanted subjects from the RELIEVE-HF study for five years; a single-arm new enrollment post-approval study with a performance goal; and a post-approval registry for all commercial U.S. patients not included in the post-approval study. Please discuss the strengths and limitations of the proposed approach to postmarket data collection. Please also comment on whether any additional study objectives, design features or surveillance are recommended.

01:29:01 Dr. Lange: Clyde, can I call on you? Because I thought you were pretty articulate about how things are evolving and what's changing. Would that postmarket survey proposal satisfy you?

01:29:19 Dr. Yancy: Rick, I'll be honest with you, I'm uncertain.

01:29:22 Dr. Lange: Okay. Dr. Blankenship? Thank you, Clyde.

01:29:27 Dr. Blankenship: It looks to me like the proposed plan would provide evidence of safety because you'd get an assessment of complications, but I don't see how it would provide evidence of effectiveness. So, I guess that's one question perhaps for the sponsors or for the trialists on this call: would this provide any evidence of efficacy?

01:29:48 Dr. Lange: Dr. O'Connor?

01:29:50 Dr. O'Connor: Yeah. One way to augment or improve this would be to have a study that was randomized so that we could get the efficacy. But you could do a two-to-one randomization and with the device receiving the two versus one control, that would give you, again, more safety data of the device long term, but also get you the

adequate control comparator because of really, in my view, a 200-patient randomized trial is too small.

01:30:28 Dr. Lange: Okay. I'm going to make a comment and it's meant to put out there to elicit people that would disagree and if not, we're going to assume everybody does. I don't think the people on this Panel believe that a postmarket study will provide the information they need with regard to long-term safety and efficacy compared to a control group. Mitch?

01:30:58 Dr. Krucoff: Yeah, Rich, I'm going to modestly lean to modify your summary just because I actually do think there are some key safety, long-term etcetera variables that would almost require a postmarket approach. I think, to me, the stumbling block for even talking about a postmarket study is still on the efficacy side and the essential need for randomization probably to get to a more definitive place about who are the right patients and the capacity of this device to make them better. As I remember from the packet, the postmarket proposal was envisioned as a single-arm experience, and that's not specified here, but I think the comments already said for efficacy, I think it's going to require a randomized extension from beyond the uncertainty we're in the middle of now. But I think a lot of other kinds of safety concerns actually, probably, can only be done in the postmark.

01:32:12 Dr. Lange: Go back one slide please, Dr. Mondine. And you're right, it was a single arm. So, what I'm hearing-- Let me modify it. My comment is that this postmarket study will not address efficacy, it will give you some long-term safety data. Okay? Everybody's shaking their heads yes. I see no head shaking this away. Either that or I need to take meclizine as well, Dr. Shanker. Okay, good. All right. Does that give the FDA--? That seems to be the uniform opinion of the Panel members.

01:32:49 Dr. Bram Zuckerman: And that's fine, Dr. Lange. And again, reinforces the idea that in order to get to an approval, there must be a reasonable assurance of

safety and effectiveness such that people are more comfortable with some of the limitations of what can be obtained with postmarket data.

01:33:17 Dr. Lange: Okay, so we are at the point now where we're about to give the sponsor and the FDA--

01:33:24 Dr. Yancy: Rich?

01:33:25 Dr. Lange: Go ahead. Go ahead.

01:33:29 Dr. Yancy: Dr. Yeh's hand is up.

01:33:31 Dr. Lange: I'm sorry, I didn't see you, Rob.

01:33:32 Dr. Yancy: That's okay.

01:33:33 Dr. Yeh: Really just a quick comment. I'm just following up on Dr. O'Connor's comment about randomization in the post-approval setting, and I'm just curious about in such a study, are you envisioning sham control? I think the big-- The thing that I want to think about here to help the sponsor, I think we would say that there is hypothesis-generating data here that are interesting and I think there's some consensus that while they're interesting, they're not confirmatory, and that it's impossible to both generate hypothesis and confirm that hypothesis in the same 200 person dataset. But the limitations of being able to conduct another large sham-controlled randomized trial are also real. So, if there is-- I'm just curious of the group-- And maybe this isn't the right time to talk about that, but I'd just be curious about-- Maybe I'll start with Dr. O'Connor about what he thinks about that as a trial, and is he envisioning a sham if KCCQ is not part of the endpoint because they think it's not a good endpoint for this? Does the use of hard endpoints, does that obviate the need for sham?

01:34:40 Dr. O'Connor I think it might be a good way to go forward because obviously this enrollment rate was about one patient per site per year. As best I can tell, there were a hundred sites and it was conducted over four years, so that's not practical to

completely replicate what they did. So, in the real world, what we're doing is we're putting the device in versus medical therapy without a sham. So, I would probably randomize that way.

01:35:14 Dr. Lange: Thanks. Dr. Page?

01:35:18 Dr. Page: Yeah, I think we need to be clear on what a post-approval study is. It's after approval and I don't know, I'm not aware, Bram, you can inform us whether we randomize people to placebo or sham after a device has been approved. I don't think it would be ethical. If we believe this is approvable, it's going to be approved and all we can do is study those who receive the therapy. But you can correct me if I'm wrong, Bram, about the idea of randomizing people when a device is approved.

01:35:56 Dr. Bram Zuckerman: For all the reasons that you've mentioned, Dr. Page, and many others, it's almost impossible to do randomized trials post-approval that can answer significant effectiveness questions. And again, that's why the FDA system is set up such that prior to approval there needs to be a reasonable assurance of safety and effectiveness.

01:36:30 Dr. Lange: Right. Dr. Hauptman, I'll let you have the last comment here.

01:36:34 Dr. Hauptman: Thanks, Dr. Lange. And I may be jumping the gun a little bit because I know we have the vote coming up. We're going to be asked a question about safety. What we've heard pretty consistently in the comments is that there's the paraprocedural period and people feel, in general, it sounds like reasonably comfortable with safety, but there's uncertainty long-term, or there's some lingering questions about long-term. So, the question is how do we answer a single question about safety?

01:37:02 Dr. Bram Zuckerman: By putting on your clinical hat, Dr. Hauptman, and asking these tough questions. For example, let's take a hypothetical where a device might have a reasonable assurance of safety and effectiveness out to one year, but

because it's a chronic implant, there were always questions about longer-term safety issues. And you need to judge the data based on what has been shown in the clinical trial, what you know about the patient population and the natural history of the disease and put all these things together. This is not an easy question to answer, but you'll have the opportunity to give it your best shot in a few minutes. And I don't mean to be facetious there, but it's a difficult question, as you've said.

01:38:23 AV Support: Dr. Lange, I think you are muted. Just so you know.

Summary of Panel Recommendations

01:38:29 Dr. Lange: I'm sorry, my mouth was moving and nothing's coming out. All right. At this time the Panel will hear comments, summations, clarifications from the sponsor and you'll have up to 10 minutes. Actually, before the sponsor speaks, let me have the FDA. The sponsor should have the last word. So, let me ask the FDA to do that first. My apologies.

01:39:06 Dr. Neubrander: Thank you, Dr. Lang. We really appreciate the Panel's time. This is Rachel Neubrander, sorry. We really appreciate the Panel's time, expertise, and helpful questions and comments today. Your input on this PMA is really critical and will help inform FDA's decision. We acknowledge the significant unmet need in an important patient population and that's why we need rigorous high-quality clinical trial data that clearly demonstrates safety and effectiveness and a favorable benefit-risk profile. This shunt was appropriately designated a Breakthrough Device for which increased uncertainty may be acceptable, but uncertainty up to a point, and this doesn't change FDA's requirements for product approval.

01:39:55 As discussed today, FDA notes numerous limitations to the RELIEVE-HF trial data. While this was a well-designed, well-executed trial, the primary effectiveness endpoint for all randomized patients, the primary analysis population, was not met. In the HFrEF subgroup, there was no observed cardiovascular mortality benefit or health status benefit. That is, shunt subjects did not feel or function better versus

controls after device placement, and the heart failure outcome differences may have been driven by a few control subjects with a high rate of recurrent events. The subgroup analyses were conducted post-hoc and we believe it is not possible to estimate the type I error rate.

01:40:42 Further, the HFrEF subgroup sample size forming the basis for potential approval is only 200 patients for a device which could be expected to be used in a large heart failure patient population. Overall, these limitations contribute to significant uncertainty in the effectiveness of the device in HFrEF patients. We're also concerned about the roll-in HFrEF shunt group subjects who experienced a much higher event rate than the HFrEF shunt group randomized subjects despite sharing common enrollment criteria, assessments, treatments, and follow-up.

01:41:23 Finally, we are greatly concerned about a potential signal of shunt-associated harm in the HFpEF subgroup, which combined with uncertainty and accuracy and variability of LVEF measurements leads to substantial uncertainty in determining the shunts benefit-risk for an individual patient. While we all desire for there to be innovation to help patients who otherwise have no treatment options, we're also mindful that the public's expectation is that devices approved by FDA are both safe and effective and we need a reasonable certainty of that based on the available data. We again thank the Panel for your expertise and your time.

01:42:09 Dr. Lange: Thank you for the comments from the FDA. Let me turn to the sponsor and allow them to make summary comments.

01:42:17 Mr. Gaylord: Good evening. Matt Gaylord. I'm a vice president at J&J. I'm the GM of V-Wave. Dr. Bill Abraham had to catch a flight out, so I will offer the closing statement. So first and foremost, let me just say thank you to all on the call for your time and your attention today and your careful consideration of our data. We understand this is a very dense packet on both sides. It was a very dense presentation on both sides. It is an extremely thorough and dense discussion. So again, thank you

for a full day of your attention, your thoughts and your input. And to the FDA, thank you for your collaboration not only today, but over the course of 2025. It hasn't been easy, but we'll say thank you in advance for your continued collaboration as we find a way to amicably bring this technology, this novel technology, to patients in need that do not have any alternative therapy at the moment. So again, thank you for your consideration.

01:43:11 Dr. Lange: Thank you very much, Matt. Before we proceed to the Panel vote, I'd like to ask our non-voting members if they have any additional comments. So first, Ms. O'Sullivan-Fortin.

01:43:25 Ms. O'Sullivan-Fortin: No, thank you for letting me join you. It's been enlightening and confusing, but I do appreciate the sponsor. I do appreciate their dedication to finding a solution for people who have no solution. I think sometimes-- I don't want to forget the voices that weighed in during Public Hearing, Salina and Rhonda, in particular, as patients. I wish I could vote yes. I don't get to vote at all anyway, but I wish that we as a group were ready to move forward. But I am encouraged that there is good work coming down the road and I have absolute certainty that the expertise represented on this Panel has their best interest at heart.

01:44:32 Dr. Lange: Thank you, Kathleen, for being our Consumer Representative. Thanks for those comments. Dr. Cetnarowski?

01:44:39 Dr. Cetnarowski: Thanks, Dr. Lange. I think I'm complete. It was great discussion, great presentations, great discussion. I certainly hope that the sponsor can work with the FDA in finding a path forward that, as some alluded to, won't take five years and kind of improbable clinical research paths because this is a patient population with limited to no additional treatment options. And so I'm hopeful that they can find a path with the FDA in there for their collaboration. But no other comments. Thanks, Dr. Lange.

01:45:14 Dr. Lange: Wes, thanks for being our Industry Rep on this. I appreciate that and your comments as well. And finally, Ms. Dunn?

01:45:21 Ms. Dunn: Yes, thank you. My initial-- When I started reading the material, I was a little surprised at how small the study actually was for something so serious and invasive. So, I turn my good hopes over to the team here and thank you for letting me serve and we'll keep our fingers crossed that soon we'll have some good news out there for patients down the pipe. So, thank you very much.

01:45:50 Dr. Lange: Deborah, thanks for being our Patient Rep on this particular Panel.

01:45:52 Ms. Dunn: Thank you.

Vote

01:45:54 Dr. Lange: Great. We're now ready to vote on the Panel's recommendations-- On the recommendation to the FDA. The Panel will vote on three questions relating to the safety, effectiveness and the benefit-risk profile of the device. Ms. Kendra Brooks will now read two definitions to assist in the voting process.

01:46:12 Ms. Brooks: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket applications, PMAs, that are filed with the Agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

01:46:56 The definitions of safety and effectiveness are as follows. Safety as defined in 21 CFR subsection 860.7(d) (1): there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when

accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

01:47:39 Effectiveness as defined in 21 CFR subsection 860.7 (e) (1): there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

01:48:17 Panel members, we will now begin the voting process. I will read each of the three Voting Questions. Voting members utilize the link provided to please vote for each question. Once I read all three questions, we will tally the votes and read them into the record. Please vote "Yes, No, or Abstain" on each of the following questions.

01:48:46 Voting Question 1. Is there reasonable assurance that the V-Wave Ventura Interatrial Shunt System is safe for use in patients who meet the criteria specified in the proposed indication?

01:49:02 Voting Question 2. Is there reasonable assurance that the V-Wave Ventura Interatrial Shunt System is effective for use in the patients who meet the criteria specified in the proposed indication?

01:49:19 Voting Question 3. Do the benefits of the V-Wave Ventura Interatrial Shunt System outweigh the risk for use in the patients who meet the criteria specified in the proposed indication?

01:49:43 Dr. Lange: Thank you, Ms. Brooks. At this time, please give us a moment as we tally and verify the official votes. We'll now take a 5 to 10 minute break, and so stay tuned.

01:55:48 Welcome, everyone. The votes have been received and Ms. Brooks will now read the votes into record.

01:55:54 Ms. Brookes: Thank you, Dr. Lange. The votes have been captured and I will now read the votes into record. On Question 1, the Panel voted nine "Yes", six "No", zero "Abstain" that the data shows reasonable assurance that the V-Wave Ventura Interatrial Shunt System is safe for use in patients who meet the criteria specified in the proposed indication. On Question 2, the Panel voted zero "Yes", 15 "No", zero "Abstain" that there is a reasonable assurance that the V-Wave Ventura Interatrial Shunt System is effective for use in patients who meet the criteria specified in the proposed indication. On Question 3, the Panel voted zero "Yes", 15 "No", zero "Abstain" that the benefits of the V-Wave Ventura Interatrial Shunt System outweigh the risk for use in the patients who meet the criteria specified in the proposed indication. The three Voting Questions are now complete. I will now turn it back over to Dr. Yange-- Lange, sorry. Thank you.

01:57:12 Dr. Lange: Thank you, Ms. Yoocks [sic]. I will ask the Panel members to discuss their votes. If you answered "No" to any question, please state whether changes to labeling, restrictions on use, or other controls, would make a difference in your answer. Please state your name and how you voted for each question for the record. And I will start with Dr. Page.

01:57:30 Dr. Page: Thank you, Dr. Lange, and appreciate your leadership through this. Despite my-- I voted "No," "No," "No." Despite my emphasizing relative safety of this device prior to the question being asked of us, the definition of safety that the FDA gave us was, "Is it safe relative to probable benefit?" And there is-- At this point, I can't say that there's probable benefit. If this had reached its positive endpoint, I would've said that this device met its safety endpoint for demonstrating adequate risk for a device that showed benefit, but in the setting of lack of benefit, I also said it was not, it did not meet the safety definition that the FDA provided us this evening. Thank you.

01:58:20 Dr. Lange: Thank you, Dr. Page. Dr. Yancy?

01:58:26 Dr. Yancy: Dr. Page, thank you. Clyde Yancy here. My votes were "Yes," "No," and "No." Everything was driven by the absence of overwhelming evidence of benefit. And given the number of other opportunities to change the natural history of heart failure and all those various phenotypes, I think the evidence bar is high for everything we've done in the last decade or two to change outcomes for patients with heart failure. It's always been driven by very high-quality indisputable evidence. That's the standard that we should continue. I am one that is still very clinically active, and I understand the necessity to instill hope in our patients, but it can't be hope on a feigned basis. It has to be legitimate hope. This is not an end of this discovery, this is still version early. We need to continue to pursue this possibility. There may be benefit. And if we continue to work diligently like we have in heart failure for decades, we may be able to answer this question with more precision. So my answer is "No," but it preferably is "Just not yet."

01:59:29 Dr. Lange: Thank you, Dr. Yancy. Dr. Yuh?

01:59:33 Dr. Yuh: Thank you, Dr. Lange. I voted "Yes, "No," "No." At the end of the day, the primary effectiveness submit endpoint was not met. This procedure alters, as I mentioned before, physiology in a tenuous population. And so, I think more assurance of whether it is indeed effective, and if so, the basis for its effectiveness is really needed. Surgery is filled with examples of procedures embraced by desperate patients and physicians. Some forms of bariatric surgery, lung volume reduction surgery, even silicone injections initially met with enthusiasm, have proven not to be durable in many cases. And I fear that this may fall in that category, but I think that remains to be seen.

02:00:17 Dr. Yeh: Thank you, Dr. Yuh. Dr. Yeh?

02:00:20 Dr. Yeh: Thank you, Dr. Lange. I voted "No," "No," and "No." I voted "No" on safety, not because-- I think they're safe on the procedural things, but I think the aspects-- But I think the long-term safety is still unproven, and in light of the lack of

efficacy data has to be considered. I do think that overall, the device has some promising data, and I do hope that the sponsor continues to pursue it now that they've learned more about the design they might use as well as the population that might benefit.

02:00:49 Dr. Lange: Thank you. Bobby. Dr. O'Connor?

02:00:54 Dr. O'Connor: Chris O'Connor. I voted "Yes," "No," "No." I want to first commend the sponsors and the investigators for outstanding clinical trial conduct and analysis to understand. This to me looks like a very robust Phase 2B set of data that sets up perfectly continued development. I voted "No" because of the uncertainty around efficacy, which would be expected when you have a sample size of 200 in a relatively modest number of clinical events, mostly driven by non-fatal clinical events. And you're contrasting that to a very large population of patients who have HFrEF. And the clinical trials that are conducted today are studying a large number of patients to really narrow those confidence intervals around safety and efficacy point estimates. So, as my previous colleagues have said, I'm highly encouraged by the depth of analysis that this group has done, and they should be proud, and I hope that they will go forward with more studies. Thank you.

02:02:10 Dr. Lange: Thank you, Chris. Dr. Kumbhani?

02:02:15 Dr. Kumbhani: Yeah, thank you. So, I voted "No," "No," and "No." So, as was outlined, I don't have concerns about the procedural safety, but I think this is a device where, at least based on my review, the lines blur a little bit between efficacy and safety from a long-term standpoint, having a shunt in this population. Again, the efficacy was discussed, and I'm also grateful to the sponsor for doing this, and I'm glad that we were unanimous in our decision about not believing the efficacy, because then it also means that the harm signal on the HFpEF side is probably also hypothesis-generating, because that may have had profound impact, I think, on ongoing studies in that [Indiscernible 02:03:00].

02:03:02 Dr. Lange: Thank you, Dharam. Dr. Tchantcha-- Tchantchaleishvili? Pardon me.

02:03:08 Dr. Tchantchaleishvili: Thank you, Dr. Lange. I voted "Yes," "No," "No." And I said "No" regarding its efficacy because of essentially unclear certainty of the primary effectiveness, but it was a great study.

02:03:25 Dr. Lange: Thank you, Vakhtang. Dr. Vidovich?

02:03:29 Dr. Vidovich: So, I voted "No," "No," "No." The first "No" I struggled most about the safety, but I think what really threw me to "No" is this cutoff of 40% and difficulty of assessing ejection fraction and a certain inaccuracy, which can be present with measurements, presence of valvular disease or other varieties. Again, the trial opens a lot of possibilities, and I mentioned this before, I think we can learn a lot. I think the safety signal, why did this happen? What were the PA pressures? What was the shunt flow? I think there's a lot of opportunities to learn from this. A liter a minute is a lot. Could a different shunt flow provide different answers? What is the long-term--? I mean, I hope there's a follow-up study, and actually that leads to approval of this device in an appropriate indication. But as we know with this sample size and with sub-analysis being exploratory, I couldn't vote "Yes" on any of those.

02:04:41 Dr. Lange: Thank you very much, Mladen. Dr. Wittes?

02:04:54 Dr. Wittes: So, I voted "Yes," "No," "No." The "Yes" was a funny yes, because I pretended that in spite of the definition that if I considered the device effective, I considered it safe. So that was the "Yes." The two "No" had to do with what everybody else is saying, that there was too much uncertainty in the results. I was very troubled by the two HFrEF and HFpEF being so different in the data and therefore uncertain about what the results were. But I was very impressed with the quality of the study, the follow up and everything, and I wished that the data had been different.

02:05:42 Dr. Lange: Thank you, Janet. Dr. Leifer?

02:05:48 Dr. Leifer: Thank you. Yeah, I want to thank the sponsors for doing a very careful study, and I want to thank the Panel for the wonderful discussion today. I voted "Yes," "No," "No." As a statistician, I know to stay in my lane, and I don't want to overthink the clinical aspects of what I heard. So, I really go by the rules that the sponsor and the FDA agreed upon, the statistical rules for determining safety and efficacy. And according to the rules that were set up and prespecified, I felt that they met the safety criterion, but the efficacy criterion was unfortunately not met.

02:06:31 Dr. Lange: Thank you, Dr. Leifer. Dr. Gomes? You must have left after the vote.

02:06:48 Ms. Brooks: Dr. Gomes, you're on mute.

02:06:50 Dr. Krucoff: She's on mute.

02:06:54 Dr. Gomes: I'm sorry. I voted "No," "No," "No." And I'm very grateful to the sponsor because it addresses an important problem. And conducting a sham study is really to be lauded. I initially was acceptant of the safety aspect for the initial placement of the device, but the long-term results are uncertain, and so I voted "No" on that. And with regard to efficacy, I think that the sample size unfortunately was just too small to obtain the information on efficacy that is needed.

02:07:37 Dr. Lange: Thank you, Antoinette. Dr. Shanker?

02:07:40 Dr. Shanker: First, I want to thank you for your leadership on this Panel today. Thank the sponsors. They did a great job with this study, regardless of the results. And the Panel learned a lot about statistics today for sure. On the safety side-- So, I voted "No," "No," No." On the safety side, I was encouraged by the 30-day MACNE. However, the two-year safety data suggested a signal that for me, in my opinion, it wasn't sufficient to really provide a reasonable assurance in terms of safety. From an effectiveness perspective, the trial failed to meet the primary effective endpoint, and the post-hoc analysis was largely limited to a population of

206 patients, which again, for me, was not sufficient to provide reasonable assurance for effectiveness.

02:08:28 Dr. Lange: Thank you, Amit. Dr Hauptman?

02:08:28 Dr. Hauptman: Thank you, Dr. Lang. I voted "Yes," "No," "No." I think like some others, I struggled with the safety more than efficacy. I do think periprocedurally, this appears to be a safe procedure. I do have concerns about the long-term effects. With regard to the efficacy, it really comes down to the fact that it just was not prepared to abandon the primary endpoint because otherwise, why have a primary endpoint in a study if you then drill down and find signals elsewhere? So, you live by the primary endpoint, you die by it too. I also wasn't-- I think the bashing of the KCCQ is something that, and maybe that's a strong comment, but there is value to it because it really reflects what's important to patients, and we have to keep that in mind. So, like everyone else, I certainly would encourage the sponsor to stay with this, the technology it has promised.

02:09:31 Dr. Lange: Thank you, Paul. Dr. Blankenship?

02:09:34 Dr. Blankenship: I voted "Yes," "No," "No." Regarding safety, I think that the short-term safety is pretty well proven. I think long-term safety is not proven. However, that would show up in a post-market analysis, so I think that saying "Yes" to safety now it hedges that if it's not that we would catch it in post-market analysis. As for the efficacy, I voted "No" for the reasons that have been stated. Small data set. The sponsors are asking us to look at a data set that is hypothesis-generating and believe that the data is so convincing that we can be certain that it shows efficacy. And we pointed out all afternoon about the uncertainty of the analysis. So, that was just too much to overcome.

02:10:30 I'm sensitive to the passionate statements that were made by some of our patient advocates. And so, in the back of my mind I'm thinking, "Well, what if we're

wrong?" In fact, "Are we really denying this dramatically lifesaving life altering therapy to people who otherwise might get it? And what if we're wrong?" But it looks to me like this, best case scenario, this is a therapy that would be incrementally beneficial, superimposed on a field where we're already making pretty constant improvements in therapy. So, the penalty for making the wrong decision here, I think, doesn't outweigh the fact that you just don't know if it's efficacious. And providing a procedure that doesn't work to large volumes of people would not be ethical.

02:11:20 Dr. Lange: Thank you. Dr. Krucoff? Bring us home.

02:11:25 Dr. Krucoff: Thanks so much, Rich. Well, I will repeat with gusto thank you to you, Richard, for sailing this ship through what at times were pretty meclizine kind of waters, but great job done. I think it was a great Panel to the FDA team as always, even in the current crazy environment we live in, you guys managed to just do a stellar job. And I appreciate that so much from everybody. And as many have mentioned to the manufacturers and particularly the leadership, the last time I was on a panel that Bill Abraham presented to was for the Medtronic very first resynchronization therapy device, and it changed the world and rocked the world. And I would not be surprised if the long version of where we are today does exactly that, and I hope they do.

02:12:20 I voted "Yes," "No," "No." I voted "Yes" on safety because even though it's an intervention, my answer of "Yes" was "If this device could be effective, then the safety of putting it in is pretty reasonable." And the at least short-term effects for a patient population who not only do we all know so well as a brutally uncomfortable suffering kind for human beings as patients, but I've also been through this, like some of the patient testimonials, with my own family. So, getting further with devices. I respect medical pills for the miracles they can be, but sometimes when you just fix it with a device, you can see what happens within a 400-patient cohort and

get the device out there and help people. So, I hope that will be the course but today is not the day. And without effectiveness to take even very desperate suffering people and do an invasive intervention and install a permanently implantable device that has no definable benefit is not the ethical way to answer those needs.

02:13:52 We really need to understand who gets the benefit and where the technical side can be delivered in a clinically meaningful way. And I think as pretty much everybody has said, the primary endpoint of this trial, from my point of view as a patient-oriented, not an event-oriented endpoint, and I think that's the right way to do it. I think it was a beautifully designed and exquisitely conducted trial, and I think it was negative. And I think without efficacy, an invasively-implanted procedure compared to what else they face without having an invasive procedure leaves it short of a benefit-risk calculus that makes sense for approval.

Adjournment

02:14:41 Dr. Lange: Thank you to all the Panel members for their participation today. It's clear to me that everybody here has taken this seriously. You've been through the data in great detail, and everybody came here with an open mind to provide the FDA their perspective based upon their presentations. It makes my job much easier. So, thank you all very much, for the Panel members and for the FDA, that's been operating in times it's been very difficult. I want to extend my thanks to you all for the presentation, for the work that you do to try to improve the health of our nation. To the sponsors that provided outstanding presentations, great speakers did a very good study. And as Mitch said, unfortunately it was negative at this particular point, but as Dr. Yancy said, there's equipoise. We'd like to see this continue because we believe it may have a role. But I want to thank everybody and especially the sponsors for answering all of our questions in such a short period, and they did an outstanding job. It's clear that the FDA and J&J are working together on this. With that, let me turn it over to you, Bram, for any final comments you have.

02:15:50 Dr. Bram Zuckerman: My final comment is just to give my sincere thank you to Dr. Lange, who did a fantastic job leading an extremely important Panel meeting. Thank you, Rick. And I want to also thank the other Panel members who, as Dr. Lange indicated, came very prepared to this meeting and gave the FDA an extraordinary amount of useful information today. Thank you all

02:16:24 Dr. Lange: With that, the meeting of the Circulatory System Devices Panel is now adjourned. You're free to go to the bar. Thank you, guys.

[Participants exchange thanks and farewells.]