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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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CIRCULATORY SYSTEM DEVICES PANEL OF THE MEDICAL DEVICES ADVISORY
COMMITTEE MEETING ANNOUNCEMENT

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FEBRUARY 13, 2024

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Via Web Conference

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Consumer Representative

Rachel Brummert, MS	President of Courage to Continue, LLC Communications Lead, American Society of Pharmacovigilance & Investigator of Charlotte-Mecklenburg Community Relations	Charlotte, NC
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Patient Representative

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Bram Zuckerman, MD	Director Office of Cardiovascular Devices, Office CDRH	Silver Spring, MD
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1 Call to Order

2 Dr. Lange: Good morning. I would like to call this meeting of the circulatory system devices
3 panel of the medical devices advisory committee on February 13th, 2024 to order. It is now 9
4 a.m. Eastern Standard Time. I am Dr. Richard Lange, the chairperson of this panel. I am
5 president of the Texas Tech University Health Sciences System, excuse me, Health Science
6 Center in El Paso, and Dean of the Paul L. Foster School of Medicine. I was an interventional
7 cardiologist for 25 years, and now I'm a general cardiologist.

8 I know for the record that the voting members present constitute a quorum as required by
9 21 CFR part 14. I would also like to add that the panel members participating in today's meeting
10 have received training in FDA device law and regulations.

11 For today's agenda, the committee will discuss, make recommendations, and vote on
12 information regarding the premarket approval application, that is the PMA, for the TriClip G4
13 system by Abbott Medical. The proposed indication for use statement is as follows: The TriClip
14 G4 system is indicated for the improvement of health status in patients with symptomatic severe
15 tricuspid regurgitation, despite being treated optimally with medical therapy, who are at
16 intermediate or greater risk for surgery, and in whom tricuspid valve edge to edge repair is
17 appropriate, as determined by a heart team.

18 Panel Introductions

19 Before we begin the panel, I would like to ask our distinguished committee members and
20 FDA representatives attending virtually to introduce themselves. Committee members, please
21 turn on your video monitors if you've not done so already and unmute your phone before you
22 speak. I will call your name and I'd ask you to please state your name, your area of expertise,
23 your position, and affiliation. We'll start with Rachel Brummert.

1 Ms. Brummert: My name is Rachel Brummert. I have expertise in medical devices and
2 pharmaceutical safety. I am an investigator with the Charlotte-Mecklenberg community relations,
3 and I will be serving as the consumer representative today.

4 Dr. Lange: Thank you, Rachel. Jennifer Schwartzott.

5 Ms. Schwarzott: Hi, I'm Jennifer Schwartzott and I'm your patient representative.

6 Dr. Lange: Great. Thank you, Jennifer. Amy Cizik.

7 Dr. Cizik: Hello, I'm Amy Cizik. I'm a research assistant professor at the University of Utah. I'm
8 serving today as an expert in patient reported outcome measurement.

9 Dr. Lange: Thank you. I should have said doctor. So, thank you very much, Amy. Dr. Scott
10 Evans.

11 Dr. Evans: Good morning. Scott Evans. I'm professor and director of the biostatistics center and
12 chair of the Department of biostatistics and bioinformatics at the Milken Institute School of
13 Public Health of George Washington University. My expertise is in clinical trials and
14 biostatistics.

15 Dr. Lange: Thank you Scott for joining us. I've got Dr. David Friedman.

16 Dr. Friedman: Good morning, everyone. I'm a physician and cardiologist practicing clinical
17 medicine in the tristate area in the New York, Long Island region. I'm a heart failure specialist,
18 and I work in Optum, a UnitedHealth Group affiliated facilities.

19 Dr. Lange: Great. Thank you, David. Dr. Paul Hauptman.

20 Dr. Hauptman: Good morning. I'm a heart failure cardiologist and Dean at the University of
21 Nevada, Reno School of Medicine.

22 Dr. Lange: Thank you, Paul. Dr. Bradley Bart.

1 Dr. Bart: Good morning. I'm a cardiologist and professor of medicine at the University of
2 Minnesota. I'm the co-director of the heart failure program at the Minneapolis VA Medical
3 Center.

4 Dr. Lange: Thank you, Brad. Dr. David Yuh

5 Dr. Yuh: Good morning, everybody. My name is David Yuh. I am the chair of surgery at
6 Stanford Hospital in Connecticut. I'm a practicing cardiac surgeon. Also have an academic
7 appointment, a professor of surgery at Columbia.

8 Dr. Lange: Thanks David. Dr. Marc Katz.

9 Dr. Katz: I'm Marc Katz. I'm a cardiac surgeon and I'm a professor and chief of cardiothoracic
10 surgery at the Medical University of South Carolina in Charleston.

11 Dr. Lange: Thank you Mark. Dr. Craig Selzman.

12 Dr. Selzman: Wow. Three surgeons in a row. This is Craig Selzman. I'm chief of the division of
13 cardiothoracic surgery at the University of Utah.

14 Dr. Lange: Greg, thank you for joining us. Dr. Ralph Brindis.

15 Dr. Brindis: Hi, I'm Ralph Brindis. I'm a cardiologist by training clinical professor of medicine
16 at UCSF. Area of expertise is in outcomes, research and registries.

17 Dr. Lange: Thank you, Ralph. Dr. Mitch Krucoff.

18 Dr. Krucoff: I'm Mitch Krucoff. I'm a professor of medicine and cardiology at Duke University.
19 I am the director of the Duke Clinical Research Institute, cardiovascular devices unit. And my
20 area of expertise is in cardiovascular device clinical science.

21 Dr. Lange: Thank you, Mitch. Dr. Amit Shanker.

1 Dr. Shanker: Good morning. My name is Amit Shanker. I'm a practicing electrophysiologist and
2 chair of cardiovascular medicine at Saint Lawrence health system here in sunny upstate New
3 York.

4 Dr. Lange: Thank you, Amit. Dr. John Hirschfeld.

5 Dr. Hirshfeld: So, I'm an emeritus professor of medicine at the University of Pennsylvania. I
6 practiced interventional cardiology at Penn for 40 years. And that's basically my expertise.

7 Dr. Lange: Right. Good to have you aboard John. Thank you. Jim Blankenship. Dr. Jim
8 Blankenship.

9 Dr. Blankenship: Good morning. I'm a practicing interventional cardiologist at the University of
10 New Mexico where I'm director of cardiology.

11 Dr. Lange: Thank you, Jim. Dr. Mladen Vidovich.

12 Dr. Vidovich: Good morning. I'm a practicing interventional cardiologist, professor of medicine
13 of University of Illinois in Chicago. I'm chief of cardiology at the VA and I'm chair of the VA
14 National Cardiology Field Advisory Board.

15 Dr. Lange: Thank you for joining us, Mlad. Elijah Wreh, I see you joined us. And if you'd
16 introduce yourself,

17 Dr. Wreh: Yes. Good morning, everyone. My name is Elijah Wreh, I work for Boston Scientific
18 and I'm here today on the panel for industry representative. Thank you.

19 Dr. Lange: Thank you, Elijah for joining us. And then lastly, Dr. Zuckerman.

20 Dr. Zuckerman: Good morning. My name is Bram Zuckerman. I'm a cardiologist by background
21 and director of the FDA office of cardiovascular devices.

1 Dr. Lange: Thank you. I want to, again, thank all our distinguished panel members for agreeing
2 to spend your day with us today. Dr. Akinola Awajope, the designated federal officer for the
3 circulatory system devices panel, will now read the conflict-of-interest statement.

4 Conflict-of-Interest Statement

5 Dr. Awajope: Good morning. The Food and Drug Administration, FDA, is convening today's
6 meeting of the circulatory system device panel of the Medical Devices Advisory Committee
7 under the authority of the Federal Advisory Committee Act, FACA, of 1972, with the exception
8 of the industrial representative, all members and consultants of the panel are special government
9 employees or regular federal employees from other agencies and are subject to federal conflict of
10 interest laws and regulation.

11 The following information on the status of this panel compliance with the federal ethics
12 and conflict of interest laws covered by, but not limited to, those found at 18 USC section 208
13 are being provided to the participants in today's meeting and to the public. FDA has determined
14 that members and consultants of this panel are in compliance with the federal ethics and
15 compliance of interest laws. Under 18 USC. Section 208. Congress has authorized FDA to grant
16 waivers to special government employees and regular federal employees who have financial
17 conflict when it is determined that agency needs for the particular individual's services outweigh
18 his or her potential financial conflict of interest. Related to the discussion of today's meeting,
19 members and consultants of this panel who are special government employees or regular federal
20 employees have been screened for potential financial conflict of interest of their own as well as
21 those imputed to them, including those of their spouse or minor children, and for the purpose of
22 18 USC Section 208, their employers. These interests may include investments, consulting,

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

3 For today's agenda, the panel will discuss, make recommendation and vote on
4 information regarding the premarket approval application PMA for the TriClip G4 system by
5 Abbott Medical. The proposed indication for use statement is as follows: The TriClip G4 system
6 is indicated for the improvement of health status in patients with systematic severe tricuspid
7 regurgitation, despite being treated optimally with medical therapy, who are at the intermediate
8 or greater risk for surgery and in whom tricuspid valve edge-to-edge repair is appropriate as
9 determined by the heart team. Based on the agendas for today's meeting and all financial interest
10 reported by the panel members and consultants, no conflict-of-interest waiver has been issued in
11 accordance with 18 USC. Section 208. Mr. Elijah Wreh is serving as industry representative,
12 acting on the behalf of all related industry. Mr. Wreh is employed by Boston Scientific
13 Corporation. For the record, the agency notes that Dr. Richard Lange has consented to serve as
14 the chairperson for the duration of this meeting.

15 We would like to remind members and consultants that if the discussion involves any
16 other product or firms not already on the agenda, for which an FDA participant has a personal
17 or imputed financial interest, the participant needs to exclude themselves from such involvement
18 and the exclusion will be noted for the record. FDA encourages all participants to advise the
19 panel of any financial relationship they may have with any firm at issue. A copy of this statement
20 will be available for review and will be included as a part of official transcript. Thank you.

21 I will now read the appointment of temporary voting status memo. For the duration of the
22 circulatory system device panel meeting on February 13th, 2024, Ms. Jennifer Schwartzott has
23 been appointed as to serve as a temporary non-voting member. For the record, Ms. Jennifer

1 Schwartzott serves as patient representative, consultant to the Cellular Tissue and Gene
2 Therapies Advisory Committee in the Center for Biologics Evaluation and Research (CBER).
3 This individual is a special government employee who has undergone the customary conflict of
4 interest review and has reviewed the materials to be considered at the meeting. The appointment
5 was authorized by Rachel Bressler, Acting Director, Advisory Committee Oversight and
6 Management Staff on 12/27/2023.

7 I will now read the deputization memo. Pursuant to the authority granted under the
8 Medical Device Advisory Committee Charter of the Center for Devices and Radiological Health
9 dated October 27, 1990, and as amended August 18, 2006, I appoint the following individuals as
10 the voting members of the circulatory system device panel for the duration of this meeting on
11 February 13, 2024. Bradley A. Bart, MD. Amy M. Cizik, PhD. Scott R. Evans, PhD. Dr. David
12 A. Friedman, MD. Paul J. Hauptman, MD. John W. Hirshfeld, MD. Marc Katz, MD. Mitchell W.
13 Krucoff, MD. Craig H. Selzman, MD. Amit J. Shanker, MD. Mladen Vidovich, MD. David Yuh,
14 MD. In addition, I appoint Richard A. Lange, MD, MBA to act as a temporary voting
15 chairperson for the duration of this meeting. For the record, these individuals are special
16 government employees or regular government employees who have undergone the customary
17 conflict of interest review and have reviewed the material to be considered at this meeting. These
18 two memoranda have been signed by Dr. Jeffrey Shuren on January 29, 2024. The copy of this
19 statement will be available for review and will be included as a part of the official transcript.
20 Thank you. FDA encourages all participants to advise the panel of any financial relationship they
21 may have with any issues at hand.

22 A few general announcements are as follows. In order to help the transcriber identify who
23 is speaking, please be sure to identify yourself each and every time that you speak. The press

1 contact for today's meeting is Audra Harrison. Thank you very much. I'll hand it over back to Dr.
2 Lange.

3 Dr. Lange: Thank you. Dr. Awajope. We will now proceed to the sponsors presentation, and I
4 would like to the invite the sponsor to begin as soon as my remarks are finished. I will remind
5 the public observers at this meeting that while this meeting is open for public observation, public
6 attendees may not participate except at specific request of the panel chair, that is me. The sponsor
7 will have 90 minutes to present. And the sponsor, you may now begin your presentation. Thank
8 you.

9 Abbott Medical Presentation

10 Dr. Sondergaard: Good morning, members of the FDA and the advisory committee. I'm Lars
11 Sondergaard chief medical officer and divisional vice president of medical affairs at Abbott
12 structural heart. We are pleased to be here today to share the data supporting TriClip for patient
13 with symptomatic sever tricuspid regurgitation. The foundation of our development program was
14 built on the unmet medical need of patients with severe tricuspid regurgitation and progressive
15 disease associated with debilitating symptoms that impact patients' health status. Yet, patients in
16 the U.S. have limited treatment options to address their symptoms. The high operative risk
17 associated with tricuspid valve surgery and the lack of effectiveness of medical therapy alone has
18 left patients with severe TR vastly untreated.

19 With the patient at the forefront of our mind, we developed TriClip based off Abbott's
20 well-established MitraClip clinical experience, which received CE mark in 2008 and was
21 approved by the FDA in 2013. MitraClip is a transcatheter edge to edge repair technology for the
22 treatment of mitral regulation and has been used in more than 200,000 patients. The first report
23 of MitraClip used to treat tricuspid regurgitation was in 2015. The continued reports of off label

1 use speak to the high unmet need for a device that can specifically treat the tricuspid valve,
2 which requires different navigation. This need drove the design and development of TriClip. The
3 TRILUMINATE pivotal trial was initiated with an earlier generation TriClip system with two
4 clip sizes, the NT and XT. The TriClip G4 system is an updated system with four clip sizes along
5 with other procedural features and was incorporated halfway through the trial. Let me share a
6 video that shows the delivery system. An implantable clip is delivered into the heart by a
7 catheter via the femoral vein. The steerable guide allows access to the right atrium. The clip
8 delivery system deploys the clip with optimal orientation for easier access to the tricuspid valve.

9 Next, the clip is advanced through the tricuspid valve into the right ventricle. The
10 grippers are lowered to grasp the leaflets and the clip's arms are closed. Thereby the tricuspid
11 leaflets are pulled together to reduce tricuspid regurgitation. Once positioning is confirmed, the
12 delivery system is removed. Additional clip may be deployed, if necessary. TriClip becomes a
13 permanent implant in the heart aimed to reduce tricuspid regurgitation and improve blood flow
14 through the heart. As noted, the clinical experience, the Tricuspid repair started around 2015 with
15 the first off-label use of MitraClip for TR. The first patient entered the TRILUMINATE CE mark
16 started in 2017 and the pivotal study began in 2019 with the last patient enrolled in 2022. TriClip
17 was approved in Europe and Canada around the same time. Based on the TRILUMINATE CE
18 data. In 2020 after agreement with the FDA on the design of the pivotal trial, FDA granted
19 breakthrough device designation for TriClip based on the serious condition of tricuspid
20 regurgitation and the promising preliminary clinical evidence. The bRIGHT study is currently
21 ongoing. It's a single arm, prospective, multi center, real world study in Europe and is intended to
22 satisfy its post market clinical follow-up requirement of the CE mark in Europe. The initial
23 results of the TRILUMINATE Pivotal Trial was presented at ACC in 2023. The clinical

1 experience supports the proposed indication. If approved, the TriClip G4 system would be
2 indicated for the improvement of health status in patients with symptomatic severe tricuspid
3 regurgitation, despite being treated optimally with medical therapy, who are at intermediate or
4 greater risk for surgery, and in whom tricuspid valve edge to edge repair is appropriate, as
5 determined by a heart team.

6 Our presentation today will focus on several key considerations for benefit-risk
7 assessment. First, the TRILUMINATE trial met its primary endpoint. No differences were
8 observed in mortality and surgery or in heart failure hospitalization, but significant improvement
9 was observed in health status as assessed by the Kansas City Cardiomyopathy Questionnaire, or
10 KCCQ. We acknowledge that the open label design may introduce bias in the patient reported
11 outcomes. However, we will show today that the totality of data substantiates a real treatment
12 effect given the consistent and sustained reduction in TR and in symptoms, both relevant
13 measures for the indicated population and improvement across all KCCQ domains.

14 Additionally, the supportive data include the larger full randomized cohort with 572
15 patients, the single-arm cohort, the physiological changes, and the reverse remodeling observed
16 from the imaging sub study, which all corroborate a true treatment effect. The data we will share
17 today support a positive benefit risk for TriClip. TriClip is a minimally invasive procedure
18 specifically designed to access and treat the tricuspid valve to reduce tricuspid regurgitation in
19 patients who are symptomatic with few alternatives. As we will present today, TriClip has a
20 favorable safety profile. Despite being an elderly population with many comorbidities, 98
21 percent of the TriClip patients were free from major adverse events in 30 days and there is very
22 low procedural risk. The TriClip device was also highly effective in reducing TR and led to a
23 significant sustained improvement in the health status. The robust clinical experience is further

1 supported by outside the U.S. experience where TriClip has been successfully treated in patients
2 with severe TR since 2020. The safety and effectiveness data support a positive benefit risk for
3 patients highly in need of an approved treatment.

4 With this background, here's the agenda for today's presentation. Dr. David Adams, Chief
5 Cardiac Surgeon at Mount Sinai Health System and co-PI will review the unmet need and trial
6 design of the TRILUMINATE Pivotal Study and will then share the safety data. Dr. Paul Sorajja,
7 Interventional Cardiologist at Minneapolis Heart Institute and co-PI will then review the data
8 supporting the clinical effectiveness of TriClip. Dr. Steven Lurz, Director of Cardiology at Mainz
9 University Hospital in Germany, will add his clinical perspective as an interventional
10 cardiologist who currently uses TriClip. And I will return to conclude the presentation before
11 handing over to Dr. Spinner, who will moderate the Q & A. We also have additional experts with
12 us today. All outside experts have been compensated for their time and travel to today's meeting.
13 Thank you. I will now turn the lecture to Dr. Adams.

14 Dr. Adams: Thank you. I'm David Adams. Along with Dr. Sorajja, I was the principal
15 investigator for the TRILUMINATE study. I'm the cardiac surgeon in chief of the Mount Sinai
16 Health System. My practice is particularly focused on atrioventricular valve disease. I lead a
17 team that evaluates more than 800 patients and operates on more than 500 patients with mitral
18 and tricuspid valve disease annually. It is within this context that this trial is particularly
19 meaningful to me given our experience taking care of patients with tricuspid regurgitation, and
20 the data we present today are not only impressive, but applicable to patients we see every day. I
21 would like to begin with the discussion of the unmet need currently facing patients with tricuspid
22 regurgitation. On the left is a simple depiction of how blood flows through the cardiovascular
23 system. The tricuspid valve controls blood flow from the right atrium into the right ventricle,

1 which then pumps blood to the lungs. Oxygenated blood enters in the left atrium and then the
2 left ventricle through the mitral valve before exiting the heart through the aortic valve. The figure
3 on the right shows a normal tricuspid valve during ventricular contraction with the three leaflets
4 now preventing backward regurgitation. The most common causes of tricuspid regurgitation are
5 volume and pressure loading of the right ventricle. This condition is referred to as functional
6 tricuspid regurgitation and is most commonly related to left-sided heart disease, pulmonary
7 hypertension, and atrial arrhythmias. Leaflet malcoaptation leads to regurgitation into the right
8 atrium during ventricular contraction. Tricuspid regurgitation decreases forward cardiac output
9 and also raises right sided systemic venous pressures. This physiology can result in heart failure,
10 hepatorenal congestion and dysfunction, edema and ascites, and right-sided chamber
11 enlargement, which can exacerbate TR progression over time.

12 Tricuspid regurgitation typically progresses and is an indolent process, creating a
13 spectrum of patients suffering from this disease. Severe TR often leads to debilitating symptoms
14 that impact the quality of life of patients. Symptoms including peripheral edema, fatigue,
15 changes in appetite, and shortness of breath are common. Resolution of symptoms and reversing
16 sequela of chronic severe TR is the primary consideration for intervention for tricuspid
17 regurgitation. The ACC guidelines recommend medical therapy for patients with severe
18 symptomatic tricuspid regurgitation, which may alleviate symptoms in selected patients.
19 However, medical therapy alone is often ineffective and only used due to the lack of a suitable
20 alternative. The only current class I indication for the treatment of tricuspid valve regurgitation is
21 in patients undergoing left sided valve surgery, who often present with numerous comorbidities.
22 These are not the patients we're speaking about today. All other indications are class II, reflecting
23 the current status of evidence for intervention in the isolated setting. In yellow are highlighted

1 current indications for patients to be targeted in our trial. The guidelines note that tricuspid valve
2 surgery can be beneficial to reduce symptoms and recurrent hospitalizations, but do not mention
3 potential impact on long term mortality as the evidence base does not exist in the surgical
4 literature. The fact is, surgery is rarely performed for TR alone, mainly because of procedural
5 risk.

6 A recently published summary by Chen and colleagues of isolated tricuspid valve surgery
7 in the contemporary era from the Society of Thoracic Surgeons database highlights the high risk
8 to which patients are subjected to, to improve their clinical status. In a study of over 6,000
9 patients, the median age was 65 years. This shows that older patients are much less likely to be
10 referred for surgery, though this is primarily a disease seen in older patients. The reported
11 operative mortality rate of 7.3 percent and composite major complication rate of 32%, including
12 5.5 percent of patients requiring mechanical renal support, reflects the high risk associated with
13 tricuspid valve surgery even in the modern era. This is why we are all here today, because
14 symptomatic severe TR remains a clinical challenge. The symptoms are common and
15 debilitating. Medical therapy has a role, but many patients are unresponsive. Surgery can
16 effectively eliminate tricuspid regurgitation, but the surgery has many risks, including operative
17 mortality. Patients are usually referred for surgery late in the course of their disease due to these
18 risks and often present with long term organ dysfunctions. Clearly, new treatment strategies are
19 necessary to help patients with this disease.

20 In a recent editorial, my colleague, Pat McCarthy, described the unmet need that all of us
21 confront in treating tricuspid regurgitation, noting, “the tricuspid valve was ignored for years, but
22 this has changed. It is the hardest valve to treat successfully, however. With many anatomic and
23 physiologic challenges for evolving therapies.” This great unmet treatment challenge was the

1 basis for the TriClip design and the TRILUMINATE trial. The randomized and single arm both
2 enrolled patients with severe TR who remained symptomatic despite medical therapy. The
3 differentiation between the two arms was that randomized patients were determined likely to
4 have TR reduction to moderate or less with TriClip, while for single arm patients was more
5 likely to experience a decrease in TR with TriClip by one grade, but not to moderate or less.
6 Patients were randomized one to one, and the endpoint was a hierarchical composite while for
7 the single arm, the primary endpoint was survival with KCCQ improvement of 10 points at 12
8 months. There was also an imaging sub-study at select sites, which included subjects from both
9 the randomized and single arm who were willing to undergo additional studies related to
10 imaging. Participants in the trial were required to be symptomatic with severe TR despite being
11 optimally treated with guideline directed medical therapy for at least 30 days. The cardiac
12 surgeon, along with the site local heart team, had to agree that the patient was at intermediate or
13 greater estimated risk for mortality and morbidity with tricuspid valve surgery. Patients were
14 excluded if there was an indication for left sided or pulmonary valve correction, severe and
15 uncontrolled hypertension, or left ventricular ejection fraction less than or equal to 20%. Also
16 excluded were patients with tricuspid valve leaflet anatomy that could preclude clip
17 implantation, proper clip positioning on the leaflets or a sufficient reduction in TR. These criteria
18 supported the trial's efforts to enroll a patient population which was believed would receive
19 benefit through reducing TR. They are the same criteria that would be used in clinical practice to
20 determine a patient's eligibility for TriClip.

21 There were multiple independent review committees in our trial. We had both echo and
22 CT MRI core labs to assess TR grade and morphology, leaflet gaps, and chamber measurements.
23 The anatomic eligibility committee determined the feasibility to implant the TriClip device and

1 assigned participants to the randomized or single arm cohort. The Patient Management
2 Committee was composed of heart failure specialists who reviewed patients right heart
3 catheterization data and ensured they were appropriately managed. The CEC adjudicated key
4 safety endpoints throughout the trial. The trial used an adaptive design which allowed for sample
5 size re-estimation. Enrollment was quicker than anticipated, emphasizing the unmet medical
6 need for treatment. 17 months from initiation, 150 patients were enrolled, and just 7 months later,
7 that number more than doubled to 350 patients.

8 Due to the limited data available at the time of study design, an intro analysis was
9 designed to assess the first 150 patients at 1 year follow-up and evaluate if 350 patients would
10 appropriately power the endpoint. As you can see, more than 350 patients were enrolled prior to
11 completion of the interim analysis results. Upon confirmation that 350 patients would be
12 adequate for the primary endpoint analysis, the trial was stopped in July of 2022, with a total of
13 589 patients enrolled.

14 For today's presentation, we'll present both the primary dataset, which includes the first
15 350 patients and all randomized patients, which further supports the primary endpoint. Based on
16 the interim analysis, the primary analysis for the randomized arm was 350, but a total of 589
17 were enrolled, with 572 patients ultimately randomized. The single arm enrolled 200 patients
18 with a planned group sequential analysis at the first 100 patients. The imaging sub-study is
19 ongoing, and as of the data cut off, we had 82 patients enrolled.

20 The primary endpoint of the randomized cohort was a hierarchical composite ordered by
21 clinical importance of all-cause mortality or tricuspid valve surgery, heart failure
22 hospitalizations, an improvement of greater than or equal to 15 points as measured by the KCCQ
23 score. The Kansas City Cardiomyopathy Questionnaire, or KCCQ, was used for health status

1 assessment. The KCCQ is a 23-item self-administered questionnaire developed with input from
2 patients and clinicians to independently measure the patient's perception of their health status,
3 which includes symptom frequency, symptom burden, symptom stability, physical and social
4 limitations, and quality of life. The KCCQ was administered by blinded study personnel using a
5 standardized script and completed by the patient. KCCQ scores range from 0 to 100, with higher
6 scores indicating better health status. The minimum clinically important difference has been
7 defined as a five-point change on the KCCQ, even if a patient remains in the same symptom
8 category. A 15-point change is considered to be of moderate to large clinical benefit in the
9 randomized cohort. The primary endpoint was assessed at 12 months and tested using the
10 Finkelstein-Schoenfeld method, which provides a p value to assess statistical significance. This
11 is a non-parametric statistical test to combine endpoints in a hierarchical order determined by
12 clinical importance. Patient pairs are given only one point if they win their given comparison,
13 negative one point if they lose or given zero points if both patients fared the same. Additionally,
14 the win ratio was used to estimate the treatment effect. A win ratio summarizes the number of
15 patients who fared better versus worse for each pairing. Let me explain the comparison within
16 pairs visually.

17 The first two patients, one on device and one on control, are compared across the primary
18 endpoints in hierarchical order. Here both are alive with no tricuspid surgery, so we go to the
19 next component in the hierarchy to compare heart failure hospitalization, which both patients did
20 not experience. No points are given to either patient in these categories.

21 Next in the hierarchy is a greater than or equal to 15-point change on the KCCQ, which
22 was achieved by the device patient, but not the control patient. One point is then awarded to
23 TriClip. Device patient one is then compared to control patient two, the next control patient,

1 again, going component by component, and points are determined. In this case, device patient
2 one is alive and control patient two died. One point is awarded to TriClip, and other components
3 are not compared. This method yielded more than 30,000 comparisons. The ratio of the total
4 number of winners for the device group to the total number of winners for the control group
5 yields the win ratio. Our statistical assumptions were based on information available at the time
6 of study design. Based on the limited literature for TR alone, we assume 12-month mortality or
7 tricuspid valve surgery rates around 20 percent for control and 15 percent for device, and an
8 annualized heart failure hospitalization rate of 0.5 for control and 0.35 for device. And while we
9 were still learning about death and heart failure hospitalizations, we understood the importance
10 of the KCCQ from our earlier TRILUMINATE study experience. So, as you'll see from the data,
11 our assumptions around health status were fairly consistent with outcomes.

12 Let me briefly review the data supporting the mortality and hospitalization assumptions.
13 Our understanding of TR and how it impacts mortality and heart failure hospitalization rates has
14 evolved since trial initiation in August 2019. When designing the study, we had limited literature
15 based on the four sources shown here. We made best estimates for mortality. Based on the wide
16 range of 7 to 52 percent reported. Contemporary studies that have emerged continue to show a
17 wide mortality range, but as we further look at these patient populations, we see that higher rates
18 are associated with untreated concomitant valve disease, represented by the black dots, whereas
19 lower one year mortality rates were reported in patients with TR alone, that is, without other
20 untreated valve disease represented by the blue dots. We also had limited understanding of heart
21 failure hospitalization rates in these patients as demonstrated by the few studies and the variation
22 in rates reported prior to the trial. As more literature has emerged, as observed with mortality, we

1 see that one-year heart failure hospitalization rates are indeed quite low in patients with TR
2 alone.

3 Secondary endpoints for the randomized cohort were assessed after the first 350 patients
4 completed their 12-month follow-up visit. They were tested in the prespecified sequence shown
5 here. TR severity has historically been graded as mild, moderate, or severe. With the recent
6 development of transcatheter treatments, a new grading scheme was published by Dr. Becky
7 Hahn in 2017 and adopted for the trial to better determine efficacy, extending the three-point
8 scale to a five-point scale, which now includes grade 4 or massive, and grade 5 or torrential TR.
9 Patients with grade 3 or greater were eligible for this trial. The overall patient population was
10 consistent with that of patients with the disease. Patients were elderly with a mean age of 78
11 years and just over half were female. Of note, this population on average is about 15 years older
12 than patients undergoing surgery for TR currently in the U.S. according to the literature. These
13 are sick patients with over half with NYH class 3 or 4 and a mean KCCQ overall summary score
14 around 55 out of 100. Renal disease was present in one third of patients. The most common
15 comorbidities included atrial fibrillation and hypertension.

16 As previously mentioned, TR severity was assessed on a five-grade scale. Importantly,
17 the severity of TR was at the extreme end of that range or torrential in half of the patients. The
18 etiology was functional in nearly all patients. Overall, there was evidence of right ventricular
19 enlargement, right ventricular dysfunction, and preserved left ventricular ejection fraction.
20 Shown here is the disposition for the randomized cohort. 175 patients were randomized in each
21 of the TriClip and control groups. The primary analysis was conducted once patients were
22 randomized, with days of follow up starting on date of randomization. Three patients in the
23 TriClip group withdrew, and one patient in the control group died prior to the treatment visit.

1 Subsequently, one patient withdrew, and one patient died in both groups prior to their 30-day
2 visit. Following the 30-day visit, 15 patients in the TriClip group and 12 patients in the control
3 group died prior to 12-month follow-up resulting in the ability to assess the primary endpoint for
4 95 percent of patients with missing data balance between arms, and 100 percent of eligible
5 patients in the device group and 98.7 percent in the control group completed their 12 month
6 follow-up. Primary analysis comparisons were conducted on the common follow-up period
7 between each pair of patients. Implantation was successful in 99 percent of attempted patients
8 with a mean of 2.2 clips per patient. The first generation TriClip system with two clip sizes was
9 used in 47 percent of procedures, and the TriClip G4 system was used in 53%. Analysis showed
10 no differences in outcomes between versions of the TriClip device used.

11 Total device time, defined as the time between insertion of the steerable guide catheter
12 and retraction of the TriClip delivery system into the steerable guide catheter, was 90 minutes.
13 After implantation, the median length of hospital stay was one day. Nearly all patients were
14 discharged home afterwards. No patients died while at the hospital for the procedure. Let me
15 start our discussion of results with a brief description of the safety data. The safety profile for
16 TriClip was remarkable. Especially when compared to surgical treatment in this patient
17 population. Freedom from major adverse events were assessed in 172 patients who underwent an
18 attempted procedure. Components of MAEs were new onset renal failure, cardiovascular
19 mortality, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip
20 device related adverse events post index procedure. 98.3 percent of patients were free from
21 MAEs at 30 days post-procedure, with a lower limit of the 95 percent confidence interval of 96.3
22 percent, which was greater than the performance goal of 90 percent. To further contextualize this
23 safety profile, the combined operative mortality and new onset renal failure represents an over 8-

1 fold lower risk compared to the recent Chen report on surgical outcomes I previously presented.
2 Other adjudicated clinical safety endpoints are shown here through a 30-day follow-up. As you
3 can see, the two groups have comparable low rates through 30 days. with the exception of major
4 bleeding, which I will further clarify now. Of the nine major bleeding events, three were
5 adjudicated as procedure-related, which were all access site related and understandable due to the
6 procedural requirement for large bore venous access.

7 The remaining were four GI bleeds, one urological bleed, and one intracranial bleed.
8 None of the nine events were fatal and all resolved without serious sequelae. All nine events
9 were in patients on intensive anticoagulation therapy pre-procedure, and none of the events were
10 associated with an escalation of antithrombotic therapy post-procedure. Overall, the major
11 bleeding rates seen in the trial are consistent with the bleeding rates seen in other transcatheter
12 edge-to-edge procedures.

13 Additional adjudicated clinical safety endpoints through one year are shown here. As you
14 can see, the two groups are comparable with low rates reported through one year. It is important
15 to note that there was no device embolization or device thrombosis and comparable low rates of
16 new pacemaker requirement. Overall, an extremely safe profile for TriClip. From a surgeon's
17 perspective, it is hard to imagine such a positive safety profile for patients undergoing procedural
18 therapy for severe tricuspid regurgitation. There's never been a single surgical institution series
19 reported that can come close to the safety of the TriClip procedure. We can treat TR effectively
20 with surgery, but we can never duplicate this degree of safety. Additionally, the average length of
21 hospital stay for TriClip is one day compared to a typical length of stay of eight to 10 days
22 following tricuspid surgery, which is a reflection of the safety and truly minimally invasive
23 nature of TriClip therapy. This safety experience very much adds to the benefit risk

1 considerations for TriClip and why I feel so strongly that this therapy represents a major advance
2 for the treatment of these patients. I appreciate your attention. Dr. Sorajja will now review the
3 clinical efficacy data.

4 Dr. Sorajja: Thank you very much. I am Dr. Paul Sorajja. Along with Dr. Adams, I've had the
5 distinct pleasure to serve as a coprincipal investigator for TRILUMINATE. I've been involved
6 with this therapy since 2016 and it's been a privilege to witness the real patient benefit in my
7 hometown of Minneapolis. Our site was the top enroller for the trial and thus I've seen firsthand
8 patients benefit from this therapy. On their behalf and many of other patients in the waiting, I am
9 happy to share my portion of today's presentation. Dr. Adams has already shared with you the
10 excellent safety of the TriClip system, perhaps the safest therapy ever reported for patients with
11 TR. In addition to being very safe, the TriClip system was also highly effective in reducing TR.

12 On the left-hand side, most patients had severe massive or torrential TR, denoted by dark
13 blue at baseline. At 30 days, we see that the TriClip system reduced TR to moderate or less,
14 denoted by lighter blue in 90 percent of patients. The secondary endpoint of TR reduction at 30
15 days was met with a highly significant p value, and that degree of TR reduction was sustained at
16 one year.

17 However, most of the control patients, over 90 percent, continue to have severe, massive,
18 or torrential TR during the course of the study, from baseline to one year. The primary endpoint
19 was met with a p value of 0.03 and win ratio of 1.44. Based on the number of wins, this finding
20 translates to device patients being 44 percent more likely to have better clinical outcomes than
21 the control patients. Occurrence of death or tricuspid valve surgery was balanced between the
22 groups. Heart failure hospitalization was numerically higher in the device group, as demonstrated

1 by the greater number of wins in the controls, but as you will see later, this difference was not
2 statistically significant.

3 The third tier, an improvement in KCCQ score of 15 points or more, showed a substantial
4 treatment benefit for the device group, and drove the success of the primary endpoint. Overall,
5 there were 11,246 wins for the device group, compared to 7,791 wins for the controls.

6 Now let's look at more details for the individual components of the primary endpoint.
7 Low mortality or tricuspid valve surgery was observed at one year, consistent with what we now
8 know from contemporary literature in patients without left sided disease, but lower than assumed
9 rates based on the early literature. In fact, control patients continue to have massive or torrential
10 TR throughout the study, but they showed remarkably low mortality or surgery with a freedom
11 from these events in 89.4 percent at one year. When looking at the TriClip group, freedom from
12 all-cause mortality or tricuspid valve surgery was 90.6 percent, and the difference between
13 groups was not significant. For heart failure hospitalization, while there were large differences in
14 TR reductions with device therapy, those highly significant differences did not translate to
15 differences in heart failure hospitalization at 12 months, with 35 events for the TriClip group and
16 28 events for control. This suggests that TR alone, even when massive or torrential, is not a
17 primary driver of HFH or death in this population at 12 months. Despite the high threshold of 15
18 points for change from baseline, there was a large difference between TriClip and control, with
19 50 percent of TriClip patients and only 26 percent of control patients having met this threshold.
20 The improvement was consistent with statistical assumptions. With health status being a key
21 driver of the primary endpoint, we took this opportunity to look further into this benefit and the
22 multiple clinical metrics that support this finding. Here we show that TriClip patients were more
23 likely to improve in KCCQ no matter what thresholds were used. The left-hand side shows the

1 primary endpoint component of at least a 15-point improvement and additional five point
2 decrements and cutoffs to the right. Looking at the far right, you can see that more control
3 patients had at least a 5-point decrease in the KCCQ compared to TriClip patients. Thus, control
4 patients were more likely to get worse while device patients were more likely to get better.

5 We also see large, early, and sustained KCCQ improvement over the study with no
6 evidence of waning. TriClip patients had an average sustained increase in KCCQ score of
7 approximately 15 points. While some improvement was noted in control patients, the extent of
8 improvement was much less than in the device patients. Moreover, at one year, the difference in
9 KCCQ between the two arms is over 10 points, thus meeting another pre-specified secondary
10 endpoint that was focused on direct comparison of scores between the two groups. As discussed
11 in a recent article by Arnold et al., the observed treatment benefit of 10.4 points in the trial is
12 larger than the expected magnitude of a placebo effect around five to six points. For each
13 individual domain of the KCCQ, TriClip also shows significant benefit over medical therapy
14 alone, with the quality of life and social limitation domains showing the largest improvements.
15 When we look at the specific questions of the questionnaire, these were designed to be fairly
16 objective. When comparing treatment and control groups in an open label trial, responses in PRO
17 domains that are proximal to TriClip's mechanism of action are particularly relevant.
18 Specifically, in the physical and symptom domains, TriClip patients reported improvements in
19 edema, fatigue, and shortness of breath, known symptoms of TR.

20 Overall, there is consistency in TriClip being favored across multiple questions,
21 demonstrating internal consistency for the validity of KCCQ and its ability to assess the burden
22 of TR. We also measured edema and ascites as descriptive endpoints beyond patient reported
23 outcomes and observed improvements favoring TriClip for both measures. As a demonstration of

1 the validity of the KCCQ, looking at device patients only, we see a clear association between the
2 magnitude of TR change and the degree of health status improvement with greater improvement
3 in KCCQ corresponding to greater reduction in TR. Consistent with the KCCQ, another health
4 status survey, the SF 36, showed clinically meaningful benefit from TriClip. This benefit was
5 evident at 30 days and sustained through 12 months and included a significant difference in the
6 physical component. The changes in health status were corroborated with improvements in
7 NYHA functional class. At 12 months, 40 percent of control patients remained class III or IV,
8 compared to only 16 percent of TriClip patients, which signifies extensive symptom relief.

9 Finally, this slide summarizes the data on six-minute walk distance. It is important to note
10 that imputation was used in the prespecified analysis for the secondary endpoint. For imputation,
11 patients who experienced a heart failure related cardiovascular death, received tricuspid valve
12 surgery, or who were unable to exercise due to cardiac reasons were imputed to an assigned
13 value of zero at one year.

14 The secondary endpoint was not met. On the right-hand side are paired data without
15 imputation, where you can observe an increase in the TriClip group and a decrease in the control
16 group. Whether using imputed or paired values, the six-minute walk distance results favor the
17 device. As mentioned earlier, the study continued to enroll patients beyond the 350 patients that
18 comprised the primary randomized cohort until interim sample size re-estimation analysis was
19 completed. This group of 572 randomized patients reinforces the efficacy and safety of TriClip.
20 As you may see in the briefing documents, the additional patients in the full randomized cohort
21 had comparable baseline characteristics in disease compared to the primary randomized cohort.

22 This slide shows the primary endpoint analysis for all 572 randomized patients. In this
23 analysis, we can see that the primary endpoint win ratio increases to 1.53, meaning excluding

1 ties, device patients are 53 percent more likely to have a better outcome than control patients.
2 Death or tricuspid valve surgery is balanced between groups. There are now about 600 more
3 wins in the device group versus control for heart failure hospitalization, compared to the primary
4 350 patient analysis and health status, as measured by the KCCQ score improvement of 15 points
5 or more, again showed a substantial benefit for the device group over control. Similar to the
6 primary analysis cohort, event rates remain low for all patients randomized, with similar freedom
7 from all-cause mortality in tricuspid valve surgery. 91 percent for the device arm. and 92% for
8 the control. No differences in heart failure hospitalization between groups were seen when
9 examining the full randomized cohort, as was also seen in the primary analysis cohort.

10 Finally, when examining all randomized patients, there continue to be significant
11 improvement in health status for device compared to control patients. For the six-minute walk
12 distance, when looking at the full randomized cohort, we see the same positive trends, whether
13 imputed or paired with even larger and significant differences between the groups.

14 Let's now move to further supportive evidence of clinical benefit of TriClip in patients
15 with TR. First, let's look at the single arm cohort of TRILUMINATE. Recall that the single arm
16 cohort consists of technically complex patients with advanced disease, and in these patients, the
17 TriClip device was not expected to reduce the TR to moderate or less. Here is a comparison of
18 the single arm patients versus the randomized patients. We can see that patients in the single arm
19 were slightly older with more comorbidities. As expected, based on the selection criteria, single
20 arm patients had a higher presence of device leads, worse TR severity, and relatively more
21 dilated right sided cardiac chambers with larger right atrial volumes and larger right ventricular
22 end diastolic diameters. The tricuspid leaflet coaptation gaps also, was significantly larger in the
23 single arm patients in comparison to the randomized cohort. The primary endpoint of the single

1 arm cohort was survival with an improvement in KCCQ of 10 points or more at 12 months
2 compared to a performance goal. The performance goal was exceeded and the primary endpoint
3 for the single arm cohort was met. Just as in the randomized cohort, patients in the single arm
4 cohort had an early improvement in KCCQ, consistently higher than the pre-specified 10-point
5 change and sustained through 12-month follow-up. Thus, both the randomized and single arm
6 cohort patients showed a significant improvement in health status compared to patients who had
7 medical therapy alone.

8 Importantly, TriClip far exceeded our expectations with 80 percent of single arm patients
9 having moderate or less residual TR. Just as important, there still were no major adverse events
10 in the single arm cohort at 30 days. Taken together, these data demonstrate excellent
11 effectiveness, improvement in health status, and remarkable safety for the TriClip system, even
12 in more technically complex patients with more advanced disease.

13 For additional supportive evidence, I'd like to share the data on the physiological impact
14 of TR reduction that shows early clinical benefit. As Dr. Adams noted, TR can have further
15 consequences as the disease progresses. Most patients have abnormal anatomical values at
16 baseline, whether assessed by echo or CT measurements as shown by the dark blue bars for the
17 baseline distribution.

18 On the left, we are looking at change in anatomical measurements for baseline to 12
19 months or last available observation for TriClip compared to control. Trends are supportive of
20 TriClip for echo measurements and even greater improvements were observed for CT chamber
21 remodeling with substantial decrease in right atrial, annular, and right ventricular size. The
22 sample size for CT measurements was small given it was an imaging sub-study, but despite this
23 smaller sample, we see consistent benefit for TriClip. Moreover, when we examine pulmonary

1 forward flow as forward stroke volume in the left-hand side of this slide and pair it with effective
2 RVEF on the right-hand side, we found improvement in effective RVEF for the device patients.
3 but not in the controls. This was observed via cardiac MRI in the imaging sub-study, which has
4 remarkable precision for function and volume assessments in complex anatomical shapes. This
5 finding supports the notion that TR reduction leads to beneficial changes in RV size and function
6 that physiologically support the health status improvement with TriClip.

7 By design, TRILUMINATE did not require patients to have end stage organ disease. With
8 the exception of NT-proBNP, about half of the patients had relatively normal liver and renal
9 function for this population despite the presence of TR. It was reasonable to expect limited
10 differences between groups with a higher number of patients having normal end-organ function.
11 Nevertheless, despite approximately half of the patients having relatively normal liver and renal
12 function at baseline, there were trends in improvement in the function of these organs with the
13 TriClip system.

14 In conclusion, the primary endpoint of the TRILUMINATE pivotal trial was met, driven
15 by significant and sustained improvements in health status as measured by the KCCQ overall
16 summary score. The device accomplished its main objective of reducing TR severity, which was
17 directly associated with health status improvements, and the degree of improvement in health
18 status was directly associated with the degree of TR reduction. Effectiveness is supported by the
19 totality of data through secondary endpoints, as well as consistent data across the single arm
20 cohort, the full randomized cohort, and trends in physiological markers, all demonstrating the
21 benefit of TriClip. Importantly, the device was very safe in both the randomized and more
22 complex single arm cohort. Particularly considering the large unmet need of patients with TR,

1 the safety profile and the effectiveness data strongly support a favorable benefit-risk profile of
2 TriClip. Thank you. Dr. Lurz will now share his clinical perspective.

3 Dr. Lurz: Thank you. I'm Philipp Lurz, Director of Cardiology at University Hospital Mainz,
4 and I'm really happy to provide my perspective on the data supporting TriClip. I've actually been
5 involved in a therapy since 2017, and I started to use TriClip in my patients with severe TR since
6 the early CE-mark study and continue to do so since approval in Europe in 2020. So, throughout
7 these last years, the understanding of the importance to treat TR has certainly evolved.
8 Previously, patients with severe symptoms due to their TR have often been misdiagnosed and
9 hardly ever treated at all. We are now in a much different situation.

10 TriClip has finally given us a tool to treat our patients and has filled a needed gap that
11 existed in the field for way too long. Crucial for the success of TriClip therapy is the safety
12 profile, and as both Dr. Adams and Sorajja noted, the safety profile for TriClip is remarkable. My
13 personal experience and results of the bRIGHT post approval study corroborate the
14 TRILUMINATE pivotal experience. Across all these studies, the safety profile has been
15 consistently favorable with very few major adverse events, and there's certainly no comparison
16 to the frequent events seen with tricuspid valve surgery. Now, in addition to safety, TriClip
17 consistently showed effective reduction of TR across studies, with more recent studies showing
18 even more improvement for patients. Also, in the bRIGHT real-world registry, there's a high
19 number of patients ending up with moderate or less TR, and this is important because the
20 bRIGHT registry comprises many patients with complex anatomies and the highest degrees of
21 tricuspid regurgitation. So, what that means is that bRIGHT confirms the effectiveness of the
22 TRILUMINATE studies and this in a real world and almost all comer population, and this
23 reduction in TR is associated with improvements in quality of life, which matters for patients.

1 For KCCQ, we see consistent early and sustained improvements across all studies and
2 cohorts, and this mirrors my personal experience in individual patients. So overall, the TriClip
3 procedure is one of the most rewarding experiences I have as an interventionalist. In my personal
4 experience, in clinical practice, but also from being involved in several trials in the field, there's
5 no doubt that TR causes debilitating symptoms and that patients desire and need treatment to feel
6 better. We've learned and now understand that TR is a very heterogeneous disease with different
7 valve etiologies and signs and symptoms of heart failure. And patients also present at different
8 points in the disease spectrum and with different comorbidities, but the common thread is that all
9 patients present with symptoms that impact their daily lives and that procedure success almost
10 always leads to symptomatic relief. So, when I see patients back in clinic after TriClip procedure,
11 patients say that they regain their appetite, feeling less fatigue, can exercise and resume social
12 activities.

13 So, to sum up, the availability of TriClip has changed clinical practices in Europe, and
14 I'm fortunate to have this option to treat severely symptomatic patients. And with that, I would
15 like to conclude, hand over to Dr. Sondergaard, and thank you.

16 Dr. Sondergaard: Thank you, Dr. Lurz. Current considerations for ongoing post approval
17 commitments include following all patients involved in the TRILUMINATE Pivotal Trial for
18 five years. Upon approval, a real-world post approval study will be initiated. All patients
19 implanted with the TriClip device will be followed at 30 days and then annually through five
20 years. Baseline and outcomes at 30 days and one year will be collected using the already
21 established TVT registry. We will use this registry to further understand the impact of TriClip on
22 symptoms, health status, and physiological changes, including right side heart chamber
23 dimension, and biomarkers. Survival and heart failure hospitalization data at two through five

1 years will be collected using the CMS linkage to the TVT registry. This is an evolving field, and
2 with longer term follow-up, we will be able to better understand the potential for longer term
3 clinical benefit of TR treatment beyond early symptom review. The totality of data presented
4 today show consistent efficacy findings across studies, endpoints, and assessment measures
5 which support the benefit of TriClip and the value it can provide for patients who have no
6 effective treatment options. TriClip demonstrated KCCQ improvements early and over the
7 course of the study. While there is a potential for bias in an open label trial, the totality of data
8 support the observed effect is biologically mediated. These improvements were observed across
9 all domains of the KCCQ, many of which were objective measures, such as reduction in edema
10 and fatigue. Change in KCCQ was associated with TR. These findings were supported by an
11 improvement in additional measures, like the SF 36 and the NYHA class. Furthermore,
12 improvements in six-minute walk distance, right heart chambers, and biomarkers, both for liver
13 and kidney trends favoring TriClip and mechanistically support the importance of significant
14 reduction in TR.

15 As we presented today, TriClip is a minimally invasive therapy specifically designed to
16 access and treat the tricuspid valve to reduce tricuspid regurgitation in patients who are
17 symptomatic. The study met its primary endpoint. Significant TR reduction was demonstrated
18 and sustained through one year, and importantly, patients experienced meaningful and significant
19 symptoms relief. In addition to being effective in treating patients with severe TR, the safety
20 profile was excellent, with 98 percent freedom from major adverse events and low procedure risk
21 as evidenced by no operative mortality, no device embolization, and no device thrombosis. The
22 results support a positive benefit risk for TriClip in a highly symptomatic population with limited
23 treatment options. Thank you. Dr. Erin Spinner will now moderate your questions.

1 Questions to Abbott Medical

2 Dr. Lange: First of all, I'd like to thank the sponsor's representatives for their presentation. And
3 this is a time where individuals on the panel can ask brief clarifying questions to the sponsor that
4 the sponsor can either address now, or if they need additional time to gather data, after lunch.

5 With that, I'll open it up for the panel to ask questions. You can either raise your hand physically,
6 and I'll try to record people in the order in which I see them, or if you want to raise your hand on
7 the on the web, that's fine as well. Let me open it up for questions for the sponsor. I've got Dr.
8 Yuh and then Dr. Krucoff.

9 Dr. Yuh: Thank you. I have a question for the sponsor. This is David Yuh were there any general
10 criteria or consistent criteria that surgeons used to adjudicate operative risk amongst the
11 considered patients?

12 Dr. Spinner: Yes. Hi, I'm Erin Spinner, clinical program director at Abbott and I'll be moderating
13 the questions for today. So, when the sites assessed the risk for surgery, it was done with a heart
14 team and they were really looking at frailties and comorbidities, but what we know is that most
15 patients with TR seen in the clinic are high or intermediate risk, and in fact, less than one percent
16 of patients in our trial were rejected due to not meeting this criteria.

17 Dr. Lange: And I'll ask in this order. I've got Mitch Krucoff, Dr. Hauptman, Dr. Bart, Dr.
18 Blankenship, Dr. Brindis, Dr. Selzman, and then Dr. Vidovich. Dr. Krucoff, by the way, David,
19 does that answer your question?

20 Dr. Yuh: Yes, it did. Thank you.

21 Dr. Lange: Great. Thank you. Mitch.

1 Dr. Krucoff: Yeah. Thank you. Mitch Krucoff. Two quick questions. One, do you all have
2 characterization in the randomized cohort, primary or the larger randomized cohort, of
3 medication increase, stability, or decrease, particularly diuretics that you could share?

4 Dr. Spinner: Yes, I can speak to that, and I'll actually have Dr. Benza, who's our heart failure
5 specialist and managed the ECPM committee for us speak to the diuretics and stability of
6 medication.

7 Dr. Benza: Good morning, everyone. Ray Benza. I am a cardiologist at the Icahn School of
8 Medicine at Mount Sinai. I am a professor of medicine, and my expertise are in advanced heart
9 failure, transplantation and pulmonary vascular disease. Thank you for that question. As part of
10 the committee to evaluate patients prior to entering into study, we did detailed evaluations of
11 these patients' ongoing medical therapy, particularly if they had evidence of left sided heart
12 failure, either systolic or diastolic to make sure that they're on goal-directed medical therapy for
13 these conditions 30 days prior to entry into the study. We critically evaluated their
14 hemodynamics, particularly on their right heart catheterization, to make sure that these patients
15 were adequately decompressed from right-sided congestion, before entering into the study and
16 made comments to the investigators about particular therapies for decongestion and for control
17 of hypertension.

18 Dr. Krucoff: Sorry, my question was about that at one year.

19 Dr. Spinner: Yeah, I can comment on that. No problem. So, when we did look at diuretics and I'll
20 just show this slide here, we didn't see any changes in I.V. diuretic, excuse me, in diuretic
21 dosages when we looked at patients from baseline to one year.

22 Dr. Krucoff: So, nobody was on less medication.

23 Dr. Spinner: That's correct.

1 Dr. Krucoff: Okay. Thanks. That's all

2 Dr. Lange: Erin. I just want to make sure that the slide that you showed that was for I.V. diuretic
3 use.

4 Dr. Spinner: No, this was just for oral dosages.

5 Dr. Lange: Would you do me a favor? Would you just put it back up for a second, just so that the
6 panel members can take a look.

7 Dr. Spinner: Sure.

8 Dr. Lange: We'll go to the next question, but if you just keep it there for just a second, Mitch
9 does this address, give you the information you're looking for.

10 Dr. Krucoff: The way I'm reading it is that this is not drug doses. This is the pre versus one year
11 drug dose per patient. Is that—

12 Dr. Spinner: That's correct. It's the total daily equivalent dosage per on drug days.

13 Dr. Lange: Mitch, would you like to sponsor to provide any additional information besides that
14 regarding medication use?

15 Dr. Krucoff: No, thanks. That answers my question.

16 Dr. Lange: Great. Thank you. Dr. Hauptman.

17 Dr. Hauptman: Yes. Thank you. And I appreciate the presentation by the sponsor. I will, I'd like
18 to follow up on the question that Dr. Krucoff asked. My understanding is that diuretics included
19 mineralocorticoid receptor antagonists. I wonder if you took those out of the analyses, what
20 would what would this what would the results look like both at baseline comparing the two
21 groups versus one year? And then I'm wondering if you could do a responder analysis based on
22 baseline diuretic use, for example, greater than one diuretic versus one diuretic. Curious about

1 how many patients were on, let's say, a thiazide plus a loop diuretic versus a loop diuretic alone
2 excluding the MRAs. Then I have one quick follow up question.

3 Dr. Spinner: Yeah, so I'll have Dr. Benza speak to that. I think we have data where we can
4 address most of those questions.

5 Dr. Benza: Yes, thank you, Ray Benza from Mount Sinai. When we were looking at the baseline
6 diuretic use virtually all patients were on a loop diuretic either alone or in combination with a
7 thiazide diuretic or potassium sparing diuretic. You can see that the penetration of thiazide and
8 potassium sparing diuretics was very low in this study.

9 Dr. Lange: And so, this was at baseline and in terms of follow-up?

10 Dr. Benza: Yes. Yes, you can see here that the diuretic types and over the course of the study
11 remained relatively the same without a statistically significant difference between those who
12 were treated with the clip and those who were in the control group.

13 Dr. Lange: Dr. Hauptman does this address your questions?

14 Dr. Hauptman: It does. Certainly helpful to know what happens at one year and to compare the
15 two groups. I do have another question, if I can, on a different, somewhat different topic, and that
16 is that reference is made in the packet to a roll-in cohort, but I didn't hear anything about that
17 roll-in cohort. I wonder if that could be defined. Were these patients who had TriClip at some of
18 the investigative sites before the trial began? It was just confusing it and see data related to that
19 cohort.

20 Dr. Spinner: Yeah, that's correct. So, the roll-ins were allowed. There were up to three roll-ins
21 allowed per site prior to randomization at the site for sites with no previous experience in
22 TriClip.

1 Dr. Lange: And Erin, to Paul's question, those roll-in patients were not included in the data
2 presented. Is that correct?

3 Dr. Spinner: That's correct.

4 Dr. Lange: Okay. Great. Paul, does that answer your question?

5 Dr. Hauptman: It does. Great. Thank you.

6 Dr. Lange: I got Dr. Bart, Dr. Blankenship, Dr. Brindis, Dr. Selzman, Dr. Vidovich, and Dr.
7 Shanker. Dr. Bart.

8 Dr. Bart: Yes, thank you. I was wondering about the treatment goals that you mentioned. There
9 was a safety goal of 90%, and I think there was another goal in the single arm cohort. I'm just
10 curious how those goals were set. Like, how was the 90 percent threshold selected? How was the
11 30 percent threshold selected?

12 Dr. Spinner: Yes, so I can have Dr. Shu speak to that.

13 Dr. Shu: Good morning. I'm Yu Shu, global biometrics at Abbott. For that, we do have different
14 performance goals. In the RCT cohort, we have a secondary endpoint of MAE. The performance
15 goal for the MAE was set as a freedom from MAE rate was set at 90 percent. It was based on the
16 literature. We have assumed rate of 4.3 percent of freedom from is based on the information that
17 we gather from MitraClip studies as COAPT. The importance of that MAE performance freedom
18 from performance goal was based on the literatures about the TV surgeries.

19 As far as your second part of a question is we also have a performance goal for a single
20 arm for the primary endpoint was set as at 30 percent. It was based on two components. It was
21 based on the KCCQ performance of at least the 10 points of improvement. We estimated it based
22 on COAPT information about 42 percent. On top of that, we have assumed a 25 percent of a
23 mortality rate at 12 months. Altogether, the performance goal was set at 30 percent.

1 Dr. Lange: Brad, does that address your questions adequately?

2 Dr. Bart: It does.

3 Dr. Lange: Great, thanks. In addition to the list that I previously put, I'm going to add Dr.

4 Zuckerman to the questions as well. But first, Jim Blankenship.

5 Dr. Blankenship: Thank you, thanks for the presentation, two questions. One is why do you

6 think that the improvement in KCCQ scores did not translate into fewer heart failure

7 hospitalizations?

8 Dr. Spinner: So, I'll have Dr. Adams speak to this.

9 Dr. Adams: We're still learning about, this is David Adams, I'm the professor and chair of heart

10 surgery at Mt. Sinai. We're still learning about heart failure hospitalization in this treatment

11 group and as I showed, we're guessing what our literature, what our expectation might be for

12 that. I'm not quite sure. I think one year was short. I think that in our expanded pool, we started

13 to see a trend toward less heart failure hospitalization, and I will turn that over to David Cohen, I

14 think, to address the relationship between heart failure hospitalization and KCCQ, or Suzanne.

15 Dr. Arnold: Hi, I'm Suzanne Arnold. I'm a general cardiologist and health services researcher at

16 University of Missouri, Kansas City, and St. Luke's. One of the things that we wanted to look at

17 was that relationship between KCCQ and heart failure hospitalization, mortality because we've

18 seen that in many other disease states, whether that's heart failure that's medically managed, or if

19 that's in other disease, other disease processes with left sided heart disease. Great. We did look at

20 this in the TRILUMINATE study. So, we looked at among patients who were treated with the

21 TriClip and we found that changes in KCCQ at one month were significantly associated with

22 reduction in the risk of subsequent death, as well as heart failure hospitalizations. So, among

23 those who were treated with TriClip, those who did improve did have a reduction in heart failure

1 hospitalization, and death, and these point estimates were actually very similar to what was seen
2 in other clinical situations and heart failure, so HFREF as well as severe aortic stenosis.

3 Dr. Spinner: Thank you. So, there's one additional piece of information I'd like to add and echo
4 to what Dr. Adams said earlier. So, we did, as he mentioned, maybe one year is really too early,
5 especially given the low rate of heart failure hospitalization events in our patient population, not
6 only at baseline, but as we saw at one year. But what I'm showing here is we look at the available
7 data we have to date through two years, so keeping in mind what I'm showing here is the TriClip
8 group, as well as the control group, and the control pure. The control pure is those patients, we've
9 censored out patients that crossed over, keeping in mind patients were allowed to cross over at
10 one year. But what this shows us here is that we can start to see some separation in the curves at
11 longer terms looking at heart failure hospitalizations. This is something we'll continue to look at
12 as more and more of our patients reach their long-term follow-up.

13 Dr. Lange: And Erin, it looks like the confidence interval will be pretty wide on that. And those
14 numbers at two years, 37 patients in one group is pretty small at this point.

15 Dr. Spinner: That's correct. Yes.

16 Dr. Lange: Jim. I'm not sure if that answers your question because I'm not sure that there is an
17 answer yet, but is there anything else you want from the sponsor regarding—

18 Dr. Blankenship: I do appreciate that additional data. Just one other question, if I may.

19 Dr. Lange: Yes, sir.

20 Dr. Blankenship: I looked at a paper by Spertus from Journal of American College of
21 Cardiology 2020 about the KCCQ, and that suggested that a five-point improvement in the
22 KCCQ score generally correlates to something like 112 meter improvement in the six-minute
23 walk test, and yet the differences in the improvements in the six-minute walk test that we see

1 here are much, much smaller, and I'm wondering, is that because this is a heterogeneous
2 population or just a very different population than has been applied in other studies of the
3 KCCQ?

4 Dr. Spinner: Yes. That's correct. That's the same belief we have, and given the variability in
5 KCCQ, so it's important to keep in mind that while we didn't show a significant difference in the
6 350-patient population, we could see the trends going in the correct direction. And then when we
7 look at the full randomized cohort, so I'll show you side by side here, we do see that same trend
8 and can appreciate a statistical difference.

9 Dr. Lange: So, Jim, I think this would be good discussion points this afternoon. We talk about
10 KCCQ and its correlation with biomarkers, walk test, and heart failure hospitalization. Thanks
11 for bringing that up. Thanks for the sponsor for showing the additional data as well.

12 Dr. Blankenship: Thank you.

13 Dr. Lange: Great. I've got Dr. Brindis, Dr. Selzman, Dr. Vidovich, Dr. Shanker, and Dr.
14 Zuckerman. Let me first, Ralph.

15 Dr. Brindis: Thanks, Ralph Brindis. My question is, of all the patients who were screened for
16 clinical appropriate referral for TriClip, how many patients are actually excluded based on
17 anatomic concerns, coaptive leaflets and so forth? In other words, what percentage of patients are
18 actually suitable for the use of TriClip who meet other criteria?

19 Dr. Spinner: Yes, so I can answer that question. So, I'll show you just here's a schematic of our
20 patient and screening failures. So, and really how the patients drop out as we go through
21 assessing them. So first is really looking at after the informed consent and this is really just due
22 to general study criteria. There's various different categories here. But really, once we get down
23 after that, it's the echo core lab and really specifically the anatomical eligibility committee that

1 really assesses the patient's anatomical compatibility with the device. And so, what you can see
2 here is we had only 175 patients out of the 1,409 patients that met that initial criteria that were
3 denied. So, if we look at the full cohort of patients that were consented, it's only eight percent of
4 patients that did not have suitable anatomy.

5 Dr. Brindis: Thanks.

6 Dr. Lange: Thank you. Dr. Selzman. Craig.

7 Dr. Selzman: Hey, Craig Selzman. Great presentation, you guys. Only so much that you can
8 cover and Richard, if I may, I have three questions.

9 Dr. Lange: Yes, sir.

10 Dr. Selzman: The first is I'm trying to understand a little bit more about the relationship between
11 the reduction in the TR and the KCCQ. At one year, it appears that about 11 percent were still in
12 the severe torrential range and about 38 percent were still moderate. So almost 50 percent were
13 moderate or worse TR. Did you look at that specific group of patients and their KCCQ scores so
14 that we have an idea if there is a relationship between the severity of the residual TR and their
15 health status? That's my first question.

16 Dr. Spinner: Since this study was really specifically based on moderate or less TR, that's really
17 where we focused. But what I can share is what we shared in the core is that we saw patients
18 where we had more reduction of TR resulting in more corresponding improvement in KCCQ.

19 Dr. Selzman: It might be really interesting to know if your results are just, you had a good result.
20 You had a good repair. And of course, they felt a little bit better, but it'd be really interesting to
21 see. Let's see here.

22 Dr. Lange: So, Craig, what I'm going to do is I'm going to ask the sponsor over the break and
23 over lunch is to provide the data you asked for.

1 Dr. Selzman: Perfect.

2 Dr. Lange: And I appreciate the fact that they've sliced it differently, but you've asked. I think it's
3 an important question is, let's show the data, the individuals that have moderate or more TR and
4 what their KCCQ scores look like compared to the other group.

5 Dr. Selzman: Yes. Thank you.

6 Dr. Lange: And we'll give you time to do that. Go ahead.

7 Dr. Selzman: Great. The other thing that might need more time to look at in deep in the five
8 million pages of packet there's some stuff related to center volumes. And I saw, and I believe
9 your colleague from Minnesota was a very active enroller to the trial. It looks like there's three or
10 four centers that put in a ton of these things, like 50 or more, and that over 90 percent of the
11 centers did less than five or ten cases. I think we need some clarity about that, especially when
12 we think about real world utilization of this device. Who's going to be able to do it? Is there a
13 learning curve? And so, it would be good actually to get rid of that three or four, maybe it's only
14 two or three centers that did more than 50 devices and look at the results of the rest of us has-
15 been that are only doing a few of them and how that and how that likes out. And again, that
16 might need some time to prepare, but maybe you already have something.

17 Dr. Spinner: I can talk about that now. So yes, you're correct. And there were approximately 37
18 percent of the primary analysis enrolled by our top five centers, so 33 percent. But what we do
19 look at when we look at whether they're top enrolling sites or sites that less frequently use the
20 device, we found consistency in their ability to bring the TR down to moderate or less. So, in
21 fact, and whether it was our top five sites or the other sites, TR reduction to moderate or less was
22 89 percent and 88 percent. And likewise, we had similar low safety findings in both, whether we

1 looked at the top sites or the low sites. So, we do believe that those the use of TriClip and its
2 effectiveness and safety can be replicated.

3 Dr. Selzman: So, if I could follow up on that, because Dr. Adams nicely references the STS
4 study the large registry study. But one of the caveats in the surgical arm is that over 90 percent of
5 the enrolling patients to that registry were at centers that did less than two tricuspid valve
6 surgeries a year. So, the way that I look at this, and the data that I may actually see is that over 40
7 of your sites, which were much more, did less than four procedures. And so, I don't know where
8 the cutoff should be. You say 33 percent of your top five, but that line can move a little bit. I
9 think it would be interesting to know on centers that did less than, and I'm arbitrarily pick
10 picking this, five procedures, how do they do?

11 Dr. Lange: And yeah, so again, over the break if the sponsor will present that data, and if you'll
12 do two things. One is look at the reduction in TR again, five sites and also how the patients did in
13 terms of their death, hospitalization, heart failure. And also, with regard to KCCQ as well, that'd
14 be great.

15 Dr. Zuckerman: Maybe I can interject. Dr. Selzman, figures 4 and 5 of the FDA question set, get
16 at what you've been asking, and would you like the sponsor to present their data in that format,
17 such that you can see the clinical events broken down by volume at site?

18 Dr. Selzman: That would be nice. I'm looking at your figures, but yeah, that would work. That
19 would work.

20 Dr. Zuckerman: Because this will be a key point of discussion after lunch.

21 Dr. Selzman: Richard—

22 Dr. Lange: Got another question. Go ahead.

1 Dr. Selzman: This is probably buried in the demographics, but I didn't see any right heart cath
2 data. There was echo data, and I'm sure you have it because pulmonary hypertension was one of
3 your exclusion things, but it would be nice to see. What the right heart catheter numbers, what
4 were the PA pressures what were the right atrial pressures? And I don't know if you did right
5 heart cath follow-up. I don't think you did. You probably used echo to try to estimate right sided
6 pressures, but you had some sophisticated imaging to look at RV volumes and TAPSE and other
7 things, but looking at the hemodynamics, I was impressed with the lack of hemodynamic data,
8 but I'm sure that you might have some of that to share with us.

9 Dr. Spinner: Yeah, so we can work to get you that. I will comment that we just use the right
10 heart cath for screening and inclusion into the trial. So we only have that at baseline, but we can
11 look to get you that after the break.

12 Dr. Selzman: Thank you.

13 Dr. Lange: That'd be great. So, Dr. Selzman is asking for three things over the break. One is for
14 those individuals, moderate or more TR, what their symptom status was. Secondly is how did the
15 sites that did five or less procedures do with regard to TR reduction and clinical events. And then
16 finally right heart cath data. Thanks. Great. I've got Dr. Vidovich, Dr. Shanker, and Dr.
17 Zuckerman.

18 Dr. Vidovich: Great. Thank you for the opportunity and I think this is also my main question that
19 we talked about, the operative volume. I would just like, since most questions were asked, I
20 would like to extend this. MitraClip has been approved prior to this and it is quite likely that sites
21 with lower volume might have had experience with MitraClip which could have translated in the
22 experience on the right side. Do we have any data on the operator volume on the MitraClip that
23 might have translated in the experience to TriClip? Again, this is a same an additional question

1 and site volume while they might have been lower experience sites or lower volume with
2 TriClip, what was their prior volume of MitraClip, which would have translated. Again, if the
3 sponsor potentially has the data, I think would be helpful for some low volume sites that might
4 adopt this.

5 Dr. Spinner: I don't have that data at this time, but we'll see if we can get that. But what I can tell
6 you is that all sites that participated in the trial did have prior MitraClip experience. So, you are
7 correct. We'll see if we can get the MitraClip experience for sites.

8 Dr. Vidovich: I appreciate that. Thank you.

9 Dr. Lange: Dr. Shanker. I've got Dr. Shanker, Zuckerman, Hauptman, Hirshfeld, and Katz.

10 Dr. Shanker: Thank you very much. And thank you for that wonderful presentation. I think Dr.
11 Selzman and Vidovich have touched on a lot of what I was going to ask regarding that operator
12 learning curve. If you look at the MAE, with the TRILUMINATE CE, it was 1.3%, but with the
13 post-market registry in the EU, it was 2.5%. Which of course does suggest that there is also a
14 safety component that has to be looked into as well and emphasizing the importance of having a
15 robust training program. So having a little bit more data on that and insight would be helpful.
16 Just that was just a little largely a point, a second question I have is as an electrophysiologist. I
17 do have to ask this.

18 Approximately five percent of patients were enrolled in the single arm cohort that had
19 CIED related tricuspid regurgitation and out of curiosity, I was wondering how did those, granted
20 it is a small sample size, how did they respond to the therapy?

21 Dr. Spinner: I don't have that broken up at this time, but I'll look to see if we can get that after
22 the break. We can comment and give you more information about our training program. I don't
23 know, Dr. Lange, if you'd like us to do that now.

1 Dr. Lange: I tell you what, let's do that after the break only so that we can get all the questions
2 in. But thanks for that offer.

3 Dr. Spinner: Okay.

4 Dr. Lange: I'll write that down. Great. Thank you. Dr Shanker, we'll address both those things
5 ask the sponsor to address those after the break if that's okay. Dr. Zuckerman.

6 Dr. Zuckerman: Yes, I have two questions. First, thank you very much for a very nice
7 presentation. When Dr. Sorajja was talking, he very quickly stated in passing, I think that
8 perhaps Dr. Arnold imputed a placebo effect for the KCCQ change of five points, and he also
9 mentioned a recent paper, if you can give more details as to what you really might perceive to be
10 the placebo effect in the KCCQ change, given that this is an unblinded trial, that would be very
11 helpful.

12 Secondly when discussing the physiological and biochemical parameters that were
13 studied in the imaging and laboratory studies the presentation really only showed the ones that
14 moved in a positive direction. After lunch, though, it would be helpful to better appreciate the
15 full spectrum of echo, CT, and lab parameters. For example, the longitudinal strain data, if I
16 remember correctly, did not show a favorable effect. The BNP NT BNP lab data are confusing,
17 so if you can give us a bigger picture of how the sub study data either hang together or don't
18 hang together. Thank you.

19 Dr. Spinner: Yes, we can do that. And if we can, I'd like to address the placebo question now.

20 Dr. Lange: Sure. Go ahead.

21 Dr. Spinner: Dr. Cohen. I'll ask Dr. Cohen to speak to that.

22 Dr. Cohen: Good morning. I'm David Cohen. I'm an interventional cardiologist at St. Francis
23 Hospital and the director of clinical research at the Cardiovascular Research Foundation here in

1 New York. Dr. Zuckerman, not surprisingly, asked a very critical question about the data here,
2 which is “What is the likely magnitude of a placebo effect? And can we provide any other
3 additional information to inform that question?” I would start by saying that in an unblinded trial
4 like this one, it is not possible to, with 100 percent certainty, exclude a placebo effect that simply
5 would require a different trial design with a sham arm, which was not done. Nonetheless, I think
6 there are three lines of reasoning that suggest fairly strongly that not all of the benefit we observe
7 is a placebo. The first is the magnitude of benefit, which was Dr. Zuckerman's specific question.
8 So, there is a literature on the magnitude of placebo effect on patient reported outcomes, and
9 these come from trials where a therapeutic placebo was compared directly to no therapy. That's
10 the only way to actually measure how much a placebo does. These are not done all that
11 commonly, but there are a number, especially in the pain literature and some other areas, and the
12 usual magnitude is about a quarter of a standard deviation on a patient-reported outcome. For the
13 KCCQ overall summary score, that would be about a five-point change. If we extrapolate, we
14 can make a reasonable assumption that about a five-point change would be expected from a
15 placebo, the magnitude of change that was observed in this study was substantially larger than
16 that at all three follow up time points.

17 The second point that's very important is the durability of the benefit. Now, this is harder
18 to provide strong science on, but we generally believe and there is some evidence to suggest that
19 placebo effects again, on patient reported outcomes wane over time. And so that is, again, a very
20 important finding and that was not seen in this trial. The benefit was sustained without
21 attenuation through the one-year follow-up period. And then if I could have slide EF131 that
22 would be the last one I want to show. Great. Let me just bring this up to make my final point.

1 And the last point is about other substantiating information. So as part of the detailed
2 quality of life analysis that Dr. Arnold and I published earlier this year in JACC we pooled data
3 from across the tri the TriClip groups, not only from the randomized trial, but from the roll-in
4 patients, and also from the single arm trial to understand the relationship specifically between the
5 change in KCCQ and the change in TR grade over follow-up. And this slide summarizes that.
6 The reason we're presenting it this way rather than as a graph is because there are three things
7 that influence the follow up KCCQ score, and we need regression approaches to handle that.

8 One is the baseline KCCQ. The second is the baseline degree of tricuspid regurgitation,
9 and then the third is the change. And so, in order to account for all of those three in a data set of
10 this size, we need to use regression models. What this shows, very convincingly, is there is a
11 strong relationship with a highly statistically significant p value and a relatively narrow
12 confidence interval on the relationship between a one grade change in tricuspid regurgitation at
13 one year follow-up and the improvement in the KCCQ score, 4.1 points for every grade
14 reduction. So, if you think about a patient who starts with torrential tricuspid regurgitation, 50
15 percent of the patients in this trial had that, and goes down by three grades, down to moderate
16 from torrential they would be expected to achieve about a 12 point improvement compared with
17 baseline in the KCCQ, which is a moderate to large improvement. Thank you.

18 Dr. Lange: Dr. Zuckerman, any additional information you'd like? Again, a great question.
19 Again, FDA will present. We'll have some time discussing. Is there anything else you'd like from
20 the sponsor at this point?

21 Dr. Zuckerman: Not right now. Thank you. Okay. In addition to Dr. Hauptman, Hirschfeld, Katz,
22 I've also got Dr. Cizik as well. Dr. Hauptman.

1 Dr. Hauptman: Yes, thanks. I want to follow up on Dr. Zuckerman's question specifically with
2 regard to the imaging sub-study. How were these patients selected? For the imaging sub study,
3 I'm a little bit concerned that such a study might be biased towards patients who were better and
4 who could tolerate participation in MR and CT studies. And so, the data look pretty favorable,
5 obviously not all parameters, but whether or not we're looking at a biased sample. And then I
6 have one follow up question.

7 Dr. Spinner: Yes, I'll have Dr. Cavalcante speak to this.

8 Dr. Cavalcante: Hi, Joao Cavalcante from Minneapolis Heart Institute. It's a pleasure to present
9 here. I'm a cardiac imager and director of the imaging core lab. that provided quantitative
10 services. That's a very crucial question and actually an opportunity of the visionary wisdom that
11 both FDA and Abbott had for the opportunity to provide objective quantitative analysis for these
12 patients. Upfront decision was actually made to deliberately include all comers. So, you would
13 think that patients that would not have defibrillators, or ICDs, or pacemakers ready for
14 defibrillation would not have been included. As a matter of fact, the baseline characteristics of
15 the patients included in the imaging sub-studies are exactly the same of the main cohort for us to
16 have that external validity. And what we can see on the imaging sub-study, first is that the
17 TriClip was capable of not only reducing TR, that was measured by quantitative analysis by
18 cardiac MRI and regurgitant fraction. But what we could see with this very precise quantitative
19 metric is that the shrinkage of the right ventricle that occurred for these patients. You can see in
20 this line of regression that the greater TR reduction that was achieved with the TriClip produced
21 a substantial reverse remodeling in that right ventricle, which was then substantiated, not only
22 this is at 30 days, but also substantiated at the one-year reverse remodeling that was achieved in
23 the TriClip, which did not occur in the group treated with the GDMT.

1 Importantly, there was also a change that was favorably seen in the pulmonary forward
2 flow for these patients. Let me just go back to this slide, which translated into shunting the blood
3 from the right atrium into the pulmonary artery that produced this pulmonary forward flow
4 increase divided by the shrinkage of the RV that produced an effective improvement of RVEF.
5 Dr. Zuckerman had asked about before the unfavorable changes of the strain. I would just
6 comment by saying that whenever we remove volume, there's going to be a decrease in the RV
7 end diastolic volume, and also an unfavorable change in the RVEF. What we computed here is
8 actually the forward flow. Because you're pushing the blood now in the right direction, you're
9 going to improve that forward flow and forward stroke volume.

10 Last slide that I would like to conclude by just showing that, so what, whatever that
11 you're showing me, show me that there is some important magnitude of that. This is the slide
12 showing the relationship between the shrinkage of the RV end diastolic volume, by the
13 improvement of KCCQ change. You can see that there are more blue dots into the top left screen,
14 which suggests that obviously not all the change in the RV reverse remodeling would translate
15 into KCCQ, but there is a very positive, favorable change.

16 Dr. Lange: Let me call you back to the podium for a second please, because the question had to
17 do with how these patients were selected. And so, if you're able to answer that, if not, we can go
18 after lunch.

19 Dr. Cavalcante: Yeah.

20 Dr. Lange: The 50 patients that were selected to be imaged. How were they selected?

21 Dr. Cavalcante: Yes. Actually, I would like to correct the number that there was more than 50
22 patients. There was about 68, if I'm not mistaken, into the randomized control trial. And there are
23 another 14 for the single arm. These patients were selected, and 10 sites across the U. S. were

1 trained. So, patients, when consented for the main parent study, they were approached, whether
2 they would be actually willing to undergo additional cardiac MRI and CT at baseline, cardiac
3 MRI and CT at one month. And then CT at one year. And actually, there was an incredible uptake
4 in volunteers, which I would like to also acknowledge, by these patients to undergo additional
5 testing. So, no upfront selection. The only exclusion criteria that we used that we thought that
6 was not ethical was if they had chronic advanced kidney disease, quite advanced, a GFR below
7 30, because subjecting them to additional contrast would not be favorable to address that
8 question. But that was the only upfront exclusion criteria.

9 Dr. Lange: So, these patients were selected. at baseline prior to knowing the results. Okay, great.
10 Does that answer your question, Dr. Hauptman?

11 Dr. Hauptman: Dr. Lange, it does. If I can ask one additional question.

12 Dr. Lange: Yes, sir.

13 Dr. Hauptman: One of the key exclusion criteria was that a pacemaker or a defibrillator leads
14 that would prevent appropriate placement of the TriClip. I wonder if I get some clarification
15 about what that actually means. And are we talking mostly about atrial leads? In these patients,
16 what would have taken someone out of enrollment or randomization based on the lead?

17 Dr. Spinner: Yeah, so this was a criteria that was assessed by our anatomical eligibility
18 committee, and typically the patients that were not included due to pacemaker interaction was if
19 the leaflet was pinned or it was in the location that they would want to place the clip and they
20 wouldn't be able to achieve any TR reduction due to the lead, but in fact, you can see that we
21 randomized about 15 percent of patients and to the RCT cohort that had leads and about 30
22 percent of patients into the single arm that had leads, so we did include quite a few patients with
23 RV leads.

1 Dr. Lange: Dr. Hauptman, does that address your question?

2 Dr. Hauptman: Yes, thank you.

3 Dr. Lange: Great. I've got Dr. Hirshfeld, Dr. Katz, and Dr. Cizik that will probably take us into
4 our break. Let's see. Dr. Hirschfeld, thanks for your patience, by the way, John.

5 Dr. Hirshfeld: The whole focus of this presentation has been on TR reduction, but I think it's
6 worth at least raising the question as to what degree the device is swapping TR for TS. I noticed
7 that, for example, that the mean diastolic gradient in the device patients actually went up after the
8 TR was reduced by the clip. And also, I noticed that their mean number of clips is 2.2. So, I
9 wonder if you could provide for us more definite data about diastolic function in these patients,
10 particularly, what the overall diastolic gradients were and not just changes from baseline, but
11 what the diastolic gradients are once the patient has been treated. And similarly, what the
12 pressure half times are.

13 Dr. Spinner: Yes. We can provide that now if you'd like.

14 Dr. Lange: Go ahead.

15 Dr. Spinner: Yes, Dr. Sorajja, can you please speak to this?

16 Dr. Sorajja: Yes Paul Sorajja, Interventional Cardiologist at Minneapolis Heart, and in terms of
17 the risk of stenosis, it certainly is a balance between trying to reduce TR as well as to avoid
18 creating iatrogenic severe stenosis. We would expect some gradient to occur as noted by the
19 person who has a question. But what we saw is that even in patients who had higher gradients
20 than we had desired, there were nine patients who had gradients of five or more. Among those,
21 the gradients were never more than seven. They're between five and seven. And in fact, among
22 those nine patients with gradients at that level, all were NYHA class one or two. And the final
23 KCCQ OS was actually 81 points. So, the quality of life is actually significantly improved and

1 they're alive and well. And while certainly it's important as a proceduralist to weigh stenosis
2 versus regurgitation, we did not see any evidence or need for procedures or concern with regards
3 to stenosis that could have been created.

4 Dr. Lange: John, would you like additional information or does that adequately address your
5 question?

6 Dr. Hirshfeld: I think it's an opportunity, at least to find out what this device actually does in
7 terms of what happens to the pressure half times and what happens to the diastolic gradients
8 altogether. Because one would expect that if you reduce by as much as they are reporting, there
9 should be reductions in diastolic gradients, and we're not seeing that.

10 Dr. Lange: Right. And so, if over the break if the sponsor can present that data, that is diastolic
11 pressure, gradients pressure half times. And what I would say is changes in RA pressure as well
12 between at baseline and at after treatment. Alright. I've got Dr. Katz, Dr. Cizik, and then Dr.
13 Vidovich. Dr. Katz.

14 Dr. Katz: Given the success of the MitraClip and its broad utilization and especially the COAPT
15 data, I would assume that there should be technical expertise in utilization of device amongst the
16 centers in the study but in that brief view we had of the screen fail slide, it looked like 54 percent
17 of the enrolled consented patients failed screening and I wonder what percent of that was due to
18 visualization problems. My fear is that visualization of the tricuspid valve is much more difficult
19 echocardiographically than the mitral. And my fear is once in the wild, without a core lab saying,
20 "no, this is not an anatomically correct patient," that the results might fall way off. So again, the
21 question is what percent of the screen failures were due to poor echo visualization of the
22 tricuspid.

1 Dr. Spinner: So, I can reshow that slide if that's helpful, but we didn't specifically call out
2 denials for imaging. So, we do provide a robust imaging training. We did for the sites as well as
3 we will commercially to help them identify not only the valve but assess TR severity. So, it's
4 very low and in cases where the anatomical committee could not adequately assess the valve
5 based on imaging, the patients were asked to undergo additional echoes. And then at that time
6 where we presented it and typically could be assessed.

7 Dr. Hirshfeld: Thank you. Dr. Cizik.

8 Dr. Cizik: Yes, Amy Cizik. Thank you so much for your presentation. I have a question about
9 the in terms of what we are seeing with the discrepancy in the six-minute walk with the KCCQ
10 being a multidomain covering physical function, social function, symptom. Have correlation
11 studies been done in the past or through this trial to look at just how much that it correlates with,
12 say, a physical objective measurement, such as the six-minute walk? I think that data would be
13 interesting and helpful to see. Again, looking at your slide 58 and just seeing there seems to be
14 more favor in terms of social and quality of life domains and not necessarily a correlative
15 example with the physical function. So, I don't know if that's data you can provide, or if there's
16 existing literature in that space.

17 Dr. Spinner: Yes, I can have Dr. Arnold speak to this.

18 Dr. Arnold: Thank you. I'm Suzanne Arnold. I also would like to reference the question from
19 earlier about the Spertus et al paper showing the correlation between the 6-minute walk and the
20 KCCQ and just to direct that study that looked between those two was actually an exercise study.
21 So, it was a rehab type study. So, you would expect to see a larger change in six minute walk for
22 the same degree of KCCQ change. We actually looked at this in COAPT. So, this is a similar
23 related type of patient group who are older and have more comorbidities. This was published by

1 Sneha et al. in Circ Heart Failure. And this, we saw that a five-point change was around a 25-
2 meter improvement in six-meter walk. So, it's much smaller than what was seen in the Spertus et
3 al paper. And the one thing I also would like to note is that yes, we did see larger improvements
4 in the social limitations and quality of life domains. But those social limitations domains
5 questions are really about very specific activities. So, it's how much does your heart failure affect
6 your ability to do hobbies or work or do chores? So, it's not just about how does the patient feel
7 from a mental health perspective, but it's actually asking about very specific activities that the
8 patient's able to do.

9 Dr. Spinner: And we do have some data that I'd like to show. We did do a comparison looking at
10 patients that had improvements in KCCQ as well as what their corresponding six-minute walk is.
11 I'm asking the team to pull that data up now just to echo what Dr. Arnold said. Yes, it's been
12 reported in other studies, but we can show it in our own data as well. So, what you can see here
13 is in those patients that had KCCQ change greater than or 15 points whether it was device or
14 control, we were able to see improvement in their six-minute walk distance.

15 Dr. Lange: Great. And Amy, in the sponsors' executive summary table 7-8, I think, addresses
16 part of your question about the different domains, how they change. And so, I'll ask the sponsor
17 to put it up after the break so that you can take a look at it if you want to discuss that. Okay.

18 Dr. Cizik: I think that was the same table I was referencing. I saw that.

19 Dr. Lange: We'll ask the sponsor to put it up so you can talk about it. I've got one last question.

20 Dr. Vidovich.

21 Dr. Vidovich: Thank you for the opportunity. I'll be brief. This is a follow-up to the question that
22 some of the panelists have raised about the safety. Do you have any data, after the clip was
23 implanted, on the utilization of right heart catheterization or pacemaker placement in addition to

1 the mitral stenosis question that was raised? Did this impact the ability to perform right heart
2 cath or safely place RV leads for pacemaker placement? This might arise once this is approved in
3 a post-marketing surveillance.

4 Dr. Spinner: So, I can't comment directly on the right heart cath as that wasn't a requirement as
5 part of the study, but what I can tell you is we did in fact have 3.4 percent, five patients in the
6 device group that had a TriClip placed that did go on to have a pacemaker successfully placed.
7 Low incidence of pacemaker, but in those that needed it, they were able to receive it.

8 Dr. Vidovich: Thank you.

9 Dr. Lange: So, sponsor, just to recap, by the way, thanks again for the excellent presentation and
10 for addressing the questions. But over the break, you all will again look at Dr. Selzman's
11 question about moderate and more severe TR and the outcomes, we'll look at sites that did less
12 than five studies, the outcomes and the clinical—

13 Dr. Spinner: Dr. Lange, for the first one, we just wanted some clarification on what groups we're
14 being asked to compare. Did you say, was it moderate and greater and then those with—

15 Dr. Lange: And those with less.

16 Dr. Spinner: Okay, thank you.

17 Dr. Lange: Dr. Shanker asked about more training program information, which you'll provide.
18 And also, if there's any information about how the people with TR due to devices, how did they
19 respond. Dr. Zuckerman asked just to look at the data, sub-study data in totality. That's those it's
20 favorable. Those that's not — so we can discuss a little bit about that. If you have any
21 information about the low volume centers and how active they were in terms of their MitraClip
22 experience, and then Dr. Hirshfeld asked about the information regarding the diastolic gradient,
23 pressure halftime, and atrial pressures in the control group and those treated. I think I've

1 summarized all of the questions that were asked that weren't already answered. Questions from
2 any of the sponsors, do you understand what the panelists have asked for?

3 Dr. Spinner: Yes, thank you. Thank you. All right. No other questions at this point again.

4 Dr. Lange: I want to thank the sponsor for their presentation and for answering the questions.

5 Let's take a 15-minute break. The panelists that are here, Jim will put up a timer. And so that
6 should, we should reconvene at a 9:25 mountain time or 11:25 Eastern time and anywhere in

7 between, or to the West of me. All right. Thank you very much. 15-minute break. I'll ask

8 panelists not to discuss any of the questions or not to communicate with anybody about this, and

9 I'll ask you to turn your video off, your volume off, and come back in 15 minutes. Thank you.

10 Dr. Lange: The FDA will now give their presentation. Again, I'd like to remind the public

11 observers at this meeting that while the meeting is open for public observation, public attendees

12 may not participate except at the specific request of the panel chair, the FDA will have 90

13 minutes to present and FDA, you may now begin your presentation.

14 FDA Presentation

15 Ms. Naber: Good morning, everyone. This is FDA's presentation regarding Abbott medicals pre-

16 market approval or PMA application for the TriClip G4 system. My name is Megan Naber. I'm

17 an engineer and the lead reviewer for this PMA. You will hear from a few members of the review

18 team during this presentation, but we appreciate the contributions of the entire FDA review team

19 that has worked on this PMA.

20 This is the outline of FDA's presentation. I'll start by providing a summary of relevant

21 clinical, regulatory, and device background information. Tricuspid regurgitation, or TR, occurs

22 when valve leaflets fail to close completely during systole, which results in the regurgitation of

23 blood from the right ventricle into the right atrium.

1 TR can be divided into three etiologies. Primary TR, also called degenerative, organic, or
2 structural TR, is caused by an anatomical abnormality of the tricuspid valve apparatus.
3 Secondary TR, also called functional or non-structural TR, is caused by tricuspid annular dilation
4 secondary to other conditions such as right atrial or right ventricular enlargement. Secondary TR
5 is the most common etiology and occurs in approximately 80% of cases. Cardiac Implantable
6 Electronic Device, or CIED, induced TR is caused by the interaction of a CIED lead with the
7 valve leaflets.

8 Transthoracic echocardiography, or TTE, is the primary imaging modality used to
9 diagnose TR and assess its severity. The American Society of Echocardiography provides
10 parameters for grading chronic TR as mild, moderate, or severe using qualitative, semi
11 quantitative, and quantitative elements. To better characterize TR severity in patients treated with
12 transcatheter devices, a modified grading scale which further divides severe TR into severe TR,
13 or grade 3, massive TR, or grade 4, and torrential TR, or grade 5, was proposed in the 2017
14 publication referenced here.

15 This five-grade scale, with additional diagnostic variables as shown in this table, was
16 used in the TRILUMINATE Pivotal trial. TR is associated with signs and symptoms including
17 ascites, peripheral edema, liver dysfunction, decreased appetite, jugular vein distention,
18 abdominal fullness, and fatigue. Unfortunately, symptoms may not be seen until TR is
19 significant. By the time symptoms are evident, patients may be at high risk for cardiac surgery
20 due to comorbidities or age. Survival rates are significantly lower in patients with severe or
21 moderate TR compared to patients with mild or no TR. In the Kaplan Meier survival curve
22 shown on the right, which is from a 2004 study of over 5,000 patients, the one-year survival rate

1 was 91.7% for patients with no TR and 90.3% for patients with mild TR. However, for patients
2 with moderate TR and severe TR, the 1-year survival rates are 78.9% and 63.9%, respectively.

3 The current treatment options for TR are medical therapy and tricuspid valve surgery.
4 Medical therapy mainly consists of diuretics to manage volume overload, but it is often
5 ineffective in alleviating symptoms, preventing hospitalization, or reducing morbidity and
6 mortality, especially if the patient develops diuretic resistance.

7 TV surgery can be more effective than medical therapy, but the majority of TV surgeries
8 are performed in conjunction with other cardiac procedures. The frequency of isolated TV
9 surgeries has increased, but it is still only performed in about 15% of patients due to high
10 operative mortality rates. Most patients with moderate or severe TR are not offered TV surgery.
11 There is therefore an unmet need for an effective treatment option for patients who are refractory
12 to medical therapy but are not offered surgery.

13 The TriClip G4 system was designed to address this unmet need. The device is intended
14 to reduce TR through tissue approximation using a minimally invasive transcatheter procedure. It
15 has the same form and function as the commercial MitraClip system, which is used to treat mitral
16 regurgitation, except that the delivery system was modified for access to the tricuspid valve via a
17 25 French catheter shaft.

18 The components of the TriClip G4 system are shown on this slide. The first generation
19 TriClip system was also used in the TRILUMINATE Pivotal trial. The G4 system has two
20 additional clip sizes and several updated features compared to the first generation TriClip system,
21 but the clip designs are similar. The sponsor has requested the following indications for use
22 statement. The TriClip G4 system is indicated for the improvement of health status in patients
23 with symptomatic severe tricuspid regurgitation, despite being treated optimally with medical

1 therapy, who are at intermediate or greater risk for surgery, and in whom tricuspid valve edge to
2 edge repair is appropriate as determined by a heart team.

3 The panel will be asked to comment on the proposed indications for use, particularly on the
4 phrases “improvement of health status” and “as determined by a heart team.” The TriClip G4
5 system has undergone the non-clinical testing listed here. The non-clinical testing of the TriClip
6 G4 system is complete and acceptable.

7 TriClip was first studied in the U.S. under the TRILUMINATE Early Feasibility Study,
8 which was approved in June of 2017. Transition to the TRILUMINATE Pivotal Study was
9 approved in June of 2019. The device received Breakthrough Device Designation in November
10 of 2020. Finally, a Continued Access Study, or CAS, was initiated in August of 2022. After
11 enrollment in the TRILUMINATE Pivotal Study was completed, the CAS was most recently
12 expanded in September of 2023 with a limit of 450 patients and 70 U.S. sites.

13 I would like to provide an overview of FDA’s Breakthrough Devices Program. Per the FDA
14 guidance, a breakthrough device has the potential to provide more effective treatment or
15 diagnosis of a life threatening or irreversibly debilitating disease versus current available options.
16 The program is intended to provide patients with timely access to select devices by expediting
17 their development, assessment, and review. TriClip received Breakthrough Device Designation
18 for patients with severe symptomatic TR despite OMT.

19 A Breakthrough Device Designation allows for increased review team support, enhanced,
20 timely interactions with FDA, efficient and flexible clinical study designs, balanced pre and post
21 market data collection, and priority review of submissions. It is important to note that the
22 Breakthrough Devices Program does not alter or reduce the statutory requirement for premarket

1 approval. The totality of data must still provide a reasonable assurance of safety and
2 effectiveness.

3 For breakthrough devices, FDA may be willing to accept greater uncertainty for a
4 premarket submission along with timely post market data collection if the uncertainty in the
5 benefit risk profile can be balanced by other factors, including the probable benefit to patients
6 from earlier access to the device versus the probable risk of harm should additional data reveal
7 the device to be ineffective or unsafe.

8 The TRILUMINATE Pivotal Trial Primary Endpoint included change in the Kansas City
9 Cardiomyopathy Questionnaire Score, or KCCQ score. This score is considered a patient
10 reported outcome, or PRO. The 2009 FDA Guidance Document regarding patient reported
11 outcomes defines a PRO as a status report of a patient's health condition that comes directly from
12 the patient without interpretation of the patient's response by a clinician or anybody else.

13 PROs can be used to measure the effect of a medical intervention in a clinical trial, either
14 in absolute terms or as a change from a previous score. When reviewing PROs, FDA considers
15 the reliability and validity of the PRO instruments, as well as their ability to detect changes. FDA
16 believes that data captured by reliable PRO instruments in well-designed clinical studies can be
17 used to support product labeling claims if the claim is consistent with the instrument's
18 measurement capability. Partnering with patients is a CDRH strategic priority, and as part of this
19 commitment, the Center has encouraged increased use of PROs in regulatory decision making.

20 The KCCQ is a self-administered PRO instrument for measuring health status in heart
21 failure patients. It includes 23 items across seven domains. The Medical Device Development
22 Tools, or MDDT program, was launched in 2017 for the FDA to qualify tools that medical device
23 manufacturers can choose to use in the development and evaluation of medical devices. In 2020,

1 the KCCQ was qualified as part of the MDDT program. as a clinical outcome assessment PRO
2 instrument for adults with symptomatic heart failure.

3 While the KCCQ was originally validated for left sided heart failure, FDA agreed with its
4 use in the TRILUMINATE study based on the similarity of right and left sided heart failure
5 symptoms. The 2009 FDA guidance on PROs states that the effect of intentional unblinding is
6 important to consider in interpreting clinical trial results and acknowledges that in certain
7 situations, blinding is not feasible.

8 The TRILUMINATE trial was an open label or unblinded trial. In open label trials, it is
9 believed that PROs may be subject to bias or placebo effect because a patient's knowledge of
10 treatment assignment could impact their symptom perception and symptom severity grading.
11 Additionally, there is limited research available with no definitive conclusions regarding bias and
12 the potential magnitude of bias in open label studies.

13 There are several ways to address potential PRO bias in trials where blinding is not
14 possible. One potential strategy is to administer the PRO instrument prior to randomization and
15 retest post randomization but before the investigational intervention is performed. When
16 interpreting PRO data, several methods can be used to evaluate the degree of the placebo effect.
17 One method is to compare PRO outcomes from similar trials that differ in their design, such as a
18 blinded and an open label trial. Another consideration is that placebo effects are expected to
19 wane over time, so more durable treatment benefits are less likely to be due to placebo effect.
20 Finally, PRO responses that are closely related to the device's mechanism of action may be more
21 relevant than responses that are less closely related.

22 I will now provide a brief overview of the TRILUMINATE Pivotal Trial design. The
23 TRILUMINATE Pivotal Trial was a prospective, open label, multi center, randomized, controlled

1 clinical trial designed to test the superiority of TriClip plus optimal medical therapy, or OMT, to
2 OMT alone. The study enrolled patients with symptomatic, severe tricuspid regurgitation who
3 were at intermediate or greater risk for surgery. The randomized cohort had an adaptive design.
4 There were 350 patients in the primary analysis cohort and 572 patients in the full randomized
5 cohort. The TRILUMINATE trial also included a single arm cohort, which was intended to show
6 that any reduction in TR provides health status benefit, even if TR severity was not reduced to
7 moderate or less.

8 Patients were assigned to the single arm cohort if they were determined by the eligibility
9 committee to have a high likelihood of achieving at least one grade of TR reduction, but a low
10 likelihood of achieving moderate or less TR. Single arm cohort patients met the same eligibility
11 criteria as the randomized cohort. Patients were assigned to a cohort after meeting eligibility
12 criteria and completing a baseline visit. Patients who were assigned to the randomized cohort
13 were then randomized one to one to either the device group, which would be treated with TriClip
14 and OMT, or the control group, which would be treated with OMT alone.

15 All TRILUMINATE patients had to have symptomatic severe TR; be NYHA functional
16 class 2 or 3, or ambulatory class 4; be adequately treated with optimal medical therapy for TR
17 and medical or device therapy for other cardiac conditions; be at intermediate or greater risk for
18 TV surgery; and be a candidate for femoral vein access with the 25-inch catheter.

19 Patients were excluded if they had severe pulmonary hypertension, if they needed other
20 valve interventions in the past 60 days, or if they had a prior TV procedure or pacemaker lead
21 that would interfere with TriClip placement. Patients were also excluded if they had a left
22 ventricular ejection fraction of less than 20%, or tricuspid anatomy, which would preclude
23 treatment with TriClip.

1 I will now turn FDA's presentation over to Dr. Xuan Ye, who will discuss the statistical analysis.

2 Dr. Xuan Ye: Good morning. My name is Xuan Ye. I'm the statistical reviewer for the
3 TriClip G4 system PMA submission. I will discuss the clinical data sources and the related
4 statistical methods. I will first present the study design and analysis methods for the randomized
5 cohort.

6 For this cohort, the primary endpoint was a hierarchical composite, assessed at 12 months
7 consisting of three components based on the clinical importance. First, time to all cause death or
8 tricuspid valve surgery. Second, number of heart failure hospitalizations. And the third, the
9 incidence of an improved KCGQ score by at least 15 points versus baseline.

10 The null hypothesis was that none of the components are different between the TriClip and the
11 control group. The alternative hypothesis was that at least one component is different between
12 treatment groups. The hypothesis was tested using the Finkelstein-Schoenfeld method. Trial
13 success would be declared if the primary endpoint for the randomized cohort was met.

14 An adaptive design was pre specified for the randomized cohort with an originally
15 planned minimum sample size of 350. When the first 150 patients completed 12 months follow
16 up, an interim analysis was to be conducted to reestimate the sample size, which could be
17 increased up to the maximum sample size of 1,000 patients.

18 The Type I error rate would be controlled using the Cui, Hung, Wang method. As it
19 turned out, at the time of the internal analysis, when 150 patients completed a 12 month follow
20 up, 572 patients were already randomized due to the fast study enrollment. No sample size
21 increase was needed based on the conditional power evaluation.

22 Hence, the primary analysis cohort consists of the first 350 randomized patients.
23 Additionally, an analysis that includes all 572 available randomized patients are also presented.

1 This slide presents an overview of the Finkelstein-Schoenfeld test method, which is a
2 nonparametric test based on a hierarchical pairwise comparison; that is, a modification of the
3 generalized Wilcoxon test. In this approach, each patient is compared to every other patient. In
4 each pair, two patients are compared with respect to prespecified hierarchical components in
5 sequence. The patient who has the better outcome is assigned a score of positive one, while the
6 other patient is assigned a score of minus one.
7 If it is not possible to determine which patient has the better outcome, a score of zero is assigned
8 to both patients. When deriving a test statistic, the numerator of the test statistic is the sum of
9 positive one, minus one, and the zeros of all device group patients. Hypotheses are tested at a
10 two-sided alpha equals 0.5.

11 This diagram shows all pairs involving a specific device group patient i right in the
12 middle. This patient is compared to every patient in the control group labeled 1 through n_c . In
13 addition, this patient is compared to other patients in the same device group labeled one through
14 n_i . A score of positive one, negative one or zero is assigned to the patient for each pair
15 comparison. The score for each patient within a pair is determined based on hierarchical criteria
16 shown in this flow chart. The patient first observed with better outcome in the order of the
17 hierarchy is assigned positive one and the other assigned minus one. If neither is observed to
18 have a better outcome then both are assigned zero.

19 First, we compare the time to all cause death or tricuspid valve surgery between the two
20 patients. The patient with longer time to event is assigned a score of positive one, and the other
21 patient is assigned minus one. If the time to event is the same between the two patients, or if it's
22 indeterminable due to censoring, we move down the hierarchy to compare the number of heart
23 failure hospitalizations.

1 The patient with fewer heart failure hospitalizations is assigned a score of positive one
2 and the other assigned minus one. If it is indeterminable, we compare KCCQ improvement from
3 the baseline. The patient achieves 15 points or more in KCCQ improvement is assigned a score
4 of positive one. If the other patient does not achieve 15-point improvement. In this case, the
5 other patient is assigned a minus one. If positive one or minus one cannot be determined. A score
6 of zero is assigned to both patients. After we assign a score of positive 1, minus 1, or 0, for all
7 pairs being compared, the scores for every patient are summed. For the i -th device group patient,
8 such a sum is U_i , then we sum up these U scores from all device group patients. This summation
9 denoted as T is the numerator of the Finkelstein-Schoenfeld test statistic. The denominator is the
10 standard deviation of the score T . There's a close form formula to estimate the standard deviation
11 utilizing all U_i s. Under the non-hypothesis condition, Finkelstein-Schoenfeld test statistic
12 follows a standard normal distribution.

13 Besides the primary analysis method, Finkelstein Schoenfeld test, win ratio analysis is
14 also performed as supplementary. The purpose is to provide an estimate of the odds that a better
15 outcome occurs in a treatment group patient. In this analysis, each device group patient is
16 compared to every control group patient in the order of hierarchical endpoint criteria. The patient
17 with the better outcome is the winner. If it is not possible to determine a winner, a tie is declared,
18 and the result is not counted in the win ratio calculation. The win ratio calculation is the total
19 number of wins in device group divided by the total number of wins in control group.

20 This diagram shows the pairs to be compared in a win ratio analysis for one device group
21 patient. Each device group patient is compared to each control group patient. A winner or a tie
22 will be determined for each pair. The algorithm to determine win and tie is shown in this
23 flowchart for each pair that consists of one patient in the device group and one in a control

1 group. This is similar to the flowchart for the Finkelstein-Schoenfeld method. The difference is
2 that in the win loss analysis, one assigns a device win, a control win, or a tie instead of assigning
3 a score of positive 1, minus 1, or 0 in Finkelstein-Schoenfeld method.

4 After determining a winner or a tie for all device control patient pairs, the total number of
5 device wins and number of control wins can be obtained. The win ratio is the ratio of the two.

6 The confidence interval of win ratio can be estimated using the bootstrap method.

7 Next, I'll present a study design and analysis methods for the single arm cohort trial. This trial is
8 a prospective multicenter trial of patients treated with TriClip plus optimal medical therapy. The
9 primary endpoint is survival at 12 months and the KCCQ score improvement by at least 10
10 points at the 12 months versus baseline. The null hypothesis was that the proportion of patients
11 who meet the endpoint criteria is less than the performance goal of 30%.

12 This proportion is denoted by $P(12M)$ on the slide. The group sequential design was pre-
13 specified for the single arm cohort trial. The pre-specified statistical analysis was the exact test
14 for binomial distribution with a one-sided alpha equal to 0.025. An interim analysis was to be
15 conducted when the first 100 enrolled patients completed 12 months follow up and the study's
16 success could be claimed if the test was successful. Half of the alpha would be spent at the
17 interim analysis. If the test was not successful, the sample size for the final analysis would be
18 200. As it turned out, the hypothesis test was successful at interim with a sample size of 100.

19 That concludes my presentation. I will now give the podium to Dr. Moscucci.

20 Dr. Moscucci: Good morning. My name is Mauro Moscucci. I'm an interventional cardiologist
21 and a medical officer in the FDA Office of Cardiovascular devices. I will be discussing the
22 clinical study results. To be selected for the study, patients had to have symptomatic severe

1 tricuspid regurgitation and be at intermediate or greater risk of mortality and morbidity with
2 tricuspid valve surgery.

3 Initial screening was followed by confirmation of severe tricuspid regurgitation by the
4 echocardiography core lab and then by eligibility committee confirmation of anatomic suitability
5 for TriClip implantation and appropriate treatment with optimal medical therapy; 2,170 patients
6 provided informed consent and a total of 936 patients were approved by the eligibility committee
7 and enrolled between August 21st, 2019 and June 29th, 2022 at 75 sites in the United States,
8 Canada, and Europe. Of these, 901 patients approved by the Eligibility Committee were
9 randomized or had an attempted procedure, including 141 patients in the Roll-in cohort, 572
10 patients in the randomized cohort, and 188 patients in the single arm cohort.

11 As planned, the primary endpoint analysis was performed on the first 350 patients in the
12 randomized cohort, and the first 100 patients with an attempted procedure in the single arm
13 cohort. The primary analysis population included 296 patients enrolled in the United States, 38
14 patients enrolled in Canada, and 16 patients enrolled in Europe. In the primary analysis cohort,
15 175 patients were randomized to the device, and 175 patients were randomized to control.
16 Among patients randomized to the device, three patients withdrew consent prior to the
17 procedure.

18 One patient withdrew consent, and one patient died before the 30-day visit. Between 30
19 days and one year follow-up , there were 15 deaths, and three patients withdrew consent. In the
20 control group, there was one death prior to the treatment visit, one consent withdrawal and one
21 death before the 30 days visit, and eight consent withdrawals and 12 deaths before the one-year
22 follow-up visit.

1 Regarding study blinding, study patients, investigators, sonographers, and members of
2 the clinical event committee were unblinded to treatment groups, while research staff
3 administering the KCCQ six-minute walk test, SF-36, and New York Heart Association
4 Functional Class Assessment were blinded. However, maintenance of blinding among research
5 staff and study patients' awareness of follow up echo results were not assessed.
6 The average age in the randomized device control and single arm cohort was respectively 78, 77.
7 8, and 80.4 years; 53 to 56% of patients were women and more than 80% were Caucasian. With
8 regard to ethnicity, more than 90% of patients were non-Hispanic or Latino. Of note,
9 identification of ethnicity was declined or unknown for up to 7.4% of patients. Atrial fibrillation
10 was the most prevalent comorbidity, affecting up to 93% of patients; 35% of single arm cohort
11 patients had undergone cardiac resynchronization therapy, had an implantable cardioverter
12 defibrillator, or a pacemaker when compared with 16% and 13.7% of device and control patients,
13 respectively, in the randomized cohort.

14 The patient population had multiple comorbidities, including but not limited to liver
15 disease, renal disease, peripheral vascular disease, and prior aortic valve or mitral valve
16 interventions. The average KCCQ score ranged from 54 to 56 among the three groups, while the
17 average six-minute walk distance ranged from 236 meters to 253 meters. Up to 44% of patients
18 were classified as New York Heart Association functional class two.
19 As expected, virtually all patients had at least severe grade 3 tricuspid regurgitation, which was
20 further classified as torrential or grade 5 in more than 50% of patients. Functional tricuspid
21 regurgitation was present in 94.8% of patients in the device group and 92.9% of patients in the
22 control group; 5.1% of patients in the single arm cohort had pacemaker related or trans tricuspid
23 lead related tricuspid regurgitation. On average, 2.2 TriClip devices were implanted per patient,

1 both in the randomized and single arm cohorts. Three clips were implanted in 24% of
2 randomized cohort patients and in 35% of single arm cohort patients. The average total
3 procedure time was about 150 minutes.

4 The TriClip was successfully implanted in 170 of 172 randomized cohort patients with an
5 attempted procedure. Technical success was achieved in 98.8% of TRICLIP patients, device
6 success in 88.9%, and procedure success in 87% of patients. Through 30 days in the attempted
7 TRICLIP procedure population, there were one death and two cases of new onset renal failure.
8 There were no cases of endocarditis or of non-elective cardiovascular surgery for TRICLIP
9 device related adverse events post the index procedure.

10 Shown in this slide are selected adverse events through 12 months adjudicated by the
11 Clinical Event Committee. Rates of all-cause mortality, cardiovascular mortality, heart failure
12 hospitalization, as well as major bleeding and new onset renal failure were numerically higher in
13 the device group compared with the control group. As shown in the table on the right, there were
14 no cases of endocarditis, myocardial infarction, cardiogenic shock, or unplanned surgery for
15 TriClip complications.

16 The randomized cohort primary endpoint analysis results are shown in this slide. The
17 Finkelstein-Schoenfeld test statistic result was 2.16 with a two-sided p value of 0.0311, which
18 is less than the pre specified two-sided significance level of 0.05. The primary endpoint was met,
19 indicating the TriClip group was superior to the control group.

20 Shown in this slide are the win ratio supplemental analysis results. The win ratio is a useful
21 method for analyzing composite endpoints. It recognizes that outcomes differ in clinical
22 importance and places them in a hierarchy. In the current study, death or tricuspid valve surgery
23 are at the highest hierarchical level. Next comes heart failure hospitalizations, followed by

1 KCCQ score. Every patient in the device group is compared with every patient in the control
2 group.

3 Starting with death or tricuspid valve surgery, the device treatment and control patients
4 are labeled winners or losers, depending on who had a death or tricuspid valve surgery first. If
5 neither died or had tricuspid valve surgery, The pairs are labeled as ties, and the analysis moves
6 down to the next outcome in the hierarchy, which in this case is the number of heart failure
7 hospitalizations.

8 The ratio of the total number of wins in the device group divided by the total number of
9 wins in the control group is calculated. The win ratio point estimate of the TriClip group versus
10 the control group for the hierarchical composite end point of death or tricuspid valve surgery,
11 number of our failure hospitalizations, and a greater or equal 15-point KCCQ improvement was
12 1.44 with a 95% confidence interval of 1.03 to 2.08 in favor of the device group, which was
13 driven by improvements in KCCQ scores. There were slightly more wins in the TriClip group
14 versus the control group for all cause death and tricuspid valve surgery, but more wins for
15 number of heart failure hospitalization in the control group.

16 This slide shows a histogram of patient enrollment at clinical sites for the randomized
17 cohort intention to treat population. Among the 65 sites, 42 sites enrolled less than 5 patients, 14
18 sites enrolled 5 to 9 patients, 9 sites enrolled 10 or more patients, and 1 site enrolled 51 patients.
19 Because of the variability in enrollment volume across participating sites, post hoc analyses were
20 performed to evaluate the primary endpoint outcomes as a function of site enrollment variability
21 for the following groups: sites with less than 10 enrolled patients and sites with 10 or more
22 enrolled patients. The win ratio of the primary endpoint for sites that enrolled 10 or more patients
23 was more than two-fold higher than the win ratio for sites that enrolled less than 10 patients. This

1 difference was driven by higher death or tricuspid valve surgery rates, higher heart failure
2 hospitalization rates, and lower rates of KCCQ scores improvements in the lower enrollment
3 volume group. Similar results were obtained when different cutoffs were used to evaluate low
4 enrollment versus high enrollment volume size, such as, for example, less than five patients per
5 site versus five or more patients per site.

6 Shown in this slide are the powered secondary endpoints in the primary analysis
7 randomized cohort. For the secondary endpoints of freedom from major adverse events at 30
8 days post procedure, change in KCCQ score at 12 months versus baseline, and TR reduction to
9 moderate or less at 30 days, the endpoint was met. However, for the six-minutes walk distance
10 versus baseline at 12 months, the endpoint was not met.

11 As shown in this survival curve, freedom from all-cause mortality or tricuspid valve
12 surgery through 12 months was comparable between the device and control groups. The survival
13 curve shown in this slide illustrates freedom from heart failure hospitalization through 12
14 months, which was numerically higher in the control group when compared with the device
15 group.

16 Turning now to the KCCQ score improvement in the TriClip group, which as you recall,
17 drove the win ratio result, the left panel with device in blue and control in red shows the higher
18 proportion of TriClip patients with greater or equal 15 points KCCQ scores improvement versus
19 the control group. In addition, the right panel shows a median improvement from baseline in
20 KCCQ scores of 14.8 in the device group and 3.1 in the control group.

21 This slide shows the cumulative distribution function of KCCQ score changes at 12
22 months from baseline. This type of function illustrates the proportion of patients who experience
23 different KCCQ score change levels in each treatment group or, as an alternative, the proportion

1 of patients who experience the same level of KCCQ score change. The device is shown in blue
2 and control in red. For example, the proportion of patients experiencing a KCCQ improvement
3 greater or equal to 15 was 49.7% in the TriClip group and 26.4% in the control group. A greater
4 proportion of patients experiencing a specific KCCQ score improvement was observed
5 consistently in the TriClip group compared with the control group.

6 Of note, the KCCQ includes four different domains: physical limitations, total symptoms,
7 quality of life, and social limitations domains. As shown in this slide, the differences between
8 TriClip and control were less pronounced in the domains more proximal to TR reduction, the
9 physical limitation and total symptom domain, compared to the more general health status
10 domains, the quality of life, and the social limitation domain.

11 Shown in this slide are KCCQ scores at baseline, 30 days, 6 months, and 12 months for device in
12 blue and control in red. KCCQ scores improvements in favor of the TriClip group observed at
13 one month, were sustained at six months, and at one year. Shown here are the data on TR
14 severity changes during follow up.

15 In the device group, the proportion of patients with greater than moderate TR was 97% at
16 baseline, and it decreased to 13% at 30 days and 12% at 12 months. In the control group, TR
17 severity was greater than moderate in 99% of patients at baseline and remained greater than
18 moderate in 95% at 30 days and 92% at 12 months.

19 Lower TR severity at 12 months was associated with greater KCCQ scores improvements, as
20 shown in the left panel. In addition, greater TR severity reduction was associated with greater
21 KCCQ scores improvement, as shown in the right panel. However, there were wide standard
22 deviations in KCCQ score changes at each TR severity level and at each TR severity change
23 category.

1 SF-36 scores through 12 months are shown in this slide. The mean physical component
2 score increased by about 5 points through 12 months compared to baseline in the device group,
3 while remaining mostly unchanged from baseline through 12 months in the control group. A
4 similar trend was seen in the mental component score. While there is no standardized definition
5 of a minimal clinically important difference in SF 36 scores, a three to five points change has
6 been interpreted in some studies as clinically significant.

7 New York Heart Association functional class at baseline, 30 days and 12 months is shown
8 in this slide. At baseline, 59% of patients in the device group and 55% in the control group were
9 in functional class three or four. At 12 months, 16% of device patients were in functional class 3
10 or 4, compared to 41% of patients in the control group. The proportion of subjects in functional
11 class 1 or 2 at 12 months in the device group exceeded the control group, 84% versus 60%.

12 Unpaired and paired data for six minutes' walk distance are shown in these figures for the
13 randomized cohort intention to treat population. The six months and 12 months data include only
14 patients for whom the data were available without missing data imputation. As shown in the left
15 panel, the average six minutes' walk distance at baseline was numerically lower by 13.1 meters
16 in the device group versus the control group. At 12 months, based on complete case analysis, the
17 6-minute distance increased by 11.5 meters from baseline in the device group versus 8.7 meters
18 decrease in the control group. However, there were wide standard deviations around the point
19 estimates.

20 As shown in this slide, rates of peripheral edema requiring hospitalizations, ascites, and
21 IV diuretic administration, including outpatient clinics through 12 months, were generally low in
22 both treatment groups. The annualized rates of peripheral edema requiring hospitalization and of

1 ascites requiring hospitalization were numerically lower in the device group versus the control
2 group, while the annualized rate of IV diuretics use was numerically higher in the device group.

3 At 12 months, the mean gamma glutamyl transpeptidase, or GGT level, decreased by
4 13.2 units per liter from baseline in the device group versus 0.8 units per liter in the control
5 group, and the average model for end stage liver disease, or MELD score, decreased by 0.6 in the
6 device group versus a 0.7 increase in the control group. The absolute difference between the
7 device and control group might be considered clinically significant based on studies in chronic
8 liver disease patients.

9 There were only minor changes in GFR. The mean BNP levels decreased by 7.3
10 picograms per milliliter in the device group versus an increase of 16.4 picograms per milliliter in
11 the control group. While conversely, NT-proBNP levels increased on average by 209.3
12 picograms per milliliter in the device group versus an average decrease of 402.7 picograms per
13 milliliters in the control group. There was a substantial amount of missing data, which limits the
14 interpretation of the observed changes in biomarkers.

15 Quantitative or semi quantitative measurements of TR, including proximal isovelocity,
16 surface area, effective regurgitant orifice area, regurgitant volume, and vena contracta were
17 consistent with a marked TR reduction in the device group, with minimal or no changes in the
18 control group. In the device group, there was also a small increase in tricuspid valve diastolic
19 gradient compared to baseline.

20 This table shows additional echocardiographic measurements. There was a small
21 reduction in right ventricular end diastolic diameters in the device group, which was
22 accompanied by a small increase in right atrial volume. There were minor decreases in percent

1 right ventricular fractional area shortening and tricuspid annular plane systolic excursion or
2 TAPSE.

3 During the FDA PMA review, an additional 222 patients reached 12 months follow up, resulting
4 in a total of 572 randomized patients in the full randomized cohort. Shown in this slide is the win
5 ratio analysis of the full randomized cohort, including the 572 randomized patients who reached
6 the one year follow up. The win ratio was 1.53, with a 95% confidence interval of 1.14 to 2.06,
7 favoring the TriClip group. Like the result in the primary analysis cohort, the favorable
8 difference between the device and the control group in the full randomized cohort was driven by
9 KCCQ score changes. For the number of heart failure hospitalization, which favored the control
10 group in the primary analysis cohort, in the full randomized cohort, there was a small numerical
11 difference in favor of the device group.

12 Technical, device, and procedural success for the 172 patients treated with the TRICLIP
13 in the primary analysis cohort and the 281 patients treated with the TRICLIP in the full
14 randomized cohort are shown in this slide. The high technical device and procedural success
15 rates observed in the primary analysis cohort were also observed in the larger full randomized
16 cohort.

17 Shown in these figures are select adverse events through 12 months adjudicated by the
18 clinical event committee. Rates of all-cause mortality, cardiovascular mortality, major bleeding,
19 and new onset renal failure were numerically higher in the device group compared with the
20 control group. Rate of heart failure hospitalization and tricuspid valve surgery were numerically
21 lower in the device group, while rates of tricuspid valve intervention were numerically higher in
22 the device group. As shown in the table on the right, there were no cases of endocarditis,
23 myocardial infarction, or unplanned surgery for TriClip complications.

1 As shown in this slide, for the full randomized cohort, the Kaplan Meier estimates of
2 freedom from all-cause mortality or tricuspid valve surgery at one year were similar between the
3 device and control group. Crossover from the control group to TriClip treatment was allowed if a
4 patient had completed the 12 month follow up visit, the patient has severe TR, and the patient's
5 anatomy was suitable for treatment with TriClip. Of the 205 control patients who completed one
6 year follow-up, 102 patients crossed over to TriClip. Among 572 randomized patients, 106
7 completed the two-year follow-up visit: 58 in the TriClip group, and 48 in the control group,
8 including 35 crossovers and 13 non crossovers. The baseline characteristics for crossover and
9 non-crossover-controlled patients were generally similar.

10 Freedom from all-cause mortality at two years for all groups is also shown in this slide.
11 However, interpretation of two-year data is limited by the small sample size and crossover of
12 controlled patients to TriClip treatment. For the full randomized cohort, the Kaplan-Meier
13 estimates of freedom from heart failure hospitalization at one year were similar between the
14 device and control group.

15 At two years, freedom from heart failure hospitalization was 79.2%, 69.4%, and 63% of
16 the device control and control censored groups, respectively. The chart on the right shows
17 annualized rates of heart failure hospitalization of 0.18, 0.26, and 0.24 events per patient year for
18 the three groups, respectively. Although the device group had numerically higher freedom from
19 heart failure hospitalization rate and lower annualized heart failure hospitalization rate than the
20 control, and control censored groups at two years, interpretation of two-year data is limited by
21 the small sample size and crossover of control patient to TriClip treatment.

22 KCCQ score changes through two years are shown in this slide. As shown by the blue
23 line, the KCCQ score improvement observed in the device group at 30 days was sustained at 12

1 months and at two years. Control, non-crossover controls, and crossover control patients are
2 shown by the continuous and dotted red line. There was a mean improvement of 7.3 points in
3 KCCQ scores at one year in control patients who did not crossover. The mean KCCQ score
4 changes at one year were a negative 0.1 in control patients who subsequently crossed over to
5 TriClip treatment after one year. At two years, their mean KCCQ score had increased by 7.6
6 points.

7 Turning now to the single arm cohort, there were 100 patients with an attempted TriClip
8 procedure. The primary analysis was performed on 91 patients, which excluded patients who
9 withdrew, died, or were hospitalized due to COVID-19, or missed the 12-month visit or did not
10 complete the 12-month KCCQ assessment. The primary endpoint was survival with 10 or more
11 points improvement versus baseline in KCCQ score at 12 months; 15 patients died prior to 12
12 months. 34 had KCCQ score improvement of less than 10 points and 42 survive with KCCQ
13 score improvement of 10 or more points at 12 months. The proportion of patient who survived
14 and experienced at least at 10-point improvement in KCCQ score at 12 months from baseline
15 was 46.2%, with a lower confidence limit of 34.3%, which exceeded the performance goal of
16 30%. Thus, the primary endpoint for the single arm cohort was met.

17 Select clinical event committee adjudicated adverse event rates through 12 months in the
18 device randomized cohort shown in red and in the device single arm cohort in light blue are
19 shown on this slide. The rates of all-cause mortality, cardiovascular mortality, and heart failure
20 hospitalization were approximately two-fold higher in the single arm cohort than in the device
21 group of the randomized cohort. Other event rates were generally comparable between the two
22 groups.

1 Health status endpoints results in the single arm cohort are shown in this table.
2 Improvement at 12 months were observed in the KCCQ scores, SF-36, physical and mental
3 components scores, and the proportion of patients that improved from New York Heart
4 Association functional class three or four at baseline to functional class one or two.
5 Analyzed Annualized rates of peripheral edema requiring hospitalization, ascites, and IV diuretic
6 use at 12 months for the primary analysis randomized cohort and single arm cohort are shown in
7 this slide. The dark blue bars represent randomized TriClip patients. The red bars represent
8 randomized control patients, and the light blue bars represent single arm cohort TriClip patients.
9 Interpretation of annualized rates in the single arm cohort is limited by different baseline
10 characteristics and suitability for TriClip when compared with a randomized cohort.

11 A pre-planned exploratory imaging sub study was conducted on a subset of patients to
12 further investigate changes in TR, right ventricular size, right ventricular function, and to gain
13 additional insights into cardiac reverse remodeling. Ten sites participated and site selection was
14 based on MRI CT imaging expertise, adequate imaging equipment, and study enrollment. The
15 imaging sub study was to enroll 100 patients. A total of 82 patients enrolled and completed
16 baseline imaging as of July 3rd, 2023, with 44 patients enrolled at a single site.

17 Shown in this table are right heart chamber volumetric changes and other physiologic
18 changes in the device and control groups assessed by MRI imaging at 30 days follow up. There
19 were favorable changes in right atrial end-diastolic volume, right ventricle mass, corrected right
20 ventricle ejection fraction, and pulmonary forward flow.

21 There were also small changes in right ventricular free wall strain and right ventricular
22 ejection fraction of unclear significance.

1 Shown in this table are right heart chamber volumetric changes and other physiologic
2 changes assessed by CT imaging at 12 months follow up. There were favorable changes in right
3 atrial end-diastolic volume, right ventricular end-diastolic volume, and right ventricular mass.
4 There were changes in right ventricular ejection fraction and right ventricular free wall strain of
5 unclear significance.

6 In summary, in the primary analysis cohort, technical success was achieved in greater
7 than 98% of patients. Echocardiographic endpoints were consistent with significant TR reduction
8 through 12 months.

9 The primary effectiveness endpoint was met, driven by changes in KCCQ scores, which
10 were sustained at 12 months.

11 KCCQ improvement correlated with TR reduction.

12 All-cause mortality or tricuspid valve surgery was comparable among the two groups,
13 and freedom from heart failure hospitalization was numerically higher in the control group.
14 There were favorable changes in the tricuspid group for SF-36 scores, New York Heart
15 Association functional class, and liver function tests.

16 The open label trial design introduces uncertainty into the strength of device benefit. For
17 the full randomized cohort, the win ratio analysis favored the TriClip group, also driven by
18 improved KCCQ scores. The Kaplan Meier estimates of all-cause mortality or tricuspid valve
19 surgery at one year were similar between the device and control group. The Kaplan Meier
20 estimates of freedom from heart failure hospitalization were also similar between the device and
21 control group. Interpretation of two-year data is limited by the small sample size and crossover
22 of control patient to tracheal treatment.

1 In the single arm cohort, the primary endpoint of the proportion of patients who survived
2 and had a greater or equal 10-point improvement in KCCQ score at 12 months was met. The
3 MRI and CT imaging sub studies data showed favorable right atrial and right ventricular
4 volumetric changes, supporting favorable remodeling in the device group. There were favorable
5 changes in corrected or effective right ventricular ejection fraction and in pulmonary forward
6 flow in the device group. There were also small changes in other parameters of right ventricular
7 systolic performance, including RV ejection fraction and RV free wall strain of unclear
8 significance.

9 The study limitations include the small sample size. In addition, the long-term prognostic
10 implications are unknown. That concludes my presentation. I will now give the podium to
11 Megan Naber, the lead reviewer of this pre-market application.

12 Megan Naber: Thank you, Dr. Moscucci. I will now summarize the proposed post approval study
13 and FDA conclusions.

14 The proposed post approval study for TriClip will include long term follow up of
15 randomized and single arm TRILUMINATE study patients and continued access study patients
16 through five years. Additionally, Abbott has proposed a five-year, registry-based post approval
17 study. The TVT registry will provide patient demographics, baseline characteristics, and one-year
18 outcomes. Linkage to the CMS database will provide outcomes for years 2 through 5. This
19 paradigm has been used extensively for other heart valve repair and replacement devices. Some
20 of the goals of the registry-based study are to provide real world procedural success and adverse
21 event rates; expand data to additional patients, sites, and operators; show generalizability of the
22 premarket data to the heterogeneous U.S. population; and evaluate the procedure learning curves
23 and the training program.

1 The majority of patients enrolled in the TRILUMINATE trial were Caucasian and not
2 Hispanic or Latino. The trial underrepresented patients of nonwhite ethnicities and races in
3 comparison to the U.S. population. FDA is in initial discussions with the company to develop a
4 post market strategy to collect representative data when considering the United States
5 population.

6 As discussed earlier in this presentation, the trial demonstrated a difference in outcomes
7 for high enrolling versus low enrolling sites. This difference in outcomes warrants a rigorous
8 training program. The post approval study also offers an opportunity to see how this will
9 translate to the real world.

10 In conclusion, in the TRILUMINATE Study Randomized Cohort Primary Analysis, the
11 primary endpoint driven by KCCQ improvement, and the safety endpoint were met. Mortality or
12 TV surgery rates were similar between the device and control groups at 12 months. Heart failure
13 hospitalization was numerically higher in the device group.

14 In the full randomized cohort population, the supplementary win ratio results continued
15 to favor the device group, again driven by KCCQ improvement. Mortality or TV surgery and
16 heart failure hospitalization rates were comparable between the device and control groups at 12
17 months. The two-year data for the full randomized cohort is limited and it is challenging to draw
18 conclusions regarding two-year outcomes. Finally, the single arm cohort also met its primary
19 endpoint and safety endpoint.

20 Some strengths of the TRILUMINATE Pivotal Trial include the low major adverse event
21 rate at 30 days, the high technical, device, and procedural success rates at 30 days, and the
22 durability of TR reduction and KCCQ improvement for TriClip patients.

1 One limitation of the study is the open label design, which raises concerns about potential
2 placebo effect. Another limitation is that the randomized cohort primary endpoint success was
3 driven by KCCQ score improvement without significant reductions in mortality or heart failure
4 hospitalization rates.

5 Finally, there was a difference in win ratio results between high enrolling and low
6 enrolling sites, which raises questions about the generalizability of the results and learning
7 curves. The panel will be asked to discuss the trial's strengths and limitations as well as the post
8 approval study and proposed labeling.

9 This concludes FDA's presentation. We appreciate the panel's time and review of this
10 PMA, and we look forward to your discussion regarding this novel device.

11 Dr. Lange: Thank you, Megan, and also for the other FDA speakers, again, for an excellent
12 presentation. This affords the panel opportunity to ask the FDA any clarifying questions at this
13 time. And if I could see Dr. Krucoff. Why don't you lead off. Thank you very much.

14 Questions to FDA

15 Dr. Yuh: Thank you for the presentation. With respect to the crossover patients, I know it
16 was a limited number at about 35, but I noticed that at the one-year mark, there was an inflection
17 of improvement in KCCQ scores by about, I think, seven or eight points. Given that we're led to
18 think that perhaps the, that five points is maybe due to a placebo effect, do you have any
19 descriptive statistics about heart failure admissions or mortality in that crossover group? Try to
20 tease out Placebo effect in the crossover amongst the crossover patients to the device.

21 Dr. Kevit: Hi, this is Jennifer Kevit. I am the team lead in the heart valve devices team, and I'll
22 be helping to moderate the FDA question session. I will have this first question directed to Dr.
23 Moscucci.

1 Dr. Moscucci: The data that we showed related to the patients who ended up crossing over at one
2 year, and based on outcomes that were observed in the patient group, that group of patients was
3 a group that was not doing well, and that the reason why ended up crossing over. After crossing
4 over to device, the KCCQ improved by seven points. It is difficult to determine whether that
5 was a placebo effect or a real effect secondary to reduction in TR in that patient population.

6 Dr. Zuckerman: Okay. But I think Dr. Yuh is looking for more detailed information. Dr. Lange as
7 your point, perhaps a sponsor can provide that during the lunchtime break.

8 Dr. Lange: Thank you, Bram, to the sponsor – is to look at the outcomes with regard, not just the
9 KCCQ score, but I'm going to say the harder outcomes that is mortality and heart failure,
10 hospitalizations in that crossover group after year one. David, I think that's what you're asking
11 for, is that right?

12 Dr. Yuh: It is. Thank you so much.

13 Dr. Lange: Okay, so we'll ask the sponsor to provide that information. Great. I've got Dr.
14 Krucoff, Dr. Bart, and Dr. Blankenship in that order. Mitch.

15 Dr. Krucoff: Yeah, thanks Mitch Krucoff and equally great presentation I think from the FDA
16 team as always, as well as the sponsor this morning. And as you went back through your slides,
17 which I was waiting for, on the guidance around PROs and qualification of tests, the KCCQ,
18 which we're wrestling with so much today just brings to mind my question of whether we're
19 confusing LV symptoms and RV symptoms in trying to understand this population because there
20 is a significantly low threshold at 20% for excluding left ventricular dysfunction. And one thing
21 that I think a lot of the KCCQ, in my opinion, is driven by for LV failure, which is how it was
22 born relates to dyspnea hypoxia and air hunger. Whereas with in the tricuspid universe, I think
23 we're wrestling more with excess weight, swelling, bogginess of other organs like liver et cetera

1 and seeing the different domains move differently, it also occurs to me that what we call heart
2 failure hospitalizations, patients may sit around at home and just call their doctor to move water
3 out of their legs, but if they can't breathe, they go to a hospital. So, I wonder if FDA, or maybe
4 we could ask the sponsor later, has actually stratified any of these results relative to the baseline
5 LV function or dysfunction to understand whether the clips impact either on the KCCQ or on
6 heart failure hospitalizations. That's not necessarily a randomized feature.

7 Dr. Lange: Mitch, I just want to make sure I think it's your points very well taken. What we'd
8 like for the sponsor to do is to look at LV function more than 50%, 40 to 50, 40, 30, 20 and look
9 at outcomes with regard to hospitalizations, is that what you're asking, Mitch?

10 Dr. Krucoff: Yeah, Rich. My only question to the FDA team is have you guys already done that?
11 Have you looked at that? Have you thought about confounding factors of over a year of what's
12 going on with the left ventricle in this randomized tricuspid trial, and if not, maybe we could ask
13 the sponsor that too.

14 Dr. Lange: Okay. Your point's well taken has the FDA parsed the data out like that, if not, we'll
15 ask the sponsor to do that.

16 Dr. Kevitt: I think that's a question best for the sponsor to address.

17 Dr. Zuckerman: Okay. Hey Dr. Lang, may I interject here? I think Dr. Krucoff's question refers
18 to doing this important analysis for just this trial, but as Dr. Cohen mentioned, there was a larger
19 Heart Valve Collaboratory two sponsor effort where the validity of the KCCQ for right sided
20 heart failure was extensively examined. It may be worthwhile to ask the same question for that
21 study. Also, if the sponsor and Dr. Cohen could also address that.

22 Dr. Lange: Okay, and by the way, sponsor, when we finish here with the FDA questions, I'll ask
23 you to come up and pose these to you and see if there are any questions, but we'll ask David to

1 talk about that. Okay, I've got Dr. Bart, Dr. Blankenship, Dr. Selzman, and Dr. Vidovich. Okay,
2 Dr. Bart.

3 Dr. Bart: Hi, Brad Bart here. My question relates to the proposed labeling language. I believe the
4 language includes the expression to improve health status. And I'm wondering if the FDA can
5 comment on, a specific definition of health status and whether the various domains in the KCCQ
6 reflect health status in the opinion of the FDA.

7 Dr. Kevitt: I'll direct that question to Dr. Farb.

8 Dr. Farb: Thank you, Andy Farb. As the KCCQ is an instrument of general health status, I think
9 the question is a good one to try to look at the granularity of the individual domains to try to
10 perhaps tease out where this device has its best use in terms of a patient benefit. That may be
11 quite a challenge. And this is a question we're actually asking panel input about how they
12 interpret these data, what they see are the advantages of this device, and it's at its limitation. This
13 is something that we're proposing back to the panel to get their help to help us.

14 Dr. Lange: I've got next Dr. Blankenship.

15 Dr. Blankenship: My question was exactly the same as Dr. Bart's. I'm interested in your answer
16 and I'm wondering maybe it might be more accurately be changed to patient perception of health
17 status, but perhaps we'll have a discussion on that separately later on. But thank you for
18 answering that.

19 Dr. Lange: Great. I've got Dr. Selzman, Dr. Vidovich, Dr. Hauptman, and then Dr. Cizik.

20 Dr. Selzman: Craig Selzman here. This might be more for the sponsor, but looking at the
21 exclusion criteria it states that there had to be a two month wait between treating left sided
22 disease. This is building off a little bit of Dr. Krucoff's question. There was this two month wait.
23 So if somebody had a mitral valve operation done and they have severe TR, if they waited two

1 months, they could theoretically be a part of this trial, and so I'm curious to know, of the
2 randomized cohort patients, how many actually had the left sided disease because sometimes left
3 sided disease takes a little while to manifest its connection on the right side and so of the
4 numbers that met exclusion, i.e., within the first, 60 days, but that's not the question, the question
5 is how many people actually waited the two months had interventions or had prior left sided
6 disease that were then brought into this, that were brought into this trial, because almost all of
7 these are functional, right? They're 94% or whatever the number was. We're all functional TR.
8 And is that because somebody has bad lungs and then their RV dilated or did, they have treated
9 left sided disease and we're still in a window of them getting better? Does that make sense?
10 What I'm trying to ask?

11 Dr. Lange: Yeah. And just to help the sponsor out, we say left sided disease and I understand
12 what you're saying. Remember the average left side is about 50. Do you want to define left sided
13 disease as mitral valve disease, either regurgitation or stenosis, or how do you want to define left
14 sided for the sponsor?

15 Dr. Selzman: So, I would say anybody that had an intervention on a left sided valve, aortic valve,
16 mitral valve, or perhaps they had bypass surgery. Or a percutaneous intervention, something that
17 enabled the left side to get a little bit better before and as they enter into the clinical trial. And
18 what percentage of the of your enrollees met that kind of group.

19 Dr. Lange: Okay. So, we would like we want Abbott, not right now, but we want them to provide
20 information about what percentage have this prior to their enrollment in the study. Aortic valve.

21 Dr. Spinner: Yeah, we have that information.

22 Dr. Lange: Super great. Okay. Thank you, Craig, for that. Dr. Vidovich.

1 Dr. Vidovich: Thank you for the opportunity. So, there's a two-prong question. One is which
2 confuses me a little bit is that there is somewhat discrepant data between the BNP NT-proBNP
3 and MELD scores and the estimated GFR. So, this is a question probably for both the FDA and
4 the sponsors. How much data are we missing there? And could we make some more sense out of
5 this? Because this is an interesting, maybe like a secondary measure of function of the RV.

6 And then the second question I have is, I just noticed on the FDA presentation, which was
7 absolutely terrific. This is an AFib study as well. There are 90% of patients were in AFib and is
8 this also confounding our ability to interpret the findings because it is quite plausible that again,
9 as someone from a previous discussion mentioned you're struggling with the right sided failure,
10 left sided failure, how much did AFib contribute to any of the observed outcomes? Again, I don't
11 know if this is a comment or question, or could we maybe be more granular about that?

12 Dr. Lange: Okay the I'll let the FDA answer the question about the discrepancies and then Erin,
13 I'll ask you to come back as well and does the FDA have an explanation for the disparities in
14 BNP versus NT-proBNP.

15 Dr. Kevitt: Dr. Moscucci can address this question.

16 Dr. Moscucci: Yes, the trial allowed the collection of BNP or NT-proBNP, and so when you look
17 at the total numbers based on the data that we have, about 50% of patient had a BNP assessed,
18 and about 50% of patient had NT-proBNP, so based on the incomplete ascertainment in terms of
19 all BNP or all NT-proBNP, it's difficult to draw any specific conclusion regarding to this
20 biomarker.

21 Dr. Lange: Okay, they're not paired samples in the same patient population?

22 Dr. Moscucci: Exactly. There are some subsets of patient that have paired sample.

23 Dr. Lange: Okay, this is luck of the draw. Erin, do you want to add anything else to that?

1 Dr. Spinner: No, that's correct. Sites had the option to either collect BNP or NT-proBNP, so not
2 for the same patients.

3 Dr. Lange: Alright, thank you. Dr. Hauptman. Dr. Cizik. Cizik, excuse me. And then Dr. Shanker.

4 Dr. Hauptman: Thank you, Dr. Lange. Question for Dr. Moscucci and then a follow up. On slide
5 67, you demonstrated that IV diuretic usage was greater in the device arm. But incidents of
6 peripheral edema and ascites was lower. Is that is there a relationship their patients in the device
7 aren't perhaps getting more IV diuretic therapy and responding to it? So that's question number
8 one. I think Dr. Krucoff made some reference to this as well. Do we know anything about
9 predictors of response, let's say of an improvement in KCCQ above and beyond what's already
10 been discussed or conversely, nonresponse to this therapy and so no increase? And that this could
11 apply to the randomized cohort of the open label cohort as well. And then finally just the issue of
12 AFib came up. I'm just curious whether we have numbers of, we have data on the numbers of
13 patients who may have received an ablation after TriClip and whether that could have
14 contributed to improvement in KCCQ.

15 Dr. Lange: All right if you'll put slide 67 back up, if it's, let's see, and if the FDA would like to
16 address the question of diuretic use and the treatment of whether that affected, and if not, we'll
17 turn it over to, and we'll have the sponsor also address the question.

18 Dr. Kevitt: Dr. Moscucci do you want to address the question?

19 Dr. Moscucci: I'm not sure that we can at this stage, based on the data, provide any additional
20 analysis of differences between annualized rates of hospitalization for ascites or peripheral
21 edema versus the administration of IV diuretics. I don't know if the sponsor would like to
22 comment on that.

23 Dr. Spinner: Also, we'll have Dr. Benza speak about the IV diuretic usage.

1 Dr. Benza: Okay. Ray Benza, Mount Sinai. There are no statistical differences in the use of IV
2 diuretics between the control group and the TriClip group. In addition, if you look at the amount
3 of diuretic changes that occurred between the groups numerically, there was a greater number of
4 diuretic changes in the control group as compared to the device group. But again, this was
5 statistically not significant.

6 Dr. Lange: Dr. Hauptman, does that adequately address your question? I'm not sure that it does.

7 Dr. Hauptman: Yeah, it's I'm not sure that it does either. You have a number of days of IV
8 diuretic usage might be helpful also in the number of patients who received IV diuretics. It could
9 be that some patients received it a lot, most didn't receive it at all, but it just strikes me that if
10 you're getting more IV diuretic usage, you may have less ascites and less peripheral edema or
11 more. Obviously, the fact that IV diuretic therapy is being used could be in response to declining
12 clinical condition. On the other hand, it could be that this cohort is just the device cohort is being
13 treated more aggressive.

14 Dr. Lange: Over lunch, why don't you see what you can find out the patients that got IV diuretic
15 use. When you say it's not statistically any different, it looks like certainly the numbers of
16 patients are different. So, you would expect, I'm not sure what statistic you're throwing out when
17 you say it's not statistically different. You talk about IV diuretic use per patient or the total
18 amount over the population?

19 Dr. Benza: If we can show some slides that would be. That'd be great. As you can see in this
20 slide that the again, the use of IV diuretics is relatively equivalent both in the device and the
21 control group. And thus, the significant changes that we've seen. Both in peripheral edema and
22 ascites that were demonstrated clinically are likely from the decongestive ability of the device on
23 right sided heart failure that is independent of the IV diuretic use.

1 Dr. Lange: It's an unusual way to express IV diuretic use as annualized rate for a patient
2 population. And I think that's what Dr. Hauptman may be, and others may be having difficulty
3 with. It's just so unusual to express diuretic use in here, Paul, am I, are you, am I reading that?

4 Dr. Hauptman: I think so. But actually, just looking at back at slide 67, I think we, we do have
5 the numbers of patients who received IV diuretics. That's more meaningful. Can you put that
6 back up?

7 Dr. Lange:

8 Dr. Benza: Yeah, we back up there. There we go.

9 Dr. Lange: Hey, Paul, does that address your question or at least give you enough to talk about
10 during the discussion?

11 Dr. Hauptman: I believe so. Yes. Thank you for that. Okay.

12 Dr. Lange: Okay. Thank you. Dr. Cizik.

13 Dr. Cizik: Dr. Hauptman, did you have another question?

14 Dr. Hauptman: It was the issue of whether there were predictors of response to or non-response.
15 Yeah, baseline biomarker or some other parameters. Maybe more specifically non-response,
16 whether it was anatomical or how do we, how can we parse out who's going to get the greatest
17 benefit from an intervention?

18 Dr. Lange: Thank you, Paul. Go ahead. FDA. Jennifer. Who would like to address this?

19 Dr. Moscucci: This is Mauro Moscucci, medical officer from FDA. There was an additional
20 analysis that was performed in order to identify responders and compare responders with non-
21 responders. Basically, the request was to evaluate patients who had a TR reduction to moderate
22 or less but had no improvement in KCCQ scores at follow-up. There were a total of 23 non-
23 responders in the device group and three in the control group. The baseline KCCQ score in the

1 non-responders, meaning patients who had TR reduction to moderate or less was 71.3 in the non-
2 responders compared to 55 in all other patients. The baseline KCCQ score, which was defined as
3 good to very good, meaning the KCCQ score ranging from 75 to 100, was 42.3% in the non-
4 responders compared to 26% in all the other patient group. And finally, non-responders, quote
5 unquote, had a lower percentage of patients with baseline New York Heart Association functional
6 Class III or IV. The take home message about this is that non responders were less symptomatic
7 at baseline and with good quality of life possibly explaining why they were non responders and
8 less likely to have improvement in KCCQ score of that magnitude.

9 Dr. Lange: Paul, is that the information you're looking for?

10 Dr. Hauptman: That's helpful. I think we can discuss this more on the other side of lunch. Okay.

11 And with putting at risk your generosity of giving me time, just curious about the whether there's
12 data on intervention, such as atrial fibrillation after TriClip and whether there are differences
13 between the groups.

14 Dr. Lange: Absolutely. Erin does the sponsor have any information regarding patients that had
15 atrial fibrillation after the TriClip?

16 Dr. Spinner: We don't have that information at this time.

17 Dr. Lange: Okay. Is that something that you can get over the break or you just won't have access
18 to that?

19 Dr. Spinner: We'll look to see if we can get that after the break.

20 Dr. Lange: Okay. That'd be great. Thank you. Paul. Thanks. Dr. Cizik.

21 Dr. Cizik: Yes. Amy Cizik. Dr. Farb a clarifying question. You mentioned that the FDA considers
22 KCCQ a general health status questionnaire. Did I hear that correctly?

1 Dr. Farb: No, not, I think it had to do with the terminology in the indications of health status, that
2 language that is now part of the proposed indication of use and that the KCCQ when applied to
3 this patient population is an acceptable instrument to assess that so it's specific for this
4 population.

5 Dr. Cizik: Thank you.

6 Dr. Lange: Yeah, Dr. Shanker and Dr. Friedman. Amit.

7 Dr. Shanker: Yeah, thank you very much. And an excellent presentation. Less of a question, more
8 of a commentary, piggybacking on what Dr. Hauptman had alluded to do, we have that slide on
9 the baseline characteristics in the primary analysis cohort for NYHA class.

10 Dr. Kevitt: Give us one moment to try to pull that up.

11 Dr. Shanker: While you pull that up, at least from my interpretation more than and I think we
12 also saw this in the summary, approximately 97% of the patients had NYHA two or three
13 symptoms.

14 Dr. Lange: Slide 47, 45? I'm sorry, go ahead. This slide right here?

15 Dr. Shanker: Yes. Perfect. Yeah, they about 95 to 97%, 94 to 97% of patients had class two or
16 class three symptomatology. That in combination with the high incidence of AF I'm hoping
17 that's something that we will take into account as the FDA will take into account as they come up
18 with a labeling indication as an electrophysiologist maintenance of sinus rhythm does really
19 result, I've seen, and we've all seen results in significant symptomatic improvement. And my
20 question is would this therapy be appropriate in patients who are in sinus rhythm because the
21 KCCQ scores might not be as dramatic of, you might not see as dramatic of an improvement in
22 those patients who are already in sinus rhythm. So that's just one commentary I wanted to make.

1 Dr. Lange: Let's talk about that for lunch as well. Let's make sure you bring that up again. Dr.
2 Friedman.

3 Dr. Friedman: I just wanted to play off one of the previous commentators about the BNP and the
4 potential confounding of that. Was there any kind of, further breakdown of the medication uses
5 in the control arm? Number one and number two, as it relates to the BNP N-terminal BNP, I
6 guess it was a site-specific choice of proBNP or the N-terminal. I believe the N-terminal is a
7 longer acting inert molecule, and that's going to be the longer window as to an earlier heart
8 failure decompensation event as opposed to the more acute ProBNP the acute BNP check. So I
9 was just wondering if there was a breakdown in the medication use in that regard. And then my
10 second, follow up question is why was there no sham arm in this? And I know some trials are
11 leaning away from sham because it's maybe considered unethical in some places, but in this
12 regard, since there's no direct relationship with a surgical intervention in the tricuspid situation,
13 to compare a deployment of a clip and TriClip versus optimal medical therapy, I'm not sure if
14 that's the best way to look at this.

15 Dr. Lange: And David I'd like information on medication use, not just on the device, but the
16 control groups, both groups at baseline and study completion. Let's see, is a sponsor able to
17 present that information?

18 Dr. Spinner: We can show baseline medication usage. We have diuretics, beta blockers, ACE,
19 ARBs, and vasodilators, both for device and control. We're showing that here.

20 Dr. Lange: So, there's a baseline. And are we able to show it at 12 months as well?

21 Dr. Spinner: We can see if we can get the specifics, but I can comment that there was little to no
22 change in any of these medications shown here.

1 Dr. Lange: Terrific, which implies the analysis has been done. So, we'll take a look at that after
2 lunch. Okay, that'd be great.

3 Dr. Spinner: Would you like us to address the sham control at this time?

4 Dr. Lange: Yes, ma'am.

5 Dr. Spinner: Okay. I'll have Dr. Adam speak to this.

6 Dr. Adams: Okay, well, in retrospect, your question is obviously an important one. We did not
7 consider a sham control trial at the time. Perhaps we should have, knowing what we know today,
8 but at the time, we really thought we had a trial that was going to show us more in terms of the
9 harder end points and at one year again, we probably didn't wait long enough to see the hard end
10 points. We also had a measurable effect, which was reduction of TR that we were going to be
11 very confident in, and we set up secondary analysis to look at anatomic and physiologic
12 consequences of reducing the TR. So, we felt very good about the trial design and honestly,
13 never consider a sham control.

14 Dr. Lange: Appreciate that explanation. Easy through the retrospective scope. And I'm sure that
15 will be a discussion again after lunch about the softer versus the harder end points and how to
16 reconcile the two. Let me summarize. Erin, if you'll get back on for a second there were several
17 things that the panelists had asked for and I just want to make sure, present those to you and see
18 if there are any questions. One is for the crossover patients to provide information of the hard
19 outcomes. Dr. Yuh asked for that. Dr. Krucoff asked about left sided heart failure and excuse me,
20 the left sided failure and heart failure hospitalizations and how much of this was due to LV issues
21 and relationship of LV dysfunction and KCCQ scores. And then Bram (Dr. Zuckerman) had
22 mentioned the fact that this has been looked at in two studies. We'll ask David to come up and
23 talk a little bit about those and try to put it in perspective for us, if that's okay.

1 Dr. Selzman had wanted again to know how many had left sided heart disease prior to
2 entrance to the study, aortic valve disease, mitral valve disease, CABIs, or PCI. We've talked a
3 little bit about the discrepancies between BNP and proBNP. It's a little disconcerting if it's
4 randomized, even though some group had picked one over the other, you wouldn't expect them
5 to move in different directions. And so I'm wondering if there's a little bit better explanation if
6 you guys have thought about that other than just saying it's it's they're not paired and that's
7 helpful. but I'm wondering if we can explain that.

8 Dr. Hauptman had asked how many patients had an ablation after the clip had been placed, and
9 then finally, the issue regarding medication use at 12 months, and whether there's any difference
10 between the groups. Okay, so is all that pretty clear?

11 Dr. Lange: So, super any other questions. And the people that ask questions that I summarize it
12 appropriately, if not now's the time to give that to the sponsor. Okay. Great. Okay.

13 We are about 15 minutes ahead, so let me ask, I want to make sure the sponsor is
14 adequate time. We can either make it a 1-hour lunch. In which case we'll be on time and give
15 you a little bit more time or perhaps do it have lunch for 45 minutes is what we're planning on. I
16 want to make sure that sponsors adequate time to address these last issues you have that. And by
17 the way, we have another hour time where we have public speakers as well. If there's no, if the
18 sponsor feels like they 45-minute lunch. It'll give us a little bit more time to discuss in this
19 afternoon. Are you okay with that?

20 Dr. Spinner: Yeah, I think that's fine. If you wouldn't mind, we could address the crossover now,
21 which would give us a little more time later to answer the other questions.

22 Dr. Lange: Sure.

23 Dr. Spinner So I'll have Dr. Sorajja speak to this. Okay.

1 Dr. Sorajja: Yeah. So, in terms of the crossovers. It's Paul Sorajja here again. The request for
2 crossovers was made by the physician and patients in the context of persistent severe
3 symptomatic TR. We did have, as mentioned, 102 patients, about half of the control population
4 of crossover. And if we look at some of the data that we have out to two years, these are some of
5 the data on some of the events. This is a heart failure hospitalization through two years for the
6 patients who we have some of that data. So the control pure as mentioned previously, these are
7 the patients in whom there was no crossover and then the control, that it does include patients
8 who did cross over and the trends are there for differences in HFH for device versus control do
9 the follow up that we have with the context also knowing how many patients that we had too.
10 Getting out to two years, the numbers get a little smaller, but one can see at 540 days that the
11 number at risk for the control pure arms still is at 47. Still not the whole cohort, but hopefully it
12 gives you a glimpse of where they were through two years. Oh, and I've been asked to also share
13 the mortality one, too. This is the two-year data for the full randomized cohort. Similar trends
14 again. The number of risks is a little bit higher at 540 days and at 730. But with this limited
15 sample here, we can see that the trends, at least in numerically are in the right direction for
16 device versus control.

17 Dr. Lange: David does that address the question you asked?

18 Dr. Yuh: That was actually very helpful. Great.

19 Dr. Lange: All right, it's 1105. Excuse me. It's 1105 here in El Paso, but it's 105 there. We're on
20 the East Coast. We're going to take a 45-minute lunch. I'll ask Jim to set the timer again. I'll
21 remind the panel members not to discuss any of the any of the products and discussion we've
22 had. Please enjoy a good lunch and I'll see you back here promptly in 45 minutes. Thank you.

1 Open Public Hearing

2 Dr. Lange: Good afternoon. It's just before 2 PM eastern standard time. I would like to resume
3 this panel meeting. We'll now proceed with the open public hearing portion of the meeting. This
4 is where public attendees are given an opportunity to address the panel to present data
5 information or views relevant to the meeting agenda. Dr. Akinola Awojope will read the open
6 public hearing disclosure process statement at this time.

7 Dr. Akinola Awojope: Both the Food and Drug Administration, FDA, and the public believe in
8 the transparency process for information gathering and decision making. To make sure such
9 transparency at the open public hearing section of the advisory committee meeting, FDA believe
10 that it is important to understand the context of individual presentation.

11 For this reason, FDA encourages you, the open public hearing speakers, at the beginning
12 of your written or oral statement to advise the committee of any financial relationship that you
13 may have with any company or group that may have been affected by the topic of this meeting.
14 For example, this financial information may include companies or groups' payment of your
15 travel, lodging, or other expenses in connection with your attendance at the meeting.

16 Likewise, the FDA encourages you, at the beginning of your presentation, to advise the
17 committee if you do not have any such financial relationship. If you choose not to address these
18 issues of financial relationship at the beginning of your statement, it will not preclude you from
19 speaking. Thank you very much.

20 Dr. Lange: Thank you. Dr. Awojope. The FDA has received 15 requests to speak prior to the final
21 date published in the federal register. These are prerecorded, so we'll begin with speaker number
22 one and then progress from there. The first speaker is Dr. Stefan Van Bordeleven.

1 Dr. Stefan Van Bordeleven: Hello, my name is Rolf Stefan Van Bordeleven. I'm a professor of
2 medicine, cardiology, and specialist for interventional heart valve therapies from the University
3 of Medicine in Mainz, Germany. My personal experience is for about 15 years TR therapy with
4 the MitraClip and other devices with a total volume of about 2000 human procedures many first
5 in world or early in world trials in repair and replacement and a personal experience in tricuspid
6 therapy of about 400 cases in total.

7 What is key to the patients is their quality of life for their residual five to ten years; that
8 is, their main perspective of life expectancy. So, while we see in single arm trials and also in
9 subsets of patients that have excellent results in the TR reductions, a possible indicator for
10 mortality reduction, the main benefit is quality of life and functional benefit.

11 And this may be benefit in this very heterogeneous population. This population is driven by a
12 number of at least seven different disease entities, which is left heart myocardial, which is left
13 heart diastolic, which is rhythm associated, which is left sided valvular disease, but also other
14 causes to the right ventricle itself.

15 And the evidence base of transcatheter methods has reached a range, especially in
16 isolated disease, more than in concomitant mitral tricuspid disease that now even exceeds
17 surgical experience over the last four decades. We have to see that the risk benefits favor TR
18 therapy, the results favor TR therapy.

19 We know that we can achieve results like moderate TR, mild, or no TR nowadays in the
20 range of 85 to 93%. So, we should open our field that we know for long term that right sided
21 heart failure is more important than the guidelines depicted. We know from both congenital and
22 acquired valvular disease that the reduction of pulmonary or tricuspid regurgitation increases
23 cardiac output.

1 We treat more than 800 adults per year, and these adds an additional reduction in the
2 burden of an impairment of quality of life to our patients. It improves the congestion of these
3 patients. It improves the cardio renal and cardio hepatic interaction for these patients. So, fatigue,
4 the inability to eat and cachexia is being addressed in those patients. And I think it's a beneficial
5 therapy where we will still learn over the upcoming years in further randomized trials. But I
6 think that we already have enough evidence to treat those patients to improve their lives. And I
7 think for most patients, we have similar or better data on trans catheter methods than we have on
8 a lot of surgical techniques to treat the same disease.

9 Thank you very much for your attention.

10 Ms. Asma Hussaini: My name is Asma Hussaini. I'm a physician assistant. I have been
11 working with transcatheter valve therapies for over 20 years now, and I have been involved with
12 the TRILUMINATE Pivotal Study since its inception and have still been working with this
13 patient population day in and day out.

14 We are currently enrolling in the continued access registry which is ongoing. And I can
15 honestly say that I have seen a far more profound clinical improvement in patients that are
16 treated with TriClip. And this affects their daily lives. I recall one patient of mine, Marcella, who
17 randomized actually to the control arm of the TRILUMINATE study, and she had already
18 received the MitraClip procedure about a year prior. And during that control arm period where
19 she was just on medical therapy, she continued to have heart failure admissions. She could not
20 sleep comfortably because of symptoms of orthopnea.

21 Finally, when that year was up and she got the TriClip procedure, she felt so much better.
22 And in fact, she came into the office saying, I want to be the poster child for this procedure, this
23 is amazing. She was staying on her medications, but she no longer had the swelling. She was

1 able to sleep better and did so much better. And that's what I see all the time. Having seen both
2 the mitral valve repair patients with MitraClip and then the TriClip patients have symptoms that
3 affect their daily lives. And this is due to right heart failure symptoms. Most of them sleep in a
4 recliner chair because they're not able to sleep in bed because of orthopnea. They often can't eat
5 a normal meal because of hepatic congestion. They can't wear normal shoes usually because they
6 have so much leg edema. They oftentimes will wear compression stockings and then they
7 sometimes require wound care because of open ulcerations due to all the swelling in their legs.
8 So, a huge change occurs once the procedure is performed.

9 And, a lot of these patients, because they're high risk, they have poor kidney function. And the
10 only treatment we have for these patients right now is diuretic therapy, and that oftentimes is
11 limited due to poor renal function. Just, surgeons I've seen have done tricuspid valve repairs
12 when they repair other valves, such as when they go for mitral valve repair or aortic valve
13 replacement or repair procedures, they don't leave behind tricuspid regurg because they know
14 it's a bad thing. So, just as surgeons have an option, I think the interventional cardiologist should
15 have an option, a treatment plan that they can offer their patients if they have this therapy
16 approved. Then patients will have a complete package for their valve disease. Currently, they
17 have no other options other than diuretic therapy. So, I would love to see the TriClip procedure
18 get FDA approval.

19 Dr. Anita Asghar: So, hi, my name is Anita Asghar. cardiologist at the Montreal Heart Institute.
20 I'm primarily specialized in structural heart disease intervention, and I've been practicing here
21 for about 15 years. I am a member of SCCHI, and I'm a fellow of the American College of
22 Cardiology, and in fact, the governor for Quebec for the American College of Cardiology. I want

1 to talk to you today about my experience with the tricuspid edge to edge repair in particular with
2 the TriClip device. And I want to take you back to a time in 2020.

3 So, I've had extensive experience over the past 15 years with both aortic and mitral
4 interventions, and so felt very experienced with dealing with valvular heart disease. You don't
5 always understand the magnitude of a problem until you're in the middle of it. And that's how I
6 feel about my experience with tricuspid valve disease.

7 And so in 2020 in April is when we started participating in the TRILUMINATE trial. And as all
8 you remember, in March of 2020 is when COVID hit. In Canada, the public health care system,
9 we were bracing for COVID, but we also had to deal with a system where we had a hospital bed
10 limitations and trying to manage the inflow and outflow of patients.

11 And so unfortunately for us, because of the COVID crisis that we had going on, all our
12 research trials were stopped, and research trial procedures were also stopped. We had already
13 started recruiting for TRILUMINATE, so we had a large population of tricuspid regurgitation
14 patients that suddenly were coming to hospital with decompensated heart failure, but we weren't
15 able to treat because the procedures were put on hold.

16 This continued for months until the hospital administration realized we could no longer
17 function with the number of tricuspid regurgitation patients that were coming into hospital with
18 right sided heart failure. And so, they eventually allowed us to participate in the trial and start the
19 procedures in October of 2020 due to the massive impact of these patients blocking hospital
20 beds. We also got permission from the government of Quebec at the time. to do these procedures
21 for the same reason. These patients were essentially occupying beds in the hospital during a time
22 when the public health care system was overrun.

1 Since 2020, I've had three years of experience with tricuspid edge to edge repair, almost
2 a hundred patients that I've treated personally, and I've learned so much about the disease. I've
3 learned about the natural history of the disease, but most importantly, I've seen how these very
4 sick patients can improve their quality of life, how safe the procedure is. They come in the
5 morning of the procedure. They leave the following day without really any kind of
6 inconvenience. But importantly, how they've seen their quality of life improve. These patients
7 are back to doing the things they want to do. And from a public health care perspective, they're
8 no longer coming back to hospital with right sided heart failure. They're not blocking our beds
9 which are limited in our healthcare system, and they're able to get back to a quality of life that's
10 important to them.

11 And so, this experience has taught me a lot about tricuspid valve disease and things I
12 didn't understand about the condition. But importantly, how we can contribute, how we can treat
13 these patients, improve their lives. and improve bed utilization for the hospital. So, that's just my
14 experience that I wanted to share with you today, and I hope it becomes helpful for you in your
15 deliberations.

16 Dr. Price: Thank you. Hi there, I'm Matthew Price, Director of the Cardiac Catheterization
17 Laboratory and Interventional Cardiologist at Scripps Clinic in La Jolla, California. I've been
18 involved in structural interventions for many years. I'm going to thank you for the opportunity to
19 speak with you today. I have been involved in tricuspid TEER for many years now and enroll
20 patients in the TRILUMINATE trial, and I have learned so much about tricuspid regurgitation
21 and what is meaningful for patients with this disease through my experience in the trial, because
22 I've seen patients come to me with severe TR and really horrific symptoms of fatigue, satiety,
23 legs like tree trunks, needing paracenteses, and just feeling miserable, and in my anecdotal

1 experience, dealing with these patients, that addressing their tricuspid regurgitation in a safe and
2 relatively easy fashion has really been an eye opener for me when I follow these patients over
3 time.

4 For example, I've had patients at a patient early on in the trial with chronic non healing
5 ulcers of her legs because of her just almost elephantiasis of lower extremity edema and she
6 hadn't had a prior heart failure hospitalization, but her life was miserable. We addressed her
7 tricuspid regurgitation in the trial. She was randomized to device and her lower extremity edema
8 went away and her ulcers went away as well. And these are little things that are so hard to
9 capture.

10 I had another patient who stopped needing paracenteses, had to go to the GI doctor every
11 couple of months to be addressed. I had another patient who I saw two years later after doing a
12 tricuspid clip procedure I was doing an angiogram on, he had coronary heart disease. And he
13 reminded, I'd forgotten that I had treated him. He said, Hey, Dr. Price. I just wanted to thank you
14 again. It was like a light switch went off in my body after you addressed this. And this is two
15 years later.

16 And what's really just big picture is what should we care about when we treat patients?
17 And it's their day to day lives, how they interact with their families, if they can go shopping, if
18 they can put on their socks. These are things that we saw in this trial, and I actually didn't know
19 much about really the day-to-day life of patients with tricuspid regurgitation before enrolling
20 patients in these trials.

21 I'm an interventional cardiologist, and I've really learned what TR means to patients and
22 what resolving their TR means, and I've been really impressed in the trial. In patients who are
23 randomized to device, in follow up the joy of the families and the patients afterwards, it can't be

1 measured and has really meant a lot to me, and that's why I have been so enthusiastic about this
2 therapy and I want to thank the panel to look at this data and to remember the patients that are
3 behind the numbers who can now put on socks, who can go gardening, who can shop and who
4 can play with their grandchildren. I think that's really important. So, thank you very much.

5 Mrs. Geneva Franks: My name is Geneva Gail Franks. I will be 80 years old in March, and I
6 currently live in Franklin, Tennessee with my husband, Will. Thank you for allowing me this
7 time to share my experience as a participant in the TRILUMINATE study. In approximately
8 2014, while my husband and I were training to walk a half marathon, I began experiencing
9 debilitating periods of arrhythmia and extreme exhaustion.

10 My internist referred me to a cardiologist that specialized in arrhythmias. An extensive
11 cardiac MRI showed that I had severe tricuspid regurgitation and right sided cardiac hypertrophy.
12 Following a cardiac cath to rule out pulmonary hypertension, my cardiologist discussed
13 treatment options. Open heart surgery for a valve replacement or trying to control my symptoms
14 with medication. I opted for the medication route.

15 In 2019, while hiking in Exmoor, England, I realized I had to rethink this treatment path.

16 Exertion was triggering severe arrhythmias, shortness of breath, and again that unrelenting
17 exhaustion. The exhaustion was to the point that I had to prioritize activities. Hiking in the

18 morning meant my day was done. Dinner out at night meant I couldn't do much during the day.

19 While discussing my worsening symptoms with my cardiologist, he shared with me that

20 Centennial Heart would be participating in a new clinical trial in 2020 involving a clip repair of
21 the tricuspid valve. He arranged an appointment with the cardiologist in charge of the trial for me
22 to learn about the new procedure and possible participation in January of 2020, Dr.

23 [indiscernible] called me call to advise me, I had been accepted into the clinical trial. In February

1 of that year, I had the procedure done after an overnight stay in the hospital. I was released home
2 with almost no limitations.

3 The results of the procedure were noticeable almost immediately. Within the week, I was
4 able to climb stairs with minimal shortness of breath and this has continued to improve to the
5 point that shortness of breath is the exception rather than the rule. There was also an immense
6 improvement in my atrial fibrillation. I have not had a major AFib event since the procedure.
7 This has been particularly true at altitude. Prior to the procedure, I could not be at an altitude
8 over 5,000 feet without prolonged periods of arrhythmia. It was to the point that I feared I would
9 no longer be able to visit our daughter and granddaughter in Santa Fe, which happens to be over
10 7,000 feet.

11 Over the last three years, I have had several extended visits in Santa Fe with no AFib
12 episodes. And the most striking improvement has been a life without exhaustion. I no longer
13 have to prioritize my activities during the day. Hiking in the morning and going out in the
14 evening is no longer a challenge. This procedure offers the opportunity to experience an
15 improved quality of life and possible improvement of medical situations without the inherent risk
16 of undergoing open heart surgery.

17 As you proceed with your decision making, I hope you will remember my story and the
18 benefits I have shared after undergoing this procedure. It will always be, I will always be grateful
19 that I had the opportunity to take part in the clinical trial and hope that this procedure will
20 become readily available to all patients who can benefit. Again, thank you for your time today,
21 and I really appreciate the opportunity to share my story with you.

22 Dr. Eugene Chung: Hello, my name is Eugene Chung. I am a heart failure LVAD transplant
23 specialist. And in addition, I serve as the heart failure part of our research team, assessing these

1 patients prior to intervention, and to try to make sure that their guideline directed medical
2 therapies are optimized. Furthermore, I'm also one of the imagers for these transcatheter
3 procedures for edge-to-edge repair.

4 My thinking on tricuspid regurgitation has evolved to a more, I think, optimistic place,
5 with the potential development of all these options. The importance of TR has been under
6 recognized over the years, and as a result, these patients have been under treated. There was a
7 time when the tricuspid valve was felt not to even be necessary in many patients. The surgical
8 data for repair and replacement are mixed. In addition, importantly, the disease process is quite
9 insidious and not as acute and rapid as many of the other diseases that we see on the left side.

10 The recognition that the coexistence of severe TR is associated with very poor outcomes
11 when you have other heart diseases has brought more attention appropriately to trying to figure
12 out what to do with these patients with severe TR and now these patients' clinical phenotype is a
13 little different than the left side.

14 Because the TR itself doesn't cause pulmonary congestion they don't typically develop
15 acute shortness of breath the way mitral regurgitation patients might these patients show up with
16 just progressive decline in their functional status, low output, poor nutrition, abdominal
17 congestion, nausea, just weakness and dizziness, a lot of swelling. And so, these patients come to
18 clinical attention in ways that are a little bit different.

19 We've also noted that with optimizing guideline directed medical therapies, particularly
20 aimed at right ventricular preload and afterload, that many of these patients do improve their
21 symptoms significantly, often with modest decline in their severity of TR. It's possible that with
22 acute closure of the TR, meaning going from severe to zero, that you create this sudden increase
23 in afterload of the right ventricle, which is much thinner with much less reserve. And these

1 patients then develop perhaps worsening of RV failure because of that process and perhaps you
2 don't need to decrease these patients TRs from severe to zero because that could actually lead to
3 a problem.

4 In the TRILUMINATE trial in specific, the procedure does what is set out to do. It
5 reduces the severity of TR in the vast majority of patients, sometimes by more than one grade or
6 two grades, and it does it in a very safe way with excellent safety profile. The hospitalization for
7 heart failure and mortality data are not different compared to control. So, I would point out that
8 the availability of this tool to reduce TR in patients with severe TR is an incredibly potentially
9 helpful tool in our armamentarium. Thank you.

10 Mrs. Erin Lambert: Hello, my name is Erin Lambert and I am married to my wonderful husband,
11 Brody Lambert. We have been married for 21 and a half years. We have four amazing kids whose
12 age range from 19 to 10: three girls and one boy. We live in Spanish Fork, Utah. We have a small
13 farm where we raise livestock along with our kids. Currently our kids show livestock. We are
14 involved with our local 4H club and different boards associated with the livestock shows.

15 Brody was diagnosed with cardiomyopathy in May 2005 at the young age of 24 years
16 old. I remember the day he was diagnosed and wondering if he would get better, the quality of
17 life he would have, and the longevity of his life. We had just started our family and our first child
18 was only six months old. Would he be around to watch her grow? To teach her? To chase the
19 boys off when she started dating? To take her camping and hunting? All those dad things.

20 Brody's heart health did improve thanks to modern medicine and a great team of doctors.
21 He was able to go to work, enjoy the outdoors, and live life. Nine years later, his heart weakened
22 to an ejection fraction below 10%. With much consideration on the medical team and our side, an

1 LVAD was implanted and sustained his life until a donor heart became available for him in
2 March 2016.

3 About a year after his transplant, Brody started having low energy and retaining some
4 fluid. After some testing was completed, the medical team found his tricuspid valve was
5 regurgitating and slowing the blood flow. This in turn made it physically hard for Brody to do
6 things he enjoyed doing, from working on the farm, helping the kids with their activities,
7 hunting, camping, and just going to work and providing for his family. The family had to rally
8 together and help pitch in to get things done that Brody would normally do himself.

9 The medical team informed us that there was a trial being conducted and he would be a
10 good candidate for it, if he chose to be a part of the trial. The trial was for a tricuspid clip to
11 anchor down the valve and stop regurgitation. With much consideration, we decided to take part
12 in the trial. The placement of the clip took a few hours. Brody spent one night in the hospital for
13 observation and was back to work and feeling better within a few days.

14 Brody has been able to get back to the things he enjoys, such as spending time with his
15 family, building barns and fences on our farm, hunting, camping, and starting his own
16 construction company. Modern medicine and all the advances have truly blessed my husband and
17 our family's lives. He wouldn't be here without it. Thank you, each and every one of you, for
18 dedicating your lives. Your sacrifices have not gone unnoticed. Our family has truly been blessed
19 for it. Thank you for taking the time and consideration for the tricuspid clip approval.

20 Dr. Pat McCarthy: Good afternoon, everyone. I'm Pat McCarthy. I'm Executive Director of the
21 Bloom Cardiovascular Institute here at Northwestern Medicine. I'm also the inventor of the MC3
22 ring, which is the most commonly used tricuspid repair ring in the world. And formerly, I was an

1 unpaid member of the TRILUMINATE board. I'm here because I believe in this new therapy.

2 Tricuspid regurgitation is a serious but insidious disease that slowly disables, then kills patients.

3 The tricuspid valve leaflets are pulled apart, so it becomes a mechanical problem. In a
4 sense, the valve is broken. The valve doesn't close, and therefore medications are of little help.

5 There is no good medical therapy when the leak becomes severe. In this condition, there's a
6 catch 22. The risk of open-heart surgery to repair or replace the tricuspid valve and stop the leak
7 is one of the highest risk elective operations that we perform in all of heart surgery.

8 Since it is high risk, then the cardiologists don't refer patients until their symptoms are
9 very advanced. It's not uncommon for me to see patients who are developing kidney, liver, and
10 heart failure. Since patients have developed these side effects before surgery, the operation is
11 high risk. A bad surgical outcome with complications and a significant risk of death confirms the
12 cardiologist's belief that surgery is too high risk and should be reserved for only the most
13 advanced cases, so that the cycle repeats.

14 In the U.S., we only do one or two thousand isolated tricuspid valve operations a year.
15 The vast majority of patients go untreated, or so-called medical management, as per the control
16 group in the study that you just saw. Dr. Adams already told you about the debilitating
17 symptoms, which eventually cause severe heart failure and death.

18 Quality of life for these medically managed patients is poor. I'm here because we have an
19 opportunity to break the cycle. When we can offer a safe, effective transcatheter therapy, more
20 patients can be treated. Hopefully, we will see them earlier in the course of the disease before
21 they have developed irreversible heart failure.

22 Most patients who go through isolated tricuspid surgery have a long hospitalization, a
23 long time recovering at home, and it's not uncommon to survive but have serious limitations

1 such as the need for dialysis. A less invasive procedure can lead to a quicker and safer recovery
2 and a much-improved quality of life as you saw in the data.

3 I'm glad that my repair ring has been used worldwide in almost 100,000 patients and it works
4 well, but I know that a significant number of those patients faced a difficult and slow recovery.
5 The data that you heard today shows that we have a new and better option. Since patients are
6 rarely referred for surgery, almost all are maintained on ineffective drug and medical therapy.

7 In the control group, there was no significant improvement in the medically treated
8 group. There is no effective medical therapy. However, the patients treated with transcatheter
9 edge to edge repair showed many improvements with a very significant reduction in the valve
10 leak. Since the valve isn't leaking as much, the patient feels better and there are significant
11 improvements of quality of life after TEER. The trial was a success for both safety and efficacy.
12 I'm here because I hope that this treatment will be approved so we can help these patients who
13 are suffering with little hope.

14 Mr. Gregory Jordan: Thank you. I'm Gregory Jordan, 76-year-old man living in
15 Sacramento with my wife. We've been married 52 years. Next month, we have four adult
16 children and 11 grandchildren and one great grandchild. I was a financial consultant, real estate
17 broker, and mortgage loan agent all at the same time. My journey to the TriClip trial began when
18 I started experiencing shortness of breath, lack of energy, and a forced restraint from my normal
19 activities. Previously, I've had a triple bypass surgery, three additional heart stents placed, kidney
20 failure, which led to six, one half years on dialysis and a kidney transplant.

21 Being my best advocate for my health, I contacted my cardiologist. and went to speak
22 with him. After prescribing several tests, he gave me my diagnosis and explained my medical
23 options. Dr. Saban indicated that the normal corrective surgery for leaking tricuspid valve would

1 be extremely risky for me due to the normal, due to my age and various health concerns. He told
2 me about a clinical trial that another cardiologist Dr. Singh, a friend of his, was going to become
3 involved in and said that he thought I might be a good candidate for the trial. I was referred to
4 Dr. Singh, who explained the procedure, risk of the surgery, devices to be used, and gave the
5 details of the trial and had me sign the consent forms.

6 Then I started the comprehensive testing process. I was qualified and the surgery was
7 successful in minimizing the tricuspid valve leakages. Recovering from the surgery has been
8 very easy for me and there's been no adverse reactions. Of course, I've had mixed moderations
9 in some of my more strenuous activities, but my quality of life has improved significantly. I golf
10 twice a week. Ride a cart, not playing eight holes. I walk two miles, six times a day or a week
11 ather. I participate as a Tai Chi student. I row on my rowing machine. I swim on occasion, and I
12 enjoy my wife, family, and friends. Sometimes I've been invited to teach high school students
13 and church congregants, the principles of money management.

14 Within our residential community, I plan and organize jazz concerts, black history
15 celebrations, and veterans' appreciation lunches. The reason I decided to share my testimony is
16 because there has to be many people who are experiencing the illness and risks that threaten my
17 health and further existence. We must share our experiences of the good and cherish the gift of
18 health for it is the foundation of all dreams. Our health is our wealth. Thank you for the
19 opportunity.

20 Ms. Suzanne Aguilar: Hi, my name is Suzanne Aguilar. I am 71 years old and have lived in
21 Woodland, California all my life. I was a fourth-grade teacher for 27 years working with low-
22 income children who showed me humility, giving, and respect. It is a job I cherished very much.
23 I was awarded a plaque for education from the Mexican American Concilio of Woodland,

1 California. I was diagnosed with AFib in November 2008, when an echocardiogram showed I
2 had a leaky mitral valve. My surgeon, Dr. Niles Smith, told me if I didn't get open heart surgery,
3 I would get congestive heart failure and could die.

4 I love life so much, I made the decision to have this surgery, although it took three
5 months of recovery. My surgery was successful, and I have a beautiful scar to prove it. I
6 continued living with AFib for many years after the surgery, going in and out of the ER for AFib.
7 I feel like I should have had my own room, room there as I was there every weekend.
8 My life was like a hill. It was extremely frustrating, especially because apart from my heart
9 condition, I didn't get sick. I was an athlete, but I was too scared to do anything for fear that
10 AFib could kill me. As the years passed, I continued to feel ill, gaining weight, even though I
11 wasn't eating much. Especially in my legs and ankles, they were very swollen. I felt as though I
12 was dying. My family encouraged me to see a specialist. And I met with Dr. Singh who put me
13 on, who put me on, actually put me on Bumetanide to reduce the water retention and admitted
14 me to the hospital for eight days. I lost a total of 105 pounds of water weight.

15 My cardiologist recommended I speak with Dr. Singh for my leaky tricuspid valve. I
16 couldn't continue to live the way I was living, as this procedure would not require open heart
17 surgery, I decided to participate, of course. I feel so lucky to have been chosen after all I had
18 been through. My recovery period was short, and I felt good. I don't struggle to breathe anymore
19 and live a normal life. My plans for 2024 are to volunteer for the [indiscernible] in Yolo County
20 Grand Jury. I served on the Yolo County Grand Jury for two years, and I look forward to
21 continuing to serve my community as a juror, a tutor for schools, and acting on the stage of the
22 Woodland Opera House, which I enjoy very much.

1 I love life so much and I'm lucky to be alive thanks to Dr. Singh and the device you are
2 reviewing today. There are so many other people like me out there in this same dilemma who are
3 just surviving and suffering because of this condition. People who love life want options that
4 give them back their lives. I ask you to think of my story and those people today as you make
5 your decision.

6 Mr. Ayers: Thank you. My name is Rich Ayers. I am 67 years of age and I live in San
7 Diego, California. I have been married for 38 years and have two adult children. I am a retired
8 Naval officer after 20 years in the Navy and permanently retired after working for the city of San
9 Diego as a safety and training manager.

10 At the age of 50, I was diagnosed with atrial fibrillation. I had been on medication to
11 control the AFib and it has impacted my lifestyle. In May of 2020, my cardiologist noticed
12 regurgitation in my tricuspid valve. At that time, it was very minor, and my doctor said to
13 monitor it. Then in November 2020, I started gaining weight. My doctor then put me on different
14 diuretics for a few months to try to keep the water weight off. However, the medications were
15 not working. My weight would plateau, but then I would start gaining weight again and would
16 need higher dose of medication.

17 During this timeframe, it really affected my lifestyle. I had a hard time sleeping at night. I
18 would be awake until 2 AM. Then go to sleep and then wake up again at seven. I had to take naps
19 during the day to try to catch up on sleep. I would try to do my usual walking every day.
20 However, I had a hard time catching my breath when I walked more than 15 minutes.

21 During this timeframe, I had gained over 40 pounds in water weight. None of my clothes
22 would fit. My wife had to buy me workout clothes that were loose fitting. In April, 2021, my

1 doctor admitted to me into the intensive care unit. I spent 19 days in ICU using stronger
2 medication to get my weight back down to normal.

3 After getting out of the hospital, my doctor said that my tricuspid valve needed to be fixed. My
4 options were to have surgery going through the ribcage to repair the valve or being a candidate
5 for the tricuspid clips. After meeting with various doctors, evaluating the risk of each procedure,
6 I decided to go with the clips.

7 It was the least risky of the surgeries, and I was told it could be reversed if it didn't work.
8 Before the clips were installed, the doctor informed me that my tricuspid regurgitation rate, on a
9 scaled one to five, with five being the max, I was at seven. After the clips were installed, my
10 regurgitation rate decreased to a moderate level. The procedure required me to be in the hospital
11 overnight. And I was released the next day. Recovery was very easy. I was able to do my usual
12 day to day functions, but nothing too strenuous right away. I still have to take some diuretics
13 every day, but my weight is being controlled. I walk every day 30 to 45 minutes and lift weights
14 three times a week.

15 My wife and I have a trailer and go camping a lot. I'm able to go on hikes and bike rides.
16 I do whatever physical activity I want to do and don't feel limited. The clips have made a big
17 difference in my life. I personally feel that anyone else that has tricuspid issues should be offered
18 the choice of having the tricuspid clip surgery made available to them. Thank you for your time.
19 Dr. Videnieks: Hi everyone. My name is Lindsay Videnieks and I serve as the Executive Director
20 for Heart Valve Voice U.S. Heart Valve Voice U.S. receives indirect funding from the sponsor for
21 a policy task force that convenes organizations who care about access and equity issues affecting
22 people living with or at risk of heart valve disease.

1 I'm here today to ask all of you to consider. The perspectives of the estimated 1.6 million people
2 living with tricuspid heart valve disease and those who care for them. As you discuss and vote on
3 recommendations regarding the pre-market approval application for Abbott's tricuspid valve
4 edge to edge repair device.

5 It goes without saying, but I'm going to say it anyway, severe tricuspid regurgitation or
6 TR by itself is a progressive and fatal disease. As you discuss the risks and benefits of this less
7 invasive treatment option for symptomatic, severe tricuspid regurgitation, please recognize this.
8 Although highly prevalent, TR is often left untreated.

9 A substantial number of patients with TR and congestive heart failure are prescribed
10 medications to manage their underlying heart failure, both to relieve symptoms and prolong
11 survival. However, a 2019 study from the Cleveland Clinic found that 65% of TR patients on
12 medical therapy alone died within approximately 3 years.

13 Options for surgery include tricuspid valve repair or replacement but estimates reveal less than
14 10,000 patients undergo tricuspid surgery per year in the U.S. Health care disparities have been
15 well documented with approximately 60% of patients undergoing tricuspid valve surgery being
16 white, compared with only 10% being black patients and 6% being Hispanic patients.

17 The in-hospital mortality after tricuspid valve surgery remains high at approximately 7 to
18 9%, but there are no available data to compare outcomes across race and ethnicity groups.
19 Tricuspid surgery may significantly alleviate symptoms, enhance one's quality of life, and
20 prolong survival. As with all operations, there are risks of bleeding, infection, formation of blood
21 clots, prolonged hospital stays, and pain following the operation, and of course, the possibility of
22 re operation.

1 Heart valve disease patients often confront unique and complex healthcare needs.
2 Necessitating specialized treatments to address their conditions effectively. Advanced medical
3 technologies designed for heart valve repair and replacement are crucial to ensuring the patients
4 have more options in treating their heart valve disease symptoms.
5 Innovative interventions, such as the one being discussed today, are a part of that equation, and
6 that is truly the crux of benefit risk, isn't it? Individuals living with heart valve disease meet with
7 their health care providers, often alongside family caregivers, to discuss the benefits and risks of
8 treatment. Understanding what matters most to people living with heart valve disease, including
9 alleviation of symptoms should be of the utmost importance. We therefore urge this advisory
10 committee and the FDA to consider the unmet patient need in the tricuspid valve disease space as
11 you help determine approval for new heart valve disease technologies. Thank you for your time
12 and your consideration.

13 Dr. Aaron Horn: My name is Aaron Horn Jr. I'm a structural and interventional
14 cardiologist practicing in northern New Jersey. I'm here representing the association of black
15 cardiologists where I am a member of the interventional cardiology committee. I'm also co-chair
16 of the structural heart committee.

17 As far as my disclosures are concerned, I have speaker honoraria from Zolifest and
18 Pfizer. As far as the Association of Black Cardiologists, we have in fact received minimal
19 contributions from Abbott in the past. The Association of Black Cardiologists was founded in
20 1974 with the goal of addressing the disparate impact of cardiovascular disease on diverse racial
21 and ethnic population.

22 ABC's mission focuses on prioritizing equity by advocating for and continuing the
23 relentless work toward the prevention and treatment of cardiovascular disease in Blacks, other

1 minorities and underserved populations and elimination of disparities through an inclusive
2 framework as it pertains to the committee's decision, looking into the approval of TriClip, I'd
3 like to bring five items to the committee's attention.

4 First, we think is incredibly important to advocate for increased diversity in clinical research,
5 including clinical trials. Secondly, we believe it's incredibly important that we emphasize the
6 need for minimally invasive treatment for patients living with severe tricuspid valve
7 regurgitation. We also think it's incredibly important that we represent the cardiovascular health
8 concerns of the African American population and advocate for tailored solutions.

9 The fourth point I'd like to make is to stress the importance of ensuring equitable access
10 for African Americans to cutting edge medical devices. The fifth point I'd like to make is that we
11 apply lessons learned from historical challenges in accessing transcatheter therapies and prevent
12 replication of access decreases. I'd like to take one last moment to bring to the committee's
13 attention as we talk about tricuspid valve disease, understanding the morbidity and mortality
14 associated with that particular disease state, also, understanding that the current modalities
15 available, be it surgical repair or replacement, do not actually bear out acceptable outcomes that
16 tricuspid valve therapies actually might be, in fact, the best option for diverse patient population.
17 I'd like to reference a November 6, 2023 abstract that was published in circulation. The title of
18 the article is racial disparities and long-term survival among patients with moderate and
19 moderate to severe tricuspid valve regurgitation. The conclusion actually of the abstract notes
20 that Black race is a potential disease modifier leading to excess mortality

21 So, I'd like to make sure that the committee is aware that with this particular disease state
22 already have in a high morbidity and mortality, and already having, in fact, what we don't deem
23 to be acceptable treatment modalities that exist. This would grant an opportunity to make sure

1 that we decrease the disparities and the health inequities that particularly exist in this tricuspid
2 valve space. The Association of Black Cardiologists appreciates the opportunity to share our
3 thoughts with you, and we look forward to maintaining open lines of communication moving
4 forward. Thank you.

5 Dr. DeBattista: Hello, everyone. I am Allison DeBattista with the Partnership to Advance
6 Cardiovascular Health. Or PATCH for short. PATCH does not receive funding from Abbott.
7 PATCH is a non-profit coalition of patient and provider organizations working together to
8 educate and advocate for the millions of Americans suffering from heart disease.
9 We work to advance public policies and practices that result in accelerated innovation and
10 improved cardiovascular health for cardiovascular disease patients. An important part of our
11 mission is to ensure patients have access to the most innovative therapies and treatments
12 available. In the ever-changing landscape of cardiovascular care, we want to bring attention to
13 the significance of groundbreaking interventions, particularly for those grappling with challenges
14 arising from cardiovascular conditions.

15 Individuals navigating the complexities of cardiovascular disease often face unique and
16 intricate healthcare needs requiring tailored treatments for effective intervention. Innovative
17 treatments offer patients a diverse array of options for managing their disease. Innovative
18 solutions are critical to achieving better outcomes.

19 We ask the FDA to include the patient perspective in its advisory role when assessing the
20 approval of novel technologies. By doing so, the FDA can enhance the quality of life for those
21 contending with cardiovascular disease, addressing unmet needs, and fostering a healthcare
22 environment that prioritizes cardiovascular patients' distinctive requirements.

1 In the evaluation of medical technologies related to cardiovascular conditions, we
2 advocate for the FDA's recognition of specific challenges confronting this unique patient
3 demographic. Embracing innovation in cardiovascular disease care not only serves the individual
4 patient's well-being, but also propels advancements in cardiovascular health care on a broader
5 scale.

6 We hope the FDA will embrace these advancements to positively influence the lives of
7 patients living with cardiovascular disease and contribute to a health care landscape that places
8 paramount importance on their distinctive health care needs. Thank you for your dedication to
9 this vital issue.

10 Dr. Cooper: Hello, everyone, and thank you for the opportunity to address today's Circulatory
11 System Devices panel of the Medical Device Advisory Committee. My name is Josie Cooper,
12 and I serve as the Executive Director of the Alliance for Patient Access. AFPA does not receive
13 support from the manufacturer of the device being discussed today. The Alliance for Patient
14 Access is a national network of policy minded healthcare providers who advocate for patient
15 centered care.

16 We support health policies that reinforce clinical decision making, promote personalized
17 care, and protect the clinician patient relationship. AFPA hosts a cardiovascular disease working
18 group that convenes cardiologists to ensure that clinicians perspectives are heard as decisions are
19 made impacting patients with cardiovascular diseases such as severe tricuspid regurgitation.

20 The working group represents physicians, nurse practitioners, and other clinicians
21 treating cardiovascular patients. More than 1.5 million Americans are living with tricuspid heart
22 valve disease. This progressive and often fatal disease has limited treatment options. Currently,

1 many patients who undergo surgical intervention may have to opt for open heart surgery, which
2 comes with its own risks and potential complications.

3 However, a new option would allow for patients to consider an alternative, minimally invasive
4 surgical approach while we at AFPA do not offer comment on the clinical effectiveness of this
5 device, we urge you to consider the unmet need for this patient population as well as the value of
6 a less invasive treatment option for those patients.

7 As mentioned, treatments for the 1.5 million Americans with tricuspid regurgitation are
8 limited. There are medications that can treat symptoms, yet this does not address the underlying
9 issue. The only curative option is surgical intervention, and yet few patients are able to benefit
10 from the current surgical options.

11 A new option would allow for more patient centered care for patients with tricuspid
12 regurgitation, as well as offer a new tool for the providers who are treating those patients.
13 Patients and providers can work together to identify the optimal treatment method to alleviate
14 symptoms, treat the underlying disease, and ultimately lead to a higher quality of life.

15 AFPA urges the FDA and this advisory committee to consider the value that a new, minimally
16 invasive treatment would offer patients living with tricuspid regurgitation. We would ask you to
17 consider the unmet need for this patient population. Thank you for the opportunity to speak.

18 Dr. Lange: That concludes the open public hearing. I pronounce that part of the FDA meeting
19 officially closed. We'll proceed with today's agenda, but first, I want to thank all of the speakers.
20 I know that they were taped or prerecorded. Their messages, your messages are both important
21 and insightful for the panel, so I want to thank you for being a part of the process.

1 Panel Deliberations

2 We'll now begin the panel deliberations. Although this portion is open to public
3 observers, public attendees may not participate except at the specific request of the panel chair.
4 Additionally, we request that throughout the rest of the afternoon, all persons who are asked to
5 speak identify themselves each time. This will help the transcriptionist identify the speakers.
6 During the next hour, this will give us an opportunity for the sponsor to address the questions
7 that we had posed beforehand. And if there are any other questions directed towards them, or
8 towards the FDA, so with that, Erin shall I run down the list and then let you present or call on
9 someone to present on behalf of the sponsor? Is that okay?

10 Dr. Spinner Okay, we can do that. I also have the list. Whichever you prefer.

11 Dr. Lange: Let me run down just so I don't miss anything. And if I do, Erin, chime in, if this isn't
12 going to be terribly disruptive to you.

13 The data we looked at the data, the FDA provided data for sites doing less than, or more
14 than ten procedures and one of the Dr. Selzman that had asked that we look at it, as we look at it
15 with respect to those that did fewer than five, or more than five can you present that data?

16 Dr. Spinner: Yes, we can show that data. So, if you'll just give us a moment here. First, in
17 combination with that, we wanted to also talk about there was a question about the MitraClip
18 experience for our sites. We think it's relevant to discuss that in this context. Okay. So, I'll show
19 that first. I'm bringing up a slide, I'm showing a slide here that shows on the X axis the total
20 TriClip enrollment per site. You can see sites that enrolled less patients on the left, those sites
21 that enrolled more patients on the right. And then what you can see here on the Y axis is the
22 average number of MitraClip cases performed before 2019. So, it's important to understand that
23 all centers that were allowed in the trial had to perform at least 50 MitraClip cases prior to

1 allowing access into the trial. But what you can see here from this distribution is whether the
2 sites enrolled low numbers in TriClip as to those that were high enrollers, they all had a very
3 similar experience with MitraClip. I just wanted to start with that before we get into talking
4 about the cutoff of the five enrollments.

5 Dr. Lange: And Dr, Vidovich I think you had that question. Does this address the question?

6 Dr. Vidovich: This is terrific data. Thank you very much for providing this.

7 Dr. Spinner: You're welcome.

8 Dr. Lange: Go ahead Erin, Thank you.

9 Dr. Spinner: So, next, when we look at sites, the question was specifically around sites that had
10 five enrollments or less. Really, when we cut this data, or sorry, excuse me, sites that only had
11 five enrollments, there was only two sites that had five enrollments. And so, while there was a
12 comment regarding the importance of imaging, we do appreciate that there was extensive
13 imaging training prior to enrollment into the study for all sites and this will be something we'll
14 continue to do as we commercialize for our sites.

15 But so, when we look at the cutoff of the five enrollments it's really difficult to do that given
16 there's few sites that have that and so really first, we want to talk about and highlight the sites
17 and their ability to effectively use TriClip and the safety that they were able to deliver.

18 So, first I'll show you here on the left. These are sites with less than or equal to five
19 enrollments in the trial. And then on the right is sites that had greater than five enrollments. And
20 what you can appreciate here is regardless of the number enrollments they had, they were both
21 able to successfully use TriClip to reduce the patient's TR to moderate or less than approximately
22 87% of the patients.

1 Dr. Lange: So, Erin, let me ask you a question because a slide from the FDA suggests there were
2 42 sites that did less than five patients, not two, there were 42. Am I mistaken about that? There
3 was one site that had 51, nine sites that had more than ten, 14 that did five to nine and 42 that had
4 less than five patients.

5 Dr. Spinner: Maybe we had an error here. Oh, there was two sites with exactly five. Sorry. So, I
6 spoke their data is correct. Yes.

7 Dr. Lange: Okay. All right.

8 Dr. Spinner: Thank you. Thank you for clarifying that. Okay, so that's --

9 Dr. Lange: So, Erin and just like a quick question. That's the TR data. Are you able to see the
10 outcome data as well with regard to death, mortality, hospital, hospitalizations and KCCQ? I
11 know we have it for less than ten. Do you all have that as well?

12 Dr. Spinner: We did look into that. I think the first thing I'd highlight is the baseline
13 characteristics. What happens when we choose these different cutoffs is we lose really our
14 randomization. What we see is the baseline characteristics of these groups are slightly different.

15 So, here you can appreciate sites on the left, sites with less than or equal to five
16 enrollments and sites with greater than five enrollments. While some factors are similar between
17 these, there are differences. So, we can appreciate one of the important factors which we saw to
18 impact patients heart failure hospitalization is their prior rates of heart failure hospitalization. So,
19 we can first appreciate a difference there. We also see that there's a different distribution of males
20 and females between this different break. So, it's difficult for us to really do a direct comparison
21 between heart failure hospitalization, and mortality, especially because in the primary endpoint,
22 we were able to see no difference. I can comment on KCCQ though.

1 Dr. Lange: I'm sorry. So, do you all you don't have the mortality data or you just you have is
2 unadjusted?

3 Dr. Spinner: We don't, we didn't run the five.

4 Dr. Lange: Okay.

5 Dr. Zuckerman: Can the FDA respond to your – Andy, or Dr. Moscucci, do we have the data for
6 the five. We did some additional analysis. We have a backup.

7 Dr. Farb: Yes, we do have a backup slide. Let us give us a moment.

8 Dr. Spinner: Would you like me to show KCCQ data while we wait or Dr. Farb. Just wait.

9 Dr. Lange: Okay. If you want to show that Erin, and we'll come back to Dr. Farb.

10 Dr. Spinner: So, when we broke it up by that enrollment, so here we're showing KCCQ. And so,
11 what we can see, appreciate first is that the baseline KCCQ is slightly different between these
12 two different groups, but we can, despite that, see a very similar change in KCCQ in the device
13 group. 14 points for those with less than five enrollments and 15 in those with more. And then as
14 I mentioned, a very similar TR reduction.

15 Dr. Lange: Dr. Vidovich does this – I can't remember whether it was Dr. Selzman that asked
16 about this.

17 Dr. Vidovich I think we both did in a certain way. I was mainly interested about volume operator,
18 MitraClips, and stuff, but this is actually very good data as well.

19 Dr. Lange: Okay. Andy, can you pull up the other data the FDA has?

20 Dr. Farb: Yes, we'll pull up our backup slide on slide 122 and 123, can you share. So, this is the
21 full randomized cohort.

22 Dr. Lange: It is expressed as a win ratio of all basically hierarchical win ratio. Andy?

1 Dr. Farb Yeah, I think we're showing this now. Do you want – Mauro can you walk us through
2 this?

3 Dr. Moscucci Yes, if you can, we also have a win ratio for center less than five or more than five.
4 We just need to retrieve that.

5 Dr. Lange: We'll do that. I'm going to run back to you, Erin, if you don't mind.

6 Dr. Spinner: Yes, not problem.

7 Dr. Lange: Because I wanted to ask about what about those that had moderate or more severity
8 versus those with less, kind of their outcomes.

9 Dr. Spinner: Yes, we can speak to that. First, I'll show a slide here. Okay. Are you guys able to
10 see this slide?

11 Dr. Lange: Yes, ma'am.

12 Dr. Spinner: Okay, great. Here you can see on the left. This is our primary analysis patient
13 population device patients only and then we actually included on the right all device patients by
14 the randomized, single-arm, or roll-in just to provide as much context as possible. So, what you
15 can appreciate on the left and on the right as well is patients with moderate TR and even those
16 that are left with more TR, keeping in mind that typically all patients, even if they didn't get to
17 moderate or less TR, did have some reduction in TR. So, you can appreciate that as there's an
18 increased improvement in the resulting TR grade, there's an increased benefit in KCCQ.

19 Dr. Lange: Dr. Selzman, does this address the question that you asked?

20 Dr. Selzman: Okay it does. Can I just ask a question because I'm not very fluent with some of
21 this stuff. If somebody has a change of ten, and we're saying that the placebo effect is five, are
22 we going to say that the net effect is really just five on the KCCQ? Maybe there's a KCCQ
23 expert out there that can explain that because if I look at that, then I'm saying, okay, if we're

1 going to call placebo, subtract five, then the net increase was five, which is I've heard maybe
2 questionable as to whether or not that's a considered a benefit.

3 Dr. Spinner: Yeah, I can have Dr. Cohen speak to this.

4 Dr. Lange: And then Scott, I'm going to direct the same thing to you. I'm going to call this
5 "fuzzy statistics," or statistics for the non-statistician. David, after you address it, I'm going to
6 ask Scott to do the same.

7 Dr. Krucoff: Rich just before we can, I just ask where the denominators on that slide really 17.

8 Dr. Lange: Go ahead and put the slide back up, Erin, if you don't mind. David, Dr. Cohen, hold
9 on for just a second.

10 Dr. Spinner: Yes, that's correct. This was showing, I believe, yes. Keep in mind that in the device
11 group, we had 89, 87% that reduced to moderate or less. We had very few patients where we, in
12 fact, had. Severe or worse TR, which is why we included the chart on the right to help see more
13 of the severe or worse because those included some more of the complex patients and single arm
14 as well as roll-ins. But you're correct. There's only 17 patients that had severe or worse.

15 Dr. Krucoff: Okay, so the here. Sorry. I just want to make sure I'm following this because it's
16 important. The denominator here is from the randomized arm of the 350?

17 Dr. Spinner: On the left side. For device patients only.

18 Dr. Lange: So, we're missing some numbers.

19 Dr. Krucoff: The 500 we're okay. This is not the whole cohort.

20 Dr. Spinner: That's correct, device only.

21 Dr. Lange: But and so how many –

22 Dr. Spinner: That's 175 in the device group,

23 Dr. Lange: Right, I'm just adding 72 and 54 and 17.

1 Dr. Spinner: Yeah, so all patients had to have – to look at this, there’s a few things they had to
2 have. Basically, they had to have TR that was evaluable at one year, right? And we had a case,
3 had to have a KCCQ for them at both baseline and one year. So, it won’t be all 175 patients. And
4 of course, they had to be alive.

5 Dr. Krucoff: But it’s a 350. It’s taken from the 350, not the 500.

6 Dr. Spinner: That’s correct. That’s correct.

7 Dr. Lange: So, there are, if I’m reading this correctly at the end of 1 year of the device patients,
8 there are only 143 that we could evaluate the TR and had symptoms in, is that right Erin?

9 Dr. Spinner: Yes, that we could evaluate the change in KCCQ. Yes. All three of those factors.

10 Dr. Lange: All right. So, we’re missing data on. About 30 patients or so we don’t have we don’t
11 have both. We don’t have the TR data and KCCQ data?

12 Dr. Cohen: Rick about 20 of the patients died before 1 year. So, you’re missing data on about
13 ten.

14 Dr. Lange: Thanks. Okay. Thanks, David. Appreciate that.

15 Dr. Cohen: Let me get back to the question that I was asked to comment on before and if I could
16 get the slides, there we go. Let me show that one. So this is tricky. And I think Rick, your
17 description of fuzzy statistics are trying to, again, trying to sort out a very complex set of
18 interactions is what is really what we’re talking about because no single factor really determines
19 the quality of life or the KCCQ for these patients.

20 We know, as I mentioned in the morning session, that where the KCCQ ends up is a function of
21 where it started, how much reduction in TR they got, and then some other factors. And that’s
22 really what’s being shown here. And that’s why, again, these singular plots where we’re looking

1 at just a single dimension of that relationship are misleading, because again, there are multiple
2 factors that all come together to tell that whole picture.

3 And that's really what we're trying to display here. In addition, I think the idea that we
4 can say with certainty that there's a five point or so placebo effect, frankly, is, is unknown. And I
5 think that it's a bit naive to try to just simply subtract that from whatever the benefit is and say
6 that's what's left over after the placebo.

7 You have to recall, again, if you look, at a, at a group of patients, the control group, that
8 they didn't get a placebo effect because again, they know what they received, but they are getting
9 better and they're getting better because of several different factors, including what we call the
10 Hawthorne effect, which is because they're in a trial and they're being observed and treated more
11 rigorously perhaps.

12 And in addition, there's something which is ubiquitous in these trials, which is called
13 regression to the mean, which means that we usually start patients in trials when they're at their
14 worst and actually, I think the patient testimonies spoke to that is these patients when they came
15 to attention here, we're at a point in their disease where they really were at the worst.

16 And that means that even just with random variation, they're going to get better. So,
17 again, it is a very complex set of relationships. What we're looking at here in this. In this
18 regression model that Dr. Arnold and I put together, and again, this is based specifically on
19 patients from the trial, both randomized and single arm, all of whom got the device, so that they
20 get the same amount of placebo effect, in a sense, because again, all of them know they got
21 treated.

22 So, we're taking the control patients out of the picture and now we are looking again at
23 the relationship between the change in TR, they came in with a certain degree, where did they

1 end up, and the baseline KCCQ, and I already highlighted the fact that it's about a four-point
2 improvement in the KCCQ for every grade change in TR on the five-level scale.

3 But in addition, the second line on this table, the baseline KCCQ per ten points, what
4 that's telling us is that this, that's really this regression of the mean and the Hawthorne effect.
5 That is what happens to these patients, again, just by, just as a basis of where they start out, and
6 so this really gives us the framework to interpret the results, but I, again, I think it is – it's
7 oversimplification to, to think that we can know, five points placebo effect for everybody. It
8 could be zero, could be five, could be two, it's really hard to know, but this is our best effort to
9 really tease that out by taking the placebo effect largely off the table by focusing on a specific
10 group of patients, all of whom received the device. I hope that is helpful. It is. It was tricky for us
11 to work on this and to get this all worked out in our own heads. And so, I'm – hopefully I've
12 been able to explain it reasonably well to you.

13 Dr. Lange: I'm going to call on Dr. Cizik in a second but David, let me, I'm not, how can you
14 claim, so I'm asking, as a non-statistician, so I'm not meant to be confrontational, but how can
15 you claim that you've taken the placebo effect out by just analyzing the device arm? There's still
16 a placebo – we may not be able to measure it. Everybody in the groups received a placebo effect.

17 Dr. Cohen: Correct. So, we've, so everybody starts with that. So, that's in there. It's baked in.
18 So, we're looking at, again, in this case, what is the additional effect of the change in TR on top
19 of everybody having gotten the placebo effect? We would have been much more; it would have
20 been much more problematic had we included the control patients who knew they didn't get
21 anything. That was my main point there is the control patients knew they didn't get something.
22 These patients all knew they got a treatment, which they came to, to seek. And so, we're level, is

1 you know, we're leveling the playing field with respect to the placebo effect. And then we're
2 looking about what is happening on top of that.

3 Dr. Lange: Dr. Cizik and then Dr. Zuckerman. Go ahead, Amy.

4 Dr. Cizik: So, I must confess, I spend a lot of time with PROMIS measures where we talk about
5 MCID, and I haven't heard that today and I wish I would have brought it up sooner. And looking
6 at anchor versus distribution-based methods to understand differences. So, again, using an
7 external question on a Likert scale, sometimes we use a global impression of change. And so, I,
8 this placebo effect is new to me in terms of, and I did my fair share of research prior to being on
9 this panel of the KCCQ and understanding that five points was considered clinically meaningful.

10 But now we keep talking about a placebo effect of five points. Back to Dr. Selzman's
11 question a little, like, is there a placebo effect of five and then we need another five of change
12 and this is, I'm probably the only person on this panel that's a little bit of an outsider from
13 statistics – and do a lot of orthopedic devices. But I think some of the conversation around just
14 PROM measurement hasn't been typical to what I hear in our PROMs world, about minimally
15 clinically important differences and using anchor distribution-based methods. Maybe someone in
16 the room at Abbott could comment. I'm also curious to hear what the FDA. Has to say about this
17 as well. Again, I spent a lot more time on the orthopedics device side. So, maybe things are a
18 little different here.

19 Dr. Lange: Dr. Cizik, thanks and so for that, I'm going to go to the FDA first to Dr. Zuckerman.
20 I'm going to come back to Abbott. The sponsor should have the last word on this. During this
21 time, so Dr. Zuckerman.

1 Dr. Zuckerman: Okay Dr. Lange, if we can pause this interesting discussion started with the so-
2 called training effect difference between small sites and large sites that Dr. Selzman was
3 interested in can FDA put up the slide where we do the cut point at five, please.

4 Dr. Farb: We have this slide of the gradient of change of the win ratio as a function of
5 enrollment size. And if we could pull up slide 124. 123. And then –

6 Dr. Zuckerman: Okay, so this slide shows that regardless of what cut point you use low volume
7 sites have a different result than the high-volume sites. And Andy, do you have a more specific
8 flow chart for the N equals five sites?

9 Dr. Farb: We have a slide; we'll pull this up. Do you have a slide?

10 Dr. Ye: I have slides there.

11 Dr. Farb: That's the one we've seen. Yeah. While we're pulling it up the as the data showed in
12 the prior slide, the gradient is consistent where the lower rolling sites had a smaller difference in
13 the win ratio versus the higher rolling sites.

14 Dr. Lange: Dr. Selzman, I know you had asked about that. Does that answer? Do you feel like if
15 you leave that up there for just a second?

16 Dr. Selzman: Yeah, there's a lot of stuff in this. It's all intuitive. If you do a lot, you're going to
17 have better. I guess the question for FDA is. Is there a cut point, is – when this goes out, are you
18 going to demand that you get mentored for ten more than five? There was this roll in of three, but
19 do you want to, how you message coming out of this? What the learning curve is and how you're
20 going to supervise when this goes out commercial? Because this is going to go out like wildfire.

21 Dr. Lange: We'll talk about that when we get to the questions if that's okay.

22 Dr. Zuckerman: That's the question for you. Dr. Selzman, and Andy and Xuan, do you have the
23 other slide?

1 Dr. Farb: We don't have the other slide available right now, Bram. There are two issues. One is
2 the issue of the lower enrolling sites seeming per the sponsor having equal ability to reduce
3 tricuspid regurgitation. However, what we see here is a gradient in the win ratio results between
4 the lower enrolling sites and the higher enrolling sites. With the higher enrolling sites showing a
5 greater difference in the win ratio in favor of device and less so in the lower enrolling sites.

6 Dr. Lange: And in fact, there's a couple of hands up before I make a comment. Dr. Vidovich and
7 then Dr. Shanker.

8 Dr. Vidovich: I just want to make a comment. I'm trying to put these two slides together. One
9 from the sponsor and one from the FDA. It appears that even the lower enrolling sites in the
10 tricuspid clip had the extensive MitraClip experience, so if I could again, I would have to
11 superimpose those two slides, but it seems that private or prior MitraClip experience, which was
12 in hundreds, 500s did not appear to help the lower enrolling sites to get a better win ratio. Is that
13 a safe way to say this?

14 Dr. Spinner: If the sponsor can, if we can comment?

15 Dr. Lange: Yeah, yes, ma'am.

16 Dr. Spinner: Yeah. So, I think it's important. While MitraClip experience does play an important
17 role, it really puts them at a threshold, but we need to keep in mind that even imaging and
18 understanding of the valve and new therapy in general, there's always a new learning curve.

19 Yes, the, while they all had comparable MitraClip experience, there is learning that is
20 gained. We can talk about our robust training plan that will roll out. But this is something that
21 with any new technology, there's always training. And I'd like to actually, if we can have our PI
22 from our post-market study from Europe where we've had the device approved for almost four
23 years now talk about how we went from clinical trials in the success that we've had in the real-

1 world experience. Because I think that's really what ultimately, this gets down to. Win ratio is
2 one way of looking at this, but it's ultimately about the outcomes that the sites can provide, both
3 TR and improvement to the patients.

4 Dr. Lange: Erin, I'm going to put that on hold. Just want to make sure we get all the questions
5 first. Not that if, and if we have time, we can do that.

6 Dr. Spinner: Okay.

7 Dr. Lange: Okay. So, Dr. Shanker, then Dr. Krucoff.

8 Dr. Shanker: Yeah, thank you. I'm having a little difficulty trying to interpret these numbers.
9 You'll have to excuse me if these sound like stupid questions. My understanding was that the
10 procedural and device success rate was very high in the actual study, in the primary randomized
11 cohort. If that is the case, and there was a significant reduction – in tricuspid regurgitation, which
12 appears to be the case. Why was there such a change in the KCCQ, which is a patient reported
13 outcome metric. That should be completely agnostic, right? The win ratio was driven by the
14 KCCQ. So, why is the PRO linked to low volume sites? I don't understand that.

15 Dr. Spinner: I can comment on that from the sponsor.

16 Dr. Lange: Yes, ma'am.

17 Dr. Spinner: So, I think that's an excellent observation. And so, one thing we found as well. So,
18 we had consistent TR, consistent reduction in KCCQ. You can appreciate that here in the win
19 ratio because what we saw happens is there's a difference in heart failure hospitalizations.

20 And what we noted as I mentioned prior is that the baseline heart failure hospitalization
21 rate of these patients was different in the centers. So, it's very, there's — it's complex. There's
22 multiple layers that can affect this win ratio. But just as you mentioned, the PRO was
23 consistently improved in the device group as compared to the control in any of these sites.

1 Dr. Zuckerman: Okay, but unfortunately, what it implies, Dr. Shanker, is that there's a more
2 adverse scenario going on with heart failure hospitalizations, such as you saw on the detailed
3 n=10 ten flow chart and you're absolutely right. this remains unexplained for FDA. So, what's
4 going on here, but I'll let you summarize it.

5 Dr. Lange: The success rate appears to be the same for both groups, but obviously the outcomes
6 appear very different. Dr. Krucoff and then Dr. Yuh.

7 Dr. Krucoff: Yeah related, Amit actually got to part of what I was going to dive into here, but I
8 think the just to separate the volume from the previous experience, I think it is quite possible that
9 we're not going to document it, but the level of experience that the sponsor showed from these
10 centers which is still going to be relevant if this device rolls out nationally may actually be very
11 protective of safety events that we're not seeing across the board and just the handling of this
12 device in a human heart, so that's not even part of the calculus of the win ratio. So, I just want to
13 try and get a couple of degrees of separation. What's going on here with the, I'll call it the
14 experience level of tricuspid clipping and how it affects probably the KCCQ or not. Or
15 something else that counterbalances the win calculations that are on the slide we're looking at, to
16 me, is a different question than the role of previous experience across these centers, which may
17 actually have helped avoid other more major complications just by understanding the control of
18 the instrument structure in general, as you then turn it from MitraValve to tricuspid.

19 Dr. Lange: Thank you Mitch. Dr. Yuh I know you had your hand up at one time question, David.

20 Dr. Yuh: Yeah, thank you. I'm still trying to reconcile and make sense of the difference in win
21 ratios between the smaller and larger centers and if indeed the difference is driven by differences
22 in heart in hospitalizations and the KCCQ changes in spite of relatively comparable technical
23 success rates. Does it imply, does the sponsor think that the populations are disparate? Is that's

1 what – is that the major driver of the differences that the patients and the smaller centers started
2 off behind in terms of their clinical status, or is there somehow some difference between the two
3 categories of centers in terms of optimal medical therapy, whereby the to help explain those
4 differences and outcomes? I'm just still having trouble understanding or trying to get a better
5 handle on the differences between the volumes that the outcomes in the different volume
6 classifications.

7 Dr. Lange: Go ahead. Sponsor Erin, go ahead.

8 Dr. Spinner: Yeah. So, first, I want to have Dr. Shu come up and really just talk a little bit about
9 the win ratio just from a statistical point of view. And then I'll have Dr. Sorajja speak to really
10 answering that question and the difference in the potential difference in the baseline
11 characteristics as well as other factors that could be contributing here.

12 Dr. Shu: Hello, I would like to provide a little bit of statistical perspective by looking at the win
13 ratio as a functions of some center size. As we know, in the overall studies, we have seen a
14 comparable – deaths or TV surgery rate and heart failure hospitalization rate and the both of the
15 rate are lower. So, when you do a cutoff like that, you will get a disproportionate difference rate,
16 and maybe the difference is really driven by one or two event because the overall rate is low.

17 Also, we have been seeing previously that when we cut the sample size like that, the
18 baseline characteristics for the small centers or large centers will be different and we have done
19 some exploratory analysis that, for example, the predictors for heart failure hospitalizations, one
20 of the contributing – the significant predictors is the heart failure hospitalizations one year prior
21 to procedure. And it was showing in the slides that we have seen that small sites may have a
22 different baseline characteristics with respect to the history of the heart failure hospitalizations.

1 Dr. Lange: And come back up, so granted that heart failure hospitalizations in the previous year
2 predict who will be hospitalized next year, but we're not seeing a treatment effect. That is that
3 one would expect that a treatment would reduce that rate regardless, even if the rates higher.

4 Dr. Shu: I think it does, but it's a put – So, I would say that the analysis by looking at the cutoff
5 is one dimension analysis, which cannot really adjust for the other baseline characteristics. As far
6 as I'm my knowledge goes that we have not had a statistical models that allowed to adjusting for
7 win ratios with respect to other baseline characteristics.

8 Dr. Lange: Thank you for that. Thank you. And Paul's going to come up and then I'll get to you,
9 Dr. Hauptman.

10 Dr. Hauptman: Thanks. So, we learned this morning that patients who scored at baseline high on
11 KCCQ generally did not have an improvement. I wonder if that baseline characteristic is
12 relevant, perhaps the lower volumes centers had patients who scored lower on the KCCQ or, that
13 could be a variable that we're forgetting about. It's really interesting too, because. It's possible
14 that there's a plateau effect. These patients often have comorbidities. If you start out feeling
15 relatively well, the benefit you're going to get from a TriClip, may be muted. Because you,
16 because there are other contributors to, to limit the fact, patients are not going to go from 70 to
17 100, they might go to 70 to 72 or 75.

18 Dr. Lange: Dr. Sorajja.

19 Dr. Sorajja: Thank you, Dr. Lange. If I may respond. Paul Sorajja, Minneapolis. So, I'd like to
20 share with you this slide here. And just looking at this slide again this looks at and a comparison
21 of patients less than five in terms of the number of patients being enrolled. Sorry, that should be
22 coming up just a moment.

1 There it is, sites with five or less versus more than five. And as was just alluded to, there
2 are some differences in the baseline KCCQ. They're not numerically very large, but certainly
3 they could be enough. And as Dr. Cohen did describe to you earlier, that there is a response
4 relation in terms of the baseline limitation as to how they do in follow up.

5 And as Erin also mentioned earlier, there are also some important baseline differences in
6 HFH at baseline. And all of these things, in terms of how they affect that win ratio, it's a
7 multifactorial process.

8 Dr. Lange: Thank you. Jennifer Schwartzott, I see your hand up.

9 Mrs. Schwartzott: I was wondering if there's additional data coming from Canada or the
10 European Union that we could look at that would back up the figures here since it's already been
11 passed there.

12 Dr. Spinner: Yes, I can have Dr. Lurz speak to this. He's the PI of our post market study in
13 Europe.

14 Dr. Lurz: So, Philip Lurz, Director of Cardiology in Mainz, Germany and if you may then I can
15 share some of our experience – European experience, especially after 2000 and 20 after device
16 got approval. And it's actually quite encouraging to see that after approval and after application
17 of the therapy in a more real-world setting, and also with many centers starting the device who
18 had no experience before, we see very similar outcomes as we see in a TRI LUMINATE pivotal
19 study.

20 And to be right, we see slightly higher rate of MACCE with 2.5%. However, I still think
21 that this is excellent considering that and that's probably to be expected in a less controlled
22 environment that in a registry, certainly sicker patients, more fragile patients, more complex

1 anatomies, and also patients with a much higher baseline TR were treated. So, almost 90% had
2 massive or torrential TR at baseline.

3 And also, effectiveness was very much comparable to what's seen in TRILUMINATE
4 Pivotal. And I think the reason for that is also – it's fair to assume that the procedure we do today
5 is not quite the same it was at the beginning of TRILUMINATE Pivotal. We have a newer device
6 iteration, which certainly is better. We continue to learn and have learned already. We have
7 improved our strategy during the procedure, imaging got better. So, all together, I think it's fair
8 to assume that the learning curve is steeper now and that we can also expect a better outcome in
9 the future.

10 And this is a group learning and the training program, which is put in place by Abbott
11 should make sure that this group learning is also passed on to those who will start with the
12 procedure.

13 Dr. Lange: Thank you. There was a question about the training program. And Erin, in the
14 interest of time, and someone can just spend no more than 2 or 3 minutes talking about that. Is
15 that okay?

16 Dr. Spinner: Yes, we can do that quickly. We'll have Dr. Sondergaard speak to that.

17 Dr. Lange: Terrific.

18 Dr. Sondergaard: Yeah, thank you. Lars Sondergaard. I'm a chief medical officer at Abbott. First
19 of all, I would say Abbott is very dedicated to provide training and procedural support in order to
20 ensure a safe and effective outcome for all our products. For TriClip specifically, we're going to
21 build the training program on the extensive experience we have for the MitraClip. So, first of all
22 when we select the sites it's going to be sites which have previously in experience with the

1 MitraClip. You can see here; they have to done at least 50 cases in the past and five cases within
2 the last six months.

3 And also, When the site is selected, it's mandatory to attend an in-person course, both for
4 the implanter and for the imager, including hands on experience. And it's highly recommended to
5 go for case observations and also during the procedure to have support for the procedure either
6 by clinical field specialist or physician proctoring.

7 So, again, this is all to try to have a safe rollout. The rollout is expected to be five to ten
8 sites per month. So, it's going to be a slow, controlled rollout. Once again, to have a safe and
9 effective procedure.

10 Dr. Lange: Great explanation. I appreciate the clarity and the brevity. Amit, does this answer the
11 question you had posed about describing the?

12 Dr. Shanker: Yes, it does. It does certainly in the U.S. and hopefully have a more robust program
13 outside the U.S. for training. I do have one question, though, regarding going back. I think Dr.
14 Sorajja had put up that slide about looking at the sites and the number of hospitalizations and
15 KCCQ. So, is it fair to say, then that the lower enrolling sites have a lower win ratio, which is
16 largely driven by higher heart failure hospitalizations?

17 Dr. Spinner: Yes, at least in the ones we have, we investigated, we didn't do an exhaustive list as
18 the FDA showed, but in the ones we looked at.

19 Dr. Shanker: And that appears to be independent of procedural or device success.

20 Dr. Spinner: That is correct.

21 Dr. Shanker: Thank you.

22 Dr. Lange: Thanks. Bram, your hand still up. I don't know if you have a question or comment, or
23 if it's just residual.

1 Dr. Zuckerman: Yes, I just had a quick question for Dr. Sondergaard. He's shown a very nice
2 training program, but a key component of this is to be able to measure KCCQ, especially at 6
3 months and 1 year. We know from the TAVR experience that that's been very, very difficult to
4 get good KCCQ follow up. What specific incentives will Abbott be thinking about to really
5 measure KCCQ so that we don't have a problem with missing data extended time periods?

6 Dr. Sondergaard: First of all, as already been mentioned, we're going to follow all arms in the
7 TRILUMINATE up to five years. We're going to work with you and FDA on the design of the
8 post market post approval study. We're going to use the TVT registry up to one year and the
9 linkage to CMS out to five years. So, we will be limited to the quality of the data in these
10 registries.

11 Dr. Zuckerman: But that's the point. Those mechanisms in the past have provided very
12 disappointing data regarding KCCQ follow up. We need new ideas here.

13 Dr. Sondergaard: One idea is that we can encourage sites to actually capture these important
14 variables, like including KCCQ, but again, it's not a sponsored – it's a real-world setting. It is
15 finally out of our control what's actually captured, unfortunately.

16 Dr. Zuckerman: I don't want to belabor this, but our regulatory oversight is for pre and post
17 market spaces, and this becomes critically important, and I do think Abbott has more of a
18 responsibility here than you're enumerating right now. But let's table that.

19 Dr. Lange: Yeah, Dr. Brindis

20 Dr. Spinner: I'll just add something —

21 Dr. Lange: I'm sorry, Erin you should go ahead and speak. I'm sorry to interrupt you. And then
22 we'll get to Dr. Brindis. My apologies.

1 Dr. Spinner: Okay, I was just going to add something to that. I think what's unique here too is
2 that these patients, the driving benefit that we were able to provide is KCCQ. Really, the clinical
3 community will be driven to continue to understand that benefit and prove that benefit. But
4 Abbott will, if necessary, if we do delve deeper and find that the TVT registry does not meet that
5 need and our ability to assess that, we are dedicated to, doing what is needed to be done with
6 FDA, for example, we have history with running post market studies just as we've done with
7 MitraClip with our EXPAND and our EXPAND G4 study. So, we are definitely open to that.

8 Dr. Lange: Thank you, Erin, for that. What I think you're hearing is what we've done so far isn't
9 working. And if this is going to be, if it is a suggestion of a post approval study, we're going to
10 want something that does work.

11 Dr. Spinner: And we would do that.

12 Dr. Lange: Thank you. Dr. Brindis and Dr. Yuh.

13 Dr. Brindis: I appreciate you bringing up the point about our 1 year follow up, for example, and
14 the TVT registry being for KCCQ being in the 50 to 60% range. We are totally dedicated the
15 NCDR to change that paradigm, particularly with the importance related to KCCQ and TriClip as
16 presented today, we're looking at a number of different mechanisms that we can try to help
17 centers in doing better, whether it be patient apps, utilization of vendors and others, but certainly
18 we would take any of the help that Abbott would want to help us in getting this past the goal line.

19 I agree totally with you and people at the NCDR are committed to try to move the needle
20 much, much further down the road in 1 year collection.

21 Dr. Lange: Maybe if they don't fill out the questionnaire, we take the clip back. Dr. Yuh.

22 Dr. Yuh: Thank you, David. You Yes, this is for the sponsor. It's my understanding that the
23 amount of diuretics remained relatively consistent throughout the one year period. Was there any

1 signal or do you see any signal that there's a possibility that diuretic requirement may be reduced
2 over time, particularly important in terms of durability of the positive effects of this device and
3 that diuretic resistance over the long term. Is there anything in your data that might suggest that
4 the diuretic requirement may decline with device patients?

5 Dr. Spinner: So, not at this time, but that is something we're particularly interested in as we
6 continue to follow these patients and learn more about these patients and how TriClip can affect
7 not only KCCQ, heart failure hospitalization, mortality, but as you mentioned, their need for IV
8 diuretics and other diuretics.

9 Dr. Yuh: So, that the static amount of diuretics over that study period was by design or it was
10 primarily by design, though.

11 Dr. Spinner: I'll have Dr. Sorajja speak to that.

12 And then I'll give Dr. Bart, Dr. Cizik, and Dr. Selzman. Go ahead, Paul.

13 Dr. Sorajja: Hi, Paul Sorajja here. No, there was no prescribed changes in diuretics that were part
14 of the protocol, either at the time of the procedure or in the follow up. So, all changes in diuretics
15 were at the discretion of the local heart team.

16 I share with you the desire to offer something to patients besides just loop diuretics for
17 the treatment of these patients with TR. Hopefully we'll be able to figure out some way – figure
18 it out somehow in the future. Anecdotally, I would say that in my experience, and you know my
19 numbers as an enroller in this study that I feel patients respond better to their current doses than
20 they did before the therapy. So, I can offer that whether that can change and follow up, I think
21 that remains to be studied.

22 Dr. Lange: Thank you, Dr. Bart. Dr. Cizik. Dr. Selzman.

1 Dr. Bart: Thank you, Brad Bart. I was hoping the sponsor could provide more details on their
2 perspective on optimal medical therapy. If I remember the consort diagram, fewer than 1% of
3 patients were eliminated because they were not on optimal therapy, which means 99% were felt
4 to be optimized. And earlier there was some discussion of GDMT and right heart
5 catheterizations. But I'm wondering if the sponsor could provide more information. Did
6 everyone have a right heart catheterization? What kind of numbers were felt to represent optimal
7 therapy? And as far as GDMT goes, really, we have some class one recommendations for those
8 with low ejection fraction, but for those who have an EF of more than 40%, really, the only class
9 one indication is diuretics and was just being on a diuretic felt to be optimal therapy, or was there
10 more of an attempt to titrate therapies? If you could provide more clarity on that would be great.

11 Dr. Lange: Erin, this is a great segue because you're going to share the right heart hemodynamics
12 and also the medication. Thank you, Dr. Bart for that segue.

13 Dr. Spinner: Perfect. Yes, totally agree with you. And we're going to have Dr. Benza comment
14 on that. And as you mentioned, we can share the right heart cath data and the medication. I think
15 it's important to answer this question

16 Dr. Lange: And then after we do that, we'll segue into Dr. Hirschfeld's question about the.
17 diastolic numbers after the procedure. So, those would be the three great things to catch up on.

18 Dr. Benza: Hi Ray Benza Mount Sinai heart cardiologist. Here's some information regarding the
19 use of medications during the, during this the study, I could maybe have access to the – okay we
20 have the right heart catheterization data here.

21 First, we can start with that. As you can see, as part of the adjudication committee for
22 patients entering the trial, we did want to make sure that people were at an adequate level. So,
23 then a procedure can, move through safely.

1 And you can see here at the right heart catheterizations, particularly focusing at the
2 central venous pressure that we're around 11 in the treated group and 12 in the control group.
3 And as many people know, really, the magic number for the right ventricle falling off its curve is
4 the CVP of 15.

5 So, we were well underneath that and felt very good about this type of number going into
6 the procedure. Our pulmonary vascular resistance was around 2.5. Again, the critical value for
7 the right ventricle is a pulmonary vascular resistance of 5. So, again, well under this. And as far
8 as our systolic blood pressures were controlled, we made sure that people who had significant
9 elevations in systolic or diastolic pressure were adequately controlled before entering the trial.

10 The only standard medical care for tricuspid insufficiency, is diuretics. But in response to
11 other comorbidities that coexisted in these patients as someone mentioned there, there was a
12 number of patients who had heart failure with reduced ejection fraction in these patients. We
13 made sure that they're on 3 pillar therapy, including adequate doses of ACE, ARBs, and ARNIs,
14 beta blockers, and mineralocorticoid antagonists if they were tolerated in the past.

15 Remember, this study is at the advent of SGLT2 inhibitors. And so the penetration of this
16 particular drug is not particularly prevalent at the time because they had yet to get the approval
17 for either heart failure, reduced ejection fraction or heart failure, preserved ejection fraction.

18 Dr. Lange: So, I'm sorry, can we show the data for – we looked at baseline medications in 12
19 months?

20 Dr. Benz Yes.

21 Dr. Lange: By the way, thanks for that hemodynamic data. That's terrific.

1 Dr. Benz: And so here again, you can see the pillars of therapy, including ACE inhibitors, ARBs,
2 and beta blockers and other vasodilators. These remain stable over the course of the therapy in
3 the majority of the patients, both in the device and in the control group.

4 Dr. Lange: Let everybody peruse it for just a second. This is very helpful. Thank you.

5 Dr. Benz: You're welcome.

6 Dr. Lange: Dr. Cizik and Dr. Selzman, questions about this?

7 Dr. Selzman: I have a comment that I'll make when it's all done.

8 Dr. Lange: Thank you. Okay. That'll be fine. Amy, a question about this.

9 Dr. Cizik: You could let Dr. Selzman go first.

10 Dr. Lange: Okay. We'll wait till the sponsor finishes with the questions. Then we'll come back to
11 you both Craig and Amy. Okay. That's great. And Dr. Hirschfeld asked about both the gradient
12 RA pressure and right heart caths done afterwards.

13 Sr. Spinner: Yes, we'll have Dr. Hahn speak to this.

14 Dr. Hahn: Thank you. Rebecca Hahn at Columbia University, chief scientific officer for the CRF
15 core lab. As you can see here, this is the increase in gradient as we had shown after the TriClip
16 device and the mean gradient increase was only up to about, I'm sorry. The mean gradient
17 increase was only was less than 3 millimeters of mercury. This is really lower than the expected
18 mean gradients after, for instance, a bioprosthetic valve replacement where the gradients tend to
19 be anywhere from 5 to 6 millimeters of mercury. And the guidelines now state the stenosis would
20 be a gradient of greater than 9 millimeters of mercury.

21 So, we believe that this increase does not represent significant tricuspid stenosis. The
22 pressure halftime, which we were asked to deliver was not – could not be measured in this

1 patient population. 90% of these patients were in atrial fibrillation, and the pressure half time is
2 inaccurate in that setting, even if you average the 5 to 10 beats, which core labs tend to do.

3 But it is just not accurate. And we know it's not accurate after valve replacements or
4 devices go in, in part because the peak velocity in diastole, the E wave is artificially increased
5 because of the slight reduction in the valve area. So, it's no longer just dependent upon the actual
6 gradient across from the atrium to the ventricle.

7 And similarly, for those reasons of the exaggerated E wave, the initial diastolic velocity
8 that goes across the valve, the estimated right atrial pressures are also not accurate and therefore
9 could not be estimated by echocardiography. But the implication of the improved forward flow
10 that we've seen, as you've already seen in the sub study of imaging that was presented by Dr.
11 Cavalcante do imply that there is enough forward flow that the diastolic higher gradients in the
12 right atrium did not impair forward systolic filling.

13 Dr. Lange: Yeah, I'm going to turn over to Dr. Selzman in just a second, but he had asked a
14 question about what percentage of people that had left sided heart disease. And after that's
15 answered, I'm going to turn it over to him for any question or comment. Erin, what can you tell
16 us about that?

17 Dr. Spinner: Yeah, so I believe this is the question around LVEF, or is this a question around
18 aortic, mitral, CABG, PCI?

19 Dr. Lange: They're two independent questions. So, if you can answer both of them, that'd be
20 great.

21 Dr. Spinner: Okay perfect. I will first address those with prior aortic and mitral intervention. As
22 we showed in our baseline characteristics there was just under 40% of patients that had prior
23 aortic or mitral valve intervention. When we looked at this as a factor, a contributing factor to

1 outcomes we conducted a subgroup analysis, which I'm pulling up here, and really what we can
2 see is whether patients had a previous mitral or aortic intervention or not the results were similar
3 and that there's really no difference or impact in all-cause mortality or tricuspid valve surgery as
4 well as heart failure hospitalization, but there was an improvement in KCCQ. So, this really
5 mimicked what we found in the primary analysis of the cohort.

6 Dr. Lange: Dr. Selzman you've had your hand up. Now I'm going to turn to Dr. Cizik and Dr.
7 Shanker.

8 Dr. Selzman: Oh, that's good stuff. Thank you for providing this. I have a little MitraClip PTSD
9 on the panel that I was on at that time where we talked about whether or not this procedure was a
10 palliative procedure. And this is a question that goes back right to the beginning and perhaps Dr.
11 Adams could address this. We have two mega leaders in our specialty, Dr. Adams and Dr.
12 McCarthy pushing this, not pushing this, but advocating for it. And Dr Yu asked the question
13 about the turndown the surgical turndowns and, it goes to this amorphous heart team and what I
14 worry about, and FDA is going to ask us about this, is indication creep, which is natural, it
15 always happens. So, here we have all these patients, these basically octogenarian 79, 80-year-old
16 folks that are getting these, and I could see how a heart team would say, hey, probably don't want
17 to operate on this, but I wonder if there's a more granular way much like PARTNER did, where
18 we had an STS score, we acknowledge that STS has a lot of deficiencies when it comes to
19 tricuspid valve disease because of the lack of information related to liver disease for example.

20 We know that really not everybody getting tricuspid valve surgery has an 8% mortality
21 rate patient selection, how you do it and what you just showed us with that hemodynamic data is
22 unlike any patient that I ever operate on for tricuspid valve disease with the CVP of 12. I'm
23 usually at 22 or 25 by the time I see these patients.

1 So, I wonder if there is the possibility or an attempt or when the study was designed, Dr.
2 Adams, that we could be a little bit more quantitative about how we approach surgical versus
3 medical versus clip management of these patients right now with MitraClip it's still this kind of
4 amorphous thing. It wasn't as amorphous with trans aortic valve – transcatheter aortic valves. So,
5 I wonder if the sponsor could comment on that or the FDA if they would like.

6 Dr. Spinner: I'll have Dr. Adams speak to this.

7 Dr. Lange: And then Dr. Cizik and Dr. Shanker, and then I will come on and then I need to wrap
8 it up before 2:00, We have a couple more questions that need to be answered, but go ahead.

9 Dr. Adams: Thank you very much for that very insightful question and observation, and this is
10 interesting to me. This is the one technology I think you will see rampant surge in support for.
11 There's not going to be a lot of creep. Most creep is toward patients we haven't studied or
12 patients that are lower risk. If there's going to be any creep in this population, I think it's going to
13 be even toward more higher risk patients as it gets. out into the community and we have this
14 chance to offer this to patients because like you said, that's the patient I typically get too, or the
15 sicker, more patients that have already had ascites that are really at the end of the trail.

16 And I do hope in the long term, this will usher in an era of earlier treatment for massive,
17 particularly for massive or torrential TR where the sequelae honestly are almost a fait accompli.
18 We cannot eliminate heart failure involvement in these patients because many still will respond
19 to heart failure medication, and we don't want to intervene too early.

20 I plead to keep surgeons involved in this space. Most tricuspid valve patients actually
21 come to surgeons first right now. That will take a while to change, and I think that the low-risk
22 patients, there will be a few, there are some patients that will benefit from concomitant treatment
23 of other valvular heart disease or other disease even if it's on the moderate side, depending on

1 their age and other risk factors, so there will still be a role for surgery. However, I think we will
2 see — I think we will see transcatheter intervention take over in this space for a majority of
3 patients based on risk. We will develop, we do need to develop new ways to adjust risk TRI-
4 SCORE was tested — honestly in healthier ventricles and healthier patients as well. I'm not sure
5 that's the answer. I think we need to think about it. And I just want to take the floor and say, I
6 could not agree with more with Dr. Brindis. And what Bram said about KCCQ.

7 Having spent my last 35 years living in the left atrium, I believe that this is a new era,
8 I've gotten so educated in this trial about the importance of quality of life in this question, and
9 we all need to think about how we intervene responsibly in this elderly population of outpatients
10 we face every day. And I hope that certainly you have the commitment of me as a leader in the
11 field. And I think all of us in this room that we're going to continue to push the evolution of the
12 adoption of KCCQ is a metric that's important to try and decipher which patients we should be
13 offering any intervention to, whether that's surgery or transcatheter therapy.

14 Dr. Lange: Thank you, Dr. Adams. Quickly, Dr. Cizik and then Dr. Shanker.

15 Dr. Cizik: Maybe to that point, I wonder if there is a role to think more about symptom related
16 measures for post surveillance and we heard a lot about in the page in the public panel about
17 shortness of breath, edema specific I wonder if there is a thought to do more of that again, when
18 the KCCQ is so multidimensional and it's hard to understand the score itself, what, what's
19 actually changing, right? You can't intervene on a score, but you can intervene on an item.

20 And then my other question was about provider type and the role of the cardiac surgeon
21 versus the interventionalist, and I think that got answered in the previous. But just some food for
22 thought as someone who comes from more generic measurement and thinking about that more
23 broadly.

1 Dr. Lange: And so, I'd say, save that thought when we came out of our discussion. FDA is going
2 to be helpful insight. Amit, Dr. Shanker.

3 Dr. Shanker: Yeah. Actually, I just wanted to, I don't want to really discuss this, but I want to get,
4 course I'm an electrophysiologist. I want to get back to the AF, is this appropriate time to do that,
5 or should I wait?

6 Dr. Lange: What I want to do is get this sponsor to answer the last couple questions.

7 Dr. Shanker: Okay.

8 Dr. Lange: And then unless it's something that needs to be directed toward the sponsor Amit?

9 Dr. Shanker: Yeah, actually, I do have, 87 to 93% of patients had AFib, and during the public
10 hearing the patient stories were very inspiring. But three patients said they had AFib, one
11 probably had persistent the hiker who didn't have AFib after the procedure. The other patient
12 was a teacher had AFib and coming to the hospital, I guess it didn't have AFib after the
13 procedure. There's someone in San Diego as well AFib. It gets back to how much of this is atrial
14 transport of, preserved with presumably seen with sinus versus those patients in AFib who don't
15 have preserved atrial transport. And how does that how might that physiologically benefit the
16 patient?

17 My question is, have you broken down those 87 or 93% of patients between paroxysmal,
18 persistent, long persistent, or permanent to see if there's a treatment effect? Because I'm, I
19 suspect there's a very strong intimate correlation between the arrhythmia and possibly
20 symptomatic relief. And I'm not sure if you'd see that same symptomatic relief in a patient who's
21 in sinus, who has preserved atrial transport.

22 Dr. Lange: And somebody to ask how many patients had an AFib ablation afterwards. Let's talk
23 about AFibs for the next 2 minutes.

1 Dr. Spinner: Okay, yeah, so I can comment on first the AFib ablation after TriClip implant. So,
2 we had four device subjects that had an ablation within 12 months, so 2%. And then I'll have Dr.
3 Adams talk about the patient population as we didn't do a specific breakout of those types of
4 patients.

5 Dr. Lange: And then Mitch, I see your hand up.

6 Dr. Adams: Thank you for that suggestion. I think you should help us look at it in one of our sub-
7 studies. I think you're absolutely right. We're going to have to get smarter now about atrial
8 fibrillation in this population. And I think I, for one, will put my hand up and assume that a lot of
9 these patients just had atrial functional – or an AFib that was atrial functional TR and MR and I
10 think that as we move forward in this field right now, that will certainly be one of the questions
11 that we need to ask. And I'll add electrophysiologist to my heart team for every single one of
12 these patients. And I actually have spoken recently to one of my electrophysiologists about this
13 very question and a patient that had moderate severe everywhere. And we're trying to decide
14 whether to do and an AFib ablation first or not, but I think you're making another really
15 important point about future management of these patients. Unfortunately, I don't have that
16 information in this study population right now.

17 Dr. Lange: Thank you Dr. Adams. Dr. Mitch, Dr. Krucoff. I'm sorry.

18 Dr. Krucoff: Thanks Mitch Krucoff. Just to extend that. The question of AV synchrony and atrial
19 fibrillation, sinus rhythm differences actually get amplified by what I hope, which is a soon to
20 come to question, which is with poorer ventricles, it's even more amplified. It may be
21 synchronized; you'll get more thematic.

22 Dr. Lange: What a great segue, Mitch, segue because Erin needs to. [multiple speakers]

1 Dr. Krucoff: The only thing I want to add that's not in the question that I hope Abbott will help
2 us answer here in a second, is that the other side of that is that with preserved ejection fraction,
3 but stiff ventricles. The same equation plays, so if you lose AV synchrony you may feel worse if
4 you are in AFib, get your tricuspid valve clipped and then are put back into sinus rhythm with a
5 stiff but systolically competent ventricle you're also going to feel better. So, these are the
6 caveats, but I would love to segue if that if it's time to know about just bad ventricles.

7 Dr. Lange: Yeah. So, let's do it. Ventricular function looks versus outcomes and Amit I'm sorry,
8 we don't have the information about either the type of AFib or post AFib and how many are
9 [indiscernible] we don't have that

10 Dr. Krucoff: But I'm with you a hundred percent on it.

11 Dr. Spinner: So, I'll comment on the LVEF. We do have that data available. So, we really broke
12 it down and patients with baseline LVEF less than or equal to 50 as we even we had a very small
13 number of patients with less than I think the comment earlier was that our cutoff was very low at
14 20. But what you can see here is we only, in fact, had 44 patients with LVEF of less than 50.

15 But that being said, the findings in these groups, regardless of this subgroup, are very
16 similar, in fact, same to what we saw in the primary analysis cohort with no difference in
17 mortality or tricuspid valve surgery. So, really not favoring TriClip or control as well as heart
18 failure hospitalization rate. But we can appreciate an improvement in KCCQ favoring device.

19 Dr. Lange: Mitch, do I have the data you're looking for?

20 Dr. Krucoff: Let's just say yes. Thank you.

21 Dr. Lange: Okay. Great. Erin, as far as I can tell, I think we've addressed every question that was
22 posed.

23 Dr. Spinner: I have a few if you. Just call them all answered, or we can address –

1 Dr. Lange: You got — we got five minutes, so run with it.

2 Dr. Spinner: Okay. So, I'll be brief. There was a question earlier about the patients that had
3 CIED-induced TR, and how did they respond to the therapy? So, there were 5% of those patients,
4 and in fact in the single arm cohort were pacemaker related, and I'll just show this slide briefly, but
5 what we found is that patients did, in fact, 100% of those patients, it's only five, had their TR
6 reduced to moderate or less, and their KCCQ change from baseline to 12 months, in fact, was
7 high with 24-point improvement and no MAEs.

8 Dr. Lange: And Mitch, you had asked for this and I'm sorry I missed it. Actually, I'm not, I'm
9 sorry. Dr. Shanker, Amit you asked for this. My apologies.

10 Dr. Shanker: I'm the electrophysiologist. Of course, I asked for it.

11 Dr. Krucoff: I'm just a plumber.

12 Dr. Lange: Go ahead Erin.

13 Dr. Spinner: There's one additional question. It's quite extensive, because it was asking about
14 looking at the full spectrum of echo, CT and lab parameters and a few other factors. So, if you'll
15 allow me, I'd really like to have Dr. Hahn speak to that and then Dr. Benza. So, we'll try and
16 keep it brief. But we just as FDA requested that we show all of them, not just in the core, I'd like
17 to take this opportunity to do that.

18 Dr. Lange: Please do so.

19 Dr. Hahn: Hi, Dr. Hahn, back again. We'll bring up the slide with the, much of the data on the
20 echo parameters through 12 months. I think the key here is to see the difference column and all
21 the obviously metrics that we have of TR severity show an improvement with the device.

22 The other trends are at least going in the right direction are some of the remodeling of the
23 RV. So, RV mid and basal dimensions did indeed go down, but were not statistically significantly

1 different. And then obviously, as you already know, the function of the ventricle appears to go
2 down, but that is just an artifact really of a reduction in the amount of volume which Dr.
3 Cavalcante had reviewed before.

4 Dr. Lange: Dr. Hahn, these is the core lab that looked at these and averaging 5 or 10 beats?

5 Dr. Hahn: These are this is all core lab adjudicate assessed, and the algorithm for us is to measure
6 as many beats as they've given us. In general, it was on average 3 to 5 but if we were able to
7 measure more than that, then we did.

8 Dr. Cavalcante: Joao Cavalcante, just to expand also what was discussed earlier in regards to the
9 imaging sub study. As you can see, the precision of the 3D measurements, despite the smaller
10 number of patients enrolled, can clearly demonstrate that at the end of the 12 months, there is
11 reverse remodeling of not only the right atrium, the tricuspid annulus, the right ventricle, and
12 also a decrement of the RV function, which is expected since you're removing volume. And that
13 is also translating to the decrease in the RV ejection fraction, but an improvement of the
14 contractility by the free wall strain. Negative numbers are actually favorable.

15 Dr. Benza: Yes, Ray Benza, Mount Sinai, just to answer some of the queries about the natriuretic
16 peptide levels. I just wanted to bring the panel's attention to this first slide again, showing the
17 relevant changes in BNP and NT-proBNP and stress that these clearly cross the unity line. So, in
18 essence, there are really no significant changes in natriuretic peptides between these two groups.

19 In addition, if you're looking at the baseline level of natriuretic peptides for the BNP
20 around 300 and NT-proBNP around 2,500, these are really very modest changes in these levels.
21 In fact, for the NT-proBNP, remember this is independently affected by age, female gender, and
22 the presence of atrial fibrillation. And so, if you're looking at an 80-year-old female, the upper

1 quartile of normal for the range for that NT-proBNP is around 2,500. So, I think these were very
2 modest changes in the NT-proBNP, not a very significant concern.

3 In fact, if you look at the changes that the FDA mentioned for both NT-proBNP and BNP,
4 these changes were very trivial in the order of 1,200 picograms per deciliter.

5 Dr. Lange: Now, we're not going to allege that people age differently over the year, or they
6 change their gender, or they change their AFib.

7 Dr. Benza: No, that's a good point. But as we do get older, and I'm feeling that myself right
8 now, I know my NT-proBNP levels are going up as I stand here.

9 Dr. Lange: Great. Lastly, I want to we've come to the end of this panel deliberation. I want to
10 thank the sponsor. Again, I think you've been very responsive to the questions.

11 I want to thank the FDA as well. We're going to take a 15-minute break. We're going to come
12 back at 2.15. Again, I'll ask the panel members not to discuss any of the meeting with anybody
13 on the panel or anybody else, and we'll come back at 2.15. At that time, we'll deliberate upon the
14 FDA questions.

15 And that will frame our discussion. So, thank you very much again to the sponsor and to
16 the FDA and I'll see the panel members in 15 minutes.

17 FDA Questions

18 Dr. Lange: It's now just after 4:15 Eastern Time, and it's time for to focus our discussion on the
19 FDA questions. Now, panel members, electronic copies of the questions have been emailed to
20 you and they're posted on the FDA website. As we go through this, a couple of things. One is the
21 FDA has cleverly disguised 12 questions as eight, so there'll be a lot of stuff to go through, and
22 my job is to facilitate the discussion. The FDA would like a robust discussion, especially
23 centered around certain questions that help them, and my job is to help facilitate.

1 Dr. Blankenship: I think, frankly, this is very — I see this as very reassuring, on these, on the
2 safety side for a structural heart intervention. So that's my — I will add what's not on here, was
3 discussed and maybe later we can get to, but re-instrumenting the — once the tricuspid valve is
4 clipped, re-instrumenting with pacemakers and defibrillator coils and swans and such, I think is a
5 future issue, but maybe more of a post-market.

6 Dr. Lange: Okay, great. Mlad , I see your hand up.

7 Dr. Vidovich: Yeah, this is Mladen Vidovich, just a quick comment. I mean, you know, we
8 talked about a a-fib. I assume all these patients were anti-coagulated. I think, given that they
9 were probably on DOAC or Warfarin, this is probably not so bad, you know, with a 25 French
10 sheath. I mean, I'm actually very encouraged about this.

11 Dr. Lange: Is there anybody on the panel that has any concerns about the MAEs? Seeing none.
12 Bram, let me ask you. It seems that the panel seems to think that these results are actually fairly
13 good, especially in the high-risk population. And I don't see any concerns about these MAEs.
14 Does this adequately address question one for the FDA?

15 Dr. Zuckerman: Yes, it adequately addresses the safety issue. Thank you. We can go on to
16 question two.

17 **Question Two**

18 Dr. Lange: Great. This question two has four parts. Megan, let me hand it over to you.

19 Mrs. Naber: Okay, great. Okay, so question two is about the primary endpoint results. The
20 primary endpoint of the TRILUMINATE Pivotal Trial was a hierarchical composite of time to
21 all-cause mortality or tricuspid valve surgery, number of heart failure hospitalizations, and a
22 greater or equal to 15-point improvement in KCCQ score from baseline at 12 months, tested
23 using the Finkelstein-Schoenfeld method at a five percent two-sided significance level. The

1 primary analysis population was the ITT population. The Finkelstein-Schoenfeld test statistic
2 result was 2.14. The two-sided p-value was 0.0311. The primary endpoint was met, indicating
3 the TriClip group was superior to the control group. A supplementary win ratio analysis was used
4 to evaluate the treatment effect of the primary endpoint.

5 For the primary analysis, which included 350 randomized patients, the number of wins,
6 losses, and ties for the TriClip group and the control group, for each component of the primary
7 endpoint, are shown in Figure 1. The win ratio point estimate was 1.44, in favor of the TriClip
8 group, with a 95 percent confidence interval of 1.03 to 2.08. Question 2A is, please discuss the
9 clinical significance of the primary endpoint results.

10 Dr. Lange: And I'll look for a hand. If not, I'll start calling on a couple people. I'm interested in
11 your opinion. Again, we're looking at the clinical significance of the primary endpoint results. I
12 saw Jim and Mitch and Marc. Dr. Blankenship, Dr. Krucoff, and Dr. Katz.

13 Dr. Blankenship: Yeah, it is statistically significantly better. I was troubled by the lack of
14 correlation between KCCQ and the heart failure hospitalization, but I was somewhat mollified by
15 the possible explanation that you get more hospitalizations for left-sided failure and less for
16 right-sided failure. So, that somewhat reassures me. But I think that the 15-point difference in
17 KCCQ represents a moderate to large difference in quality of life. And I think that is an
18 important difference.

19 Dr. Lange: Okay. Dr. Krucoff.

20 Dr. Krucoff: Yeah, I will also say, I think that it is clinically significant. I think, this isn't as a
21 right sided intervention, the way the trial was designed to include heart failure and death was
22 probably inevitable at the time. But we may learn the lesson that this is more about quality of
23 life-- than or maybe long-term death, but not within one year. I was also reassured on the heart

1 failure side. I do think we have unknowns about both rhythm and LV function, dysfunction, or
2 LV stiffness, that are not transparent in these data. But I think we also have the expanded, you
3 know, 700 patient denominator, that is not just the usual add on ad hoc, late data, but is actually
4 randomized data, in which the heart failure numbers actually look better. All in all, I am in
5 agreement, that I think this is clinically significant.

6 Dr. Lange: And specifically, clinically significant with regard to symptoms, KCCQ.

7 Dr. Krucoff: To me, the placebo issue, understanding that it's unblinded, et cetera, et cetera. I
8 would not have supported doing a sham procedure. I think this level of significance and the
9 durability of the impact of this is clinical.

10 Dr. Lange: Okay. I've got Dr. Katz, Dr. Vidovich, Dr. Brindis and Dr. Hirschfeld.

11 Dr. Katz: While we all agree this is a safe procedure, I still have some questions about its overall
12 effectiveness. It did decrease TR some, and obviously had an increase in KCCQ, but the other
13 two hard metrics really were not changed. Additionally, the patient's overall medications didn't
14 change much. I guess they may or may not have had a better response to their diuretics, but it
15 didn't decrease their overall level of medications.

16 And then, you know, looking forward, I, as I mentioned previously, have real concerns
17 about the creep that's going to occur and that there will be sicker patients who are going to be
18 addressed. And, you know, that is not going to help the results overall, especially as less
19 experienced teams get involved.

20 And then one last point is that, given that there is now an approved tricuspid valve
21 replacement, once the tricuspid is clipped, you take that off the table in the future. So, those are
22 my concerns about effectiveness.

23 Dr. Lange: Thank you, Dr. Katz, Dr. Vidovich.

1 Dr. Vidovich: So, I concur with everybody. It is safe and patients feel better. Mortality is not
2 changed. So, I think that's fine. There's a question actually for the FDA. And since I'm not a
3 statistician, but I mean, I'm sure FDA could help us. If I were to review this paper for a
4 manuscript, I would have said, could you please provide good old-fashioned analysis, statistical
5 analysis, just as a supplementary material. Throw it on as an online supplement, just to maybe
6 assuage some people who are not comfortable with the win ratio.

7 Dr. Zuckerman: Dr. Lange, would you like me to respond here?

8 Dr. Lange: Please go ahead.

9 Dr. Zuckerman: Dr. Vidovich, we're in a new age of clinical trial analysis. The win ratio was
10 actually the primary statistical analysis and use for the primary effectiveness endpoint, in the first
11 partner trial with the Finkelstein-Schoenfeld. I would urge you to go back to that New England
12 Journal paper. The point is that, over the last decade, this type of win ratio analysis, in the device
13 world, and even in the drug world, has gained a lot of traction for a number of reasons. But what
14 you're getting at is that a win ratio can appear statistically significant, but it's very important to
15 look at the individual components, just like in any composite endpoint. In the future, please be
16 prepared to see more win ratio FDA panel presentations and to remember that it's just not
17 statistics. We need to look at the, how the individual components of the composite endpoint
18 actually fared. Does that help?

19 Dr. Vidovich: Point well taken.

20 Dr. Lange: Thank you, Bram. Dr. Brindis and Dr. Hirschfeld.

21 Dr. Brindis: Yeah, Ralph Brindis. I'd like to make a couple of comments. First, we learned that
22 the hospitalization rates with these patients was much lower than what the sponsors originally
23 thought. And so, to be able to come up with some answers related to device wins with heart

1 failure hospitalizations, or even death, is clearly going to require more than one year. So, the
2 study wasn't powered enough to be able to, I think, for these hard endpoints, to determine
3 benefit, if you will, in a one-year point. So that means that we are basically relying on patient-
4 reported outcomes, in this case, KCCQ, in making our decision. And I am a big fan of KCCQ. It
5 has face and construct validity. It's reproducible. It's sensitive to change. And baseline and serial
6 measures correlate, overall, with health and prognosis in previous studies. I'm comfortable with
7 utilizing KCCQ and making the decisions on this being a positive study. In terms of the issue of
8 not having a true blinded patient population for the KCCQ, I'm comforted by a number of things.
9 One, the fact that if you had a placebo effect, the fact that this, the benefit has continued for a
10 year, I think mollifies the concern of a placebo effect.

11 The fact that we see a relationship between the degree of residual tricuspid regurgitation
12 and KCCQ, I think is reassuring. The fact that we see that the benefit of the improvement of
13 tricuspid regurgitation and KCCQ is also, in my mind, reassuring. And we have the indirect
14 evidence, if you will, of the reverse remodeling from the subgroup imaging analysis, that I also
15 think is reassuring. So, I think it's a positive study and I'm comfortable with these results.

16 Dr. Lange: Thank you, Ralph. Dr. Hirschfeld. You're on mute John.

17 Dr. Hirschfeld: There you go. Hirschfeld. The more I look at this, the more I think of what we're
18 really looking at is the real heterogeneity of the patient population. We have some patients, and
19 we heard some of their stories in the open public hearing, who clearly had spectacular clinical
20 responses to the treatment. And when we looked at the group data, I was right on the same page
21 with Dr. Selzman about looking at the hemodynamics and saying, you know, this isn't TR that I
22 think ordinarily requires intervention in most people. The right atrial pressures were like seven or
23 eight, the right ventricular end diastolic pressures were eight. That's not big time TR that's really

1 seriously threatening. And I think that may be, in part, why they failed to show a benefit in terms
2 of death or heart failure episodes. But the other thing, and I need to check with the people who
3 are more statistically sophisticated than I am, but why were there only 21 percent wins in the
4 device group over the control group?

5 Why were 80 percent of the patients, did not satisfy the win criteria? And I would think
6 that if this was — this signals, as this was this consistent across the whole patient population, we
7 should have seen a larger fraction of wins in the KCCQs data than we do. What I take away from
8 this is, inside this patient population, there was a subset of patients who had really spectacular
9 responses. Another subset, probably considerably larger than the responding subset, who really
10 didn't respond in terms of symptomatic responsiveness.

11 Dr. Zuckerman: Hey, John, excellent comments, but just for the record, the total number of wins
12 in the device column is the sum of all three. So, it's 36.7 percent versus the 25.4 in the control.
13 And then, as you point out, ties were 37.8. But your points still are quite relevant.

14 Dr. Hirschfeld: Thank you.

15 Dr. Lange: Dr. Cizik and Dr. Hauptman.

16 Dr. Cizik: Just to clarify with Dr. Hirschfeld and Dr. Zuckerman, this was hierarchical though.
17 Correct? So, the 21 percent is of the hierarchy.

18 Dr. Zuckerman: Yes.

19 Dr. Cizik: It's not-- okay.

20 Dr. Cizik: And I think some of the responder data we saw was very helpful too.

21 Dr. Lange: And any comments, Amy, about the clinical significance?

1 Dr. Cizik: I would agree with what Dr. Krucoff, . And also yeah, Dr. Brindis, in terms of a
2 PROM, the moderate to large, I think they went above and beyond, in terms of a significance and
3 an effect size, which we typically don't we — I don't see in other trials.

4 Dr. Lange: Amy, we just lost you. I'm going to go to Dr. Hauptman.

5 Dr. Hauptman: You might want to turn off your video, Amy, and just talk.

6 Cr. Cizik: Is that better?

7 Dr. Lange: Dr. Hauptman. I'll come back to you, Amy, in just a sec.

8 Dr. Hauptman: Right, so I think John is on to something, though, that you know, it's clear there
9 are some patients that are going to respond very well to this. We learned that if you score high on
10 the KCCQ, you may be less likely to respond. We also don't know much about patients who have
11 severe TR leading to a marked impact on the liver and the kidney, and whether, you know, there's
12 a period of being too late, if you will, to intervene. So, I don't know what the sweet spot is for
13 this. It would be great to know because I think there will be patients who benefit. But it's, to my
14 mind right now, it's not particularly well-defined. And I think the one safety issue that also
15 someone else mentioned, that I'm concerned about, is how much do we know about the safety of
16 placing a new defibrillator or pacemaker post-TriClip.

17 Dr. Lange: Okay. Dr. Cizik has just chatted me to say she had finished with the comments and
18 didn't have any more to add. Bram, let me summarize what I've heard, and then if you need some
19 additional clarification-- There were individuals that felt like the KCCQ was a valid measure,
20 and there was a change in the scores that was positive, that was unlikely due to just the placebo
21 effect, but there's still some uncertainty about why that hasn't translated into hard endpoints.
22 Several options, or there are several things to consider. One is it may take a longer period of time
23 to do that, so possibly. Secondly, this patient population wasn't as sick as what we see

1 historically, what we see hemodynamically, and that may account for it. And there's still some
2 uncertainty among the group about who would respond to this therapy. We didn't have very many
3 people in class four heart failure. There are clearly people that don't respond, and you saw in the
4 data. And I would even go back, again, the sites that did more than 10 and less than 10, they have
5 the same outcome with regard to reduction in TR. But still, the changes with regard to heart
6 failure and death were very discrepant. And so, I'm not sure you're going to get a clear answer on
7 this, again, other than the fact that people believe that the KCCQ is valid, but it's not measuring
8 up with hard endpoints at this particular time.

9 Dr. Zuckerman: Yes, it was a very good discussion and that's a very good summary, Dr. Lange.
10 We can go on.

11 Dr. Lange: Okay. Megan let's go to 2B.

12 Mrs. Naber: Okay. Here we go. The primary endpoint of the TRILUMINATE Pivotal Trial was
13 met, driven by KCCQ score improvement in the device group. Mortality or tricuspid valve
14 surgery rates were similar between treatment groups, and the heart failure hospitalization rate
15 was numerically higher in the TriClip group versus the control group. The results of the
16 individual components of the primary endpoint were as follows. Kaplan Meier estimates for
17 freedom from all-cause mortality or tricuspid valve surgery were 90.6 percent and 89.4 percent at
18 12 months for the TriClip group and the control group, respectively. Kaplan Meier estimates for
19 freedom from heart failure hospitalization at 12 months were 84.5 percent for the TriClip group
20 and 88.0 percent for the control group. Annualized heart failure hospitalization rates were 0.22
21 and 0.17, for the TriClip group and the control group, respectively. And a significantly higher
22 proportion of TriClip patients had a KCCQ score improvement of greater than 15 points from
23 baseline to 12 months, compared to control patients, 49.7 percent versus 26.4 percent,

1 respectively. The win ratio analysis was repeated for the full randomized cohort, which included
2 572 patients. The number of wins, losses, and ties for the TriClip group and the control group for
3 each component of the primary endpoint analysis are shown in figure two. The win ratio point
4 estimate was 1.53 in favor of the TriClip group, with a 95 percent confidence interval of 1.14 to
5 2.06. The win ratio point estimate for the full randomized cohort was similar to the primary
6 analysis cohort. The primary endpoint success continued to be driven by KCCQ improvement. In
7 the full randomized cohort, the number of device wins and control wins for heart failure
8 hospitalization were comparable, with very small numerical differences favoring the device
9 group. The TRILUMINATE Pivotal Trial was an unblinded, or open label, randomized
10 controlled trial. Patient-reported outcomes, such as the KCCQ score, could be subject to the
11 placebo effect in an unblinded trial. For question 2B, please discuss the strengths and limitations
12 of the primary endpoint results, considering KCCQ and KCCQ score improvement favoring the
13 device group, and potential placebo effects, and the lack of reduced mortality and heart failure
14 hospitalization rates through 12 months in the TriClip group versus the control group.

15 Dr. Lange: I'm going to call on a couple people who haven't really spoken up yet, just to get
16 your opinion. There has been an opinion that the KCCQ is validated. Here we have it though,
17 validated in an unblinded trial. And we really can't assess the placebo effect. We've tried. So, I'm
18 interested in hearing your opinions. Brad, you mind if I call on you? I'm interested in you.
19 David, you, and David Friedman, what your thoughts are?

20 Dr. Bart: Yes, thank you. This is Brad Bart. I agree with the previous comments about the
21 placebo effect and the KCCQ. I think it's inevitable, in an unblinded study, to have these
22 questions. But I think the sponsor went a long way to try to address these issues. I think the
23 durability of the response over 12 months is very reassuring. I think that the correlation between

1 tricuspid regurgitation at baseline and the degree of improvement after the clipping procedure
2 correlates nicely with the KCCQ. I think the remodeling data for the imaging sub-study all
3 supports that there is a real physiologic-- So, I feel that they did a good job and I feel
4 comfortable that you can't attribute all of the benefit merely to placebo. I think the data line up
5 pretty well.

6 Dr. Lange: Okay, great. Dr. Friedman.

7 Dr. Friedman: I think the KCCQ is pointing towards the quality of life, clinical indicators of
8 improvement. And, you know, as was shown with the public comments, I think a lot of people
9 just bias themselves to thinking by getting the intervention, they're going to be doing better.
10 There is that aspect. And I agree with many commentators, as have already said on the panel, that
11 the sponsor did everything possible to try to accommodate for that. But I still think that some
12 kind of treatment is better than no treatment. And if the standard of therapy is diuretics, anything
13 that's going to improve the valve will make a big difference. I think from that standpoint, there is
14 definite validity. And the Kansas City Heart Score does hold true to that. But I do think one year
15 of time of this study is not enough. We need a lot more time, and we need a bigger demographic
16 sample size. We need different types of patients, not just Caucasian. We need a lot of different
17 ethnicities represented too, going forward. You know, there's a lot of differentiation with how
18 disease presents themselves in different ethnicities. And I think that also has to bear true.

19 Dr. Lange: Okay. Dr. Yuh, Jennifer Schwartzott, and then Dr. Shanker, Dr. Blankenship. Dr. Yuh.

20 Dr. Yuh: Thank you. David Yuh. Yeah, I think my initial concerns about the placebo effects of
21 KCCQ are somewhat mollified by the durability of the effect and the differences in the KCCQ
22 score. And I think the pathophysiology of right-sided disease lend itself to a longer study, to see
23 more differences in the hard, so-called hard outcomes of heart of readmission rates or admission

1 rates and mortality. So, I'm actually, you know, very reassured by these data and the explanations
2 behind the limitations of the methodologies.

3 Dr. Lange: Okay, thank you. Jennifer Schwartzott and Dr. Shanker and Dr. Blankenship.

4 Mrs. Schwartzott: I think there's always going to be bias when you go to the patient-reported
5 outcomes. And I participated in plenty of them myself. Whether it's an unblinded study or not,
6 the patients that are coming into these studies are well-educated, they have good attitudes
7 usually, and there's always going to be a bit of the placebo effect. But the long-term consistent
8 outcomes are what makes me believe that this is a good end point. But I do agree that it needs to
9 be lengthened. One year is not enough. And I also believe that they need to adjust maybe the
10 questions for this particular trial, for the future. And I know the company was interested in that
11 also. But, the patient input is very needed, in every trial, and, you know, their outcomes should
12 have a lot of validity. Thank you.

13 Dr. Lange: Thank you. Dr. Shanker and Dr. Blankenship.

14 Dr. Shanker: Yeah, thank you. So, I am comfortable with the KCCQ score improvement. They
15 did a pretty good job of demonstrating was early, sustained and possibly correlated with some
16 hemodynamic and anatomic parameters and biomarkers that supported that. But, you know, as
17 we look at the win ratio, and I'm just looking in my reading of the win ratio and thank you for
18 sending that article. It works well when you have a low number of deaths and hospitalizations, so
19 I'm going to be curious to see how this will play out in four or five years, as the incidence of
20 heart failure and death goes up, and whether KCCQ will still continue to drive that perceived
21 benefit that we see. As regards to reduced mortality, I mean, the mortality rate is, I think, low in
22 in general, if it's in medically treated, tricuspid regurgitation, which Abbott showed us, at least
23 from the data they had. Heart failure rates, we already went through that discussion. The lower

1 volume centers probably didn't do as good of a job, but we don't quite know why. So, I think
2 that's just my perspective on those metrics.

3 Dr. Lange: Thank you, Amit. Dr. Blankenship, I want I'll let you have the last word on this.

4 Dr. Blankenship: One abstract that was presented at American College of Cardiology meetings
5 in 2022, by Conadol (phonetic), which I think has not been published yet, interested me. They
6 looked at the KCCQ scores in placebo arms of trials, and then looked at the change from before
7 versus after. And they found that about, out of 21 trials where they looked at placebo arms only,
8 about half of them had a change of about 5%, which they attributed to placebo effect. The
9 average for all 21 is a little bit higher, but I think that goes a long way towards confirming the
10 estimates that the trialists of the TriClip used were accurate and confirms the five percent that
11 was observed. And I think it makes it very unlikely that you could explain the entire difference
12 simply by placebo effect. So, I think that supports the idea that yes, there is some placebo effect,
13 but it's unlikely to account for all or even most of the benefits seen here.

14 Dr. Lange: Okay. If I was to summarize, I'd say most everybody believes there is a placebo
15 effect or a patient bias. It doesn't count for all the results that are seen with regard to the KCCQ
16 improvement, because of the durability lasting for at least 12 months, there is a relationship
17 between the change in TR and the KCCQ and the remodeling data. Again, the issue of why it's
18 not tied to improved heart failure rates or to reduced mortality has to do with the lower risk
19 population that was studied. And concerns that one year may not be sufficient alone to ascertain
20 whether there's any benefit with regard to heart failure hospitalizations or death. I think I've
21 summarized what most have said. Dr. Zuckerman, does that address 2B to your satisfaction? Or
22 would you like to have some more information?

23 Dr. Zuckerman: No, this was a very good discussion and summary. We're ready to go on.

1 Dr. Lange: Thank you. Megan, 2C.

2 Mrs. Naber: Alright. Post hoc analyses were performed to-- sorry, the slide isn't changing. Okay.

3 Post hoc analyses were performed to investigate associations between KCCQ score changes and

4 TR severity. These associations are shown in Figure 3. At 12 months, lower TR severity, and

5 greater TR severity reductions, were associated with greater KCCQ score improvements.

6 However, there were relatively wide standard deviations in the KCCQ score changes at each TR

7 severity level, and in each TR severity change category. Please discuss the clinical significance

8 of TR severity and KCCQ changes at 12 months, in supporting benefits of the TriClip device and

9 mitigating the potential placebo effects in an open label trial.

10 Dr. Lange: Dr. Blankenship, Dr. Bart, and Dr. Krucoff. Jim.

11 Dr. Blankenship: It seems like it makes intuitive sense to me. So, I think it's an important

12 observation and I don't have any problems with it.

13 Dr. Lange: Dr. Bart.

14 Dr. Bart: Yes, I think following up on my previous comments, I think, yes, the confidence

15 intervals are wide. And so, this by itself does not prove anything. But, in the totality of data that's

16 provided, all the trends are in the right direction. And so, I'm comfortable with this piece of

17 information as being supportive.

18 Dr. Lange: Okay. Dr. Krucoff.

19 Dr. Krucoff: Yeah. The same. I think, again, we're breaking this into much smaller

20 denominators. So, it's not a surprise, I think, overall the groups are not up down, up down, but

21 are truly a trajectory across the various severity indices. And then, again, this is not the primary

22 endpoint. I think the win ratio is a much more robust statistical metric, as the primary endpoint

23 goes. But I think for all of us, as we've heard multiple times, this correlation, even with the

1 confidence intervals, the correlation itself is a very clear supportive piece to go along with the
2 primary endpoint, in my opinion.

3 Dr. Lange: Okay. Thank you, Mitch. Dr. Brindis and Dr. Selzman.

4 Dr. Brindis: Yeah, Ralph Brindis. The only thing I would add, if I'm not mistaken, the sponsors
5 also presented slides with additional patients in their extended group and also the one arm group,
6 which narrowed the confidence intervals, making this correlation even stronger.

7 Dr. Lange: Okay. Dr. Selzman.

8 Dr. Selzman: I just want to bring a little bit more clinical context for FDA on this, because we
9 saw this with MitraClip, that everybody, when you do a MitraClip high fives themselves when
10 you come out with moderate MR. If we do an operation, and do a mitral valve repair, we don't
11 get any high fives for that. But the reality of it is, is these patients, when they have a decrease,
12 and it might be within these confidence intervals, they feel better. And so, I think trying to hold
13 the therapy to too tight of a-- kind of, in a statistical way, is not fair to the patients. I mean, we
14 heard a lot of violins for an hour, about these great patient stories and they're out there. Right?
15 But I think there is a lot of reality to the fact that if somebody goes from torrential, from five to
16 three, even though it doesn't look good on an echo, they feel it. And that's my own experience.
17 And I think that's what's being seen here, is that there's a lot of variability. And I wouldn't get too
18 caught up on these wide confidence intervals.

19 Dr. Lange: Alright. Is there any dissenting? If not, I'll summarize. Dr. Vidovich.

20 Dr. Vidovich: I just had a quick question. Will this impact how many, if and when it's approved,
21 how many clips will interventionalists place, seeking lower and lower regurgitation, and one may
22 be enough. Is this something that would be of concern?

23 Dr. Lange: Well, that's probably beyond the scope of our discussion.

1 Dr. Vidovich: Yeah.

2 Dr. Lange: Your point's well taken, but probably beyond the confines of what we're discussing.

3 Dr. Hauptman?

4 Dr. Hauptman: Yeah, just briefly, I just want to remind everyone that there was no reduction in
5 diuretic dosing, which is a bit of a head scratcher. One would believe that if patients were feeling
6 better, one could back off clinically on some diuretic dosing, which did not occur. That said, I
7 think this plot is very important to our discussion, and it makes the change in KCCQ quite
8 believable.

9 Dr. Lange: What I've heard is that, again, there's wide confidence intervals. When we added
10 more patients, they narrowed down, but directionally everything moved in the same direction, is
11 biologically plausible. There's still some heartburn about why there's no change in medications
12 and why there's not an overall improvement in endpoints, hard endpoints. You would think that
13 even if it took longer for the death and heart failure hospitalization to manifest, that there'll be a
14 decrease in medications with the first 12 months and there isn't. So, there's still some heartburn
15 about that. But I think people are convinced that the data are valid.

16 Dr. Zuckerman: Okay, that's very helpful, Dr. Lange, and a quick question for you. You know,
17 Dr. Cohen showed that the relationship between KCCQ and TR is a complex one, and he used a
18 multivariate regression. So, I'm not bothered by the fact that the confidence intervals are wide,
19 because this is a complex relationship. Is that your conclusion from Dr. Cohen's comments?

20 Dr. Lange: Indeed, agreed. And somebody else had brought up earlier the heterogeneity of the
21 patients. I think John Hirschfeld mentioned that as well.

22 Dr. Zuckerman: Good.

23 Dr. Lange: If you see no other comments, then we'll move to D.

1 Dr. Zuckerman: Good.

2 Dr. Lange: Thank you for a robust discussion on this.

3 Mrs. Naber: Okay to move on?

4 Dr. Lange: Please.

5 Dr. Zuckerman: Yes.

6 Mrs. Naber: Okay, question 2d. Among the 65 sites that contributed to the primary analysis
7 population, 56 sites enrolled less than 10 patients, of which 42 enrolled less than five patients,
8 nine sites enrolled 10 or more patients, and one site enrolled 51 patients. Post hoc win ratio
9 analyses were performed to evaluate the primary endpoint outcomes as a function of site
10 enrollment, for sites with 10 or more enrolled patients and sites with less than 10 enrolled
11 patients. The win ratio results of the primary endpoint, for the group of sites that enrolled more
12 than 10 patients, was more than two-fold higher, 2.19, versus the group of sites that enrolled less
13 than 10 patients, 1.06. This difference was driven by higher heart failure hospitalization rates,
14 and lower rates of KCCQ score improvements in the lower enrollment site group. The number of
15 patients in each treatment group and the number of wins, losses, and ties in the TriClip and
16 control groups, for each component of the primary endpoint, are shown in figures four and five.
17 Please discuss the primary endpoint outcome variability as a function of site enrollment, and
18 implications on the generalizability of the primary endpoint results.

19 Dr. Zuckerman: And, Megan, have you shown the second figure that goes along with this?

20 Mrs. Naber: Both figures are here on this slide. Ten or more subjects is on the left, and less than
21 less than 10 subjects is on the right.

22 Dr. Zuckerman: Gotcha. Figures four and five are on this slide.

23 Mrs. Naber: Yes. And then, just to point out, the rates of each event are also included here.

1 Dr. Lange: And I can't remember whether it was Mitch, or [indiscernible], had asked for
2 conventional statistics. So, there you have an event rate, as well, besides the win ratio. David,
3 first comment.

4 Dr. Yuh: I can't help but worry that the differences in the hard outcomes between the high and
5 low enrolling sites may be related to the differences and focus on right-sided heart failure
6 management. I mean, you have two classes of sites that get the same technical result, but
7 significantly different heart outcomes in terms of rehospitalization rates and KCCQ score rates.
8 So, I just can't help it, I mean, it may be completely unfounded, but that's what keeps coming
9 back to me when I see those differences. And I'm just curious as to what others think about that.

10 Dr. Lange: Okay. Mitch, Dr. Krucoff.

11 Dr. Krucoff: Yeah, no, I'm totally with David. I think that is very likely to be the case. But to me,
12 again, this is good news, not bad news. I think what would worry me is if the lower case volume
13 sites really did harm. And I don't think we see that. What I think is, there is something to learn,
14 and not necessarily so much technically about doing the procedure, as caring for patients with
15 this truly right-sided disorder. And not caring for them like they're having left heart failure. I
16 think there's a lot to learn. I think I want to get into this more with the post-market sort of focus,
17 but I think, to me, the signal here is a clear one, but is a clear one that belongs in the post-market
18 rollout.

19 Dr. Lange: Dr. Vidovich, then Dr. Hauptman.

20 Dr. Vidovich: Yeah, I would agree with both previous comments. I mean, the safety signal is
21 there. It seems it's safe. I still can't figure out why, their MitraClip volume is very high. So, these
22 are experienced operators. I mean, they've done 500 MitraClips and this is right sided so this
23 should be easier. And then low volume sites, which will likely be predominant in post-approval,

1 don't get-- so there's some unmeasured confounder there or a factor that we don't know what it is.

2 But again, as Dr. Krucoff said, it is safe. And there's no signal to show the lowest volume sites
3 that any arm.

4 Dr. Lange: Dr. Hauptman and Dr. Bart.

5 Dr. Hauptman: Yeah, my hand was up in there. Sorry.

6 Dr. Lange: Okay. Dr. Bart, Dr. Friedman?

7 Dr. Bart: Yes, Brad Bart. It does suggest that maybe there's an issue related to the treatment, the
8 medical treatment of the heart failure. Like others have said, I don't think we saw this, but
9 everyone had a right heart catheterization. I wonder if they looked at the adequacy of therapy
10 based on the number of subjects that they ended up doing. I mean, just trying to get a handle on
11 if there were treatment differences that could be explained here.

12 Dr. Lange: Thank you, Brad. Dr. Friedman.

13 Dr. Friedman: Yeah, and on the enrollment sites, I just was curious, what is the high value site
14 doing to enroll so many patients? Is it just an operator dependent issue? Or is this just, you know,
15 just a function of type of heart failure complications with patients at the time? Or the types of
16 patients they're seeing at different places, whether it's a tertiary center versus maybe less of a
17 tertiary center? I don't know.

18 Dr. Lange: Okay. Dr. Shanker.

19 Dr. Shanker: Yes. You know, I agree with Dr. Krucoff in that, you know, if this device is
20 approved and you start pivoting to a post-market surveillance scenario, I think, above and
21 beyond, in addition to an emphasis on procedural imaging training, is going to probably have to
22 be a focus on management of right-sided heart failure in these patients, in order for these patients

1 to ensure they have an optimal outcome. That might be something to consider as you go to the
2 post-market phase.

3 Dr. Lange: Dr. Zuckerman, what I'm hearing is that the low volume centers didn't have
4 increased adverse events. They had the same reduction in TR, but they didn't have the same
5 clinical benefit. And the two concerns expressed, is there something different baseline about the
6 patients? And more importantly, were they not treated as well medically, in the smaller centers or
7 the sites with smaller number of patients. But they didn't feel like there was anything different
8 about how the procedure was done, the results of the procedure, or any adverse events associated
9 with it. Do you want some further clarification on some further questions to the panel, Dr.
10 Zuckerman?

11 Dr. Zuckerman: No, that's a very good discussion and summary. I was wondering if Dr.
12 Hauptman could further hypothesize about what might be important to look at, in the medical
13 treatment in any study going forward, given that this is an important hypothesis here.

14 Dr. Hauptman: Yeah, there's treatment or failure--

15 Dr. Lange: I'm sorry, Paul, identify yourself for the transcriptionist.

16 Dr. Hauptman: Yeah, I'm sorry. Paul Hauptman. You know, the treatment for right heart failure,
17 there's treatment for right heart failure. Which loop diuretic is used? Torsemide generally better
18 absorbs, better bioavailability in patients who have right heart failure over Furosemide.

19 Meticulous management of thiazide diuretics, several times a week perhaps, in advance of the
20 loop diuretic helps. So, there's a lot of subtlety in taking care of these patients, and constantly
21 managing the diuretic therapy, which I think a lot of people have difficulty doing. Admittedly, if
22 someone has truly torrential TR, there's not a whole lot you're going to be able to do, even with
23 concentrated diuretic management with Torsemide and Thiazide and so forth. But it does raise

1 the question, Bram, about the language in the labeling. You know, how is the FDA going to look
2 at and define optimal medical therapy? And a failure of the same, in order to qualify for a
3 TriClip.

4 Dr. Zuckerman: Okay, thank you.

5 Dr. Lange: Thank you. Megan, let's move to question three then.

6 **Question Three**

7 Mrs. Naber: Okay. Question three is about the descriptive endpoint results. The results of key
8 descriptive endpoints at 12 months are as follows. Similar to KCCQ score changes, SF-36 score,
9 NYHA functional class, and six-minute walk distance changes numerically favored the TriClip
10 group versus the control group. The mean SF-36 physical and mental component scores
11 increased by approximately five points in the TriClip group from baseline to 12 months, while
12 the SF-36 physical and mental component scores in the control group were mostly unchanged. At
13 baseline, 59 percent of patients in the TriClip group, and 55 percent in the control group, were in
14 NYHA class three or four. At 12 months, 16 percent of patients in the TriClip group and 40
15 percent of patients in the control group were in NYHA class three or four. At 12 months,
16 unpaired six-minute walk distance increased by about 28 meters from baseline in the device
17 group versus about 13 meters in the control group, with large standard deviations present.
18 Annualized rates of hospitalizations for peripheral edema and ascites numerically favored the
19 TriClip group versus the control group. The annualized heart failure hospitalization rate was
20 numerically higher in the TriClip group versus the control group. These rates are shown on the
21 slide. Echocardiographic endpoints of PISA, EROA, PISA regurgitant volume, and vena
22 contracta width were reduced in the device group, which is consistent with TR reduction. There
23 is a small 0.18-centimeter reduction in mid right ventricular end diastolic diameter in the TriClip

1 group, and right atrial volume showed a small increase of 7.78 milliliters in the TriClip group.
2 The MRI and CT imaging sub study, which included 82 patients at 10 sites, showed that TriClip
3 use is associated with favorable right atrial and right ventricular volume changes, supporting
4 favorable RA and RV remodeling, favorable changes in corrected RV ejection fraction, and
5 pulmonary forward flow. Imaging sub study limitations included the small sample size and
6 uncertainty regarding long-term prognostic implications. So, the question here is, please discuss
7 the clinical significance of these clinical and imaging outcomes.

8 Dr. Lange: Bram, based on the previous discussion, I'll try to summarize this, to move on to
9 other questions. And when I summarize, if anybody feels like I don't represent their opinion, then
10 I please ask you to voice that. I think that what the group has said is that, whether these may or
11 may not be significant statistically, is all of these things are moving in the right direction with
12 regard to the SF-36, the KCCQ, the number of patients in New York Heart Association class
13 three or 4 at the end of 12 months, annualized rates of hospitalization for right heart failure, i.e.
14 peripheral edema and ascites, echo endpoints, MRI and CT. And although some of them are
15 small numbers it looks like everything moves in the right direction and supports the hypothesis
16 that a reduction in TR and an improvement in KCCQ correlate. I think that's what I've heard over
17 the previous discussion. Are there any dissenting opinions about that? Bram, and the FDA, does
18 that adequately answer you?

19 Dr. Zuckerman: Yes, it does. We're ready to go to the next question.

20 **Question Four**

21 Dr. Lange: Question four.

22 Mrs. Naber: Alright, question four is about the single arm cohort results. Patients in the single
23 arm cohort met the same enrollment criteria as the randomized cohort, except that patients were

1 assigned to the single arm cohort if the eligibility committee determined that there was a high
2 likelihood that tricuspid regurgitation would be reduced by one grade or more with the TriClip
3 device, but a low likelihood that tricuspid regurgitation would be reduced to moderate or less.
4 The single arm cohort was intended to show that any reduction in TR provides some health status
5 benefit, even if TR severity was not reduced to moderate or less. TR reduction by at least one
6 grade at 30 days was achieved in 98.9 percent of patients. And TR reduction to moderate or less
7 was achieved in 80 percent of patients. The primary endpoint for the single arm cohort was
8 survival at 12 months, plus a KCCQ score improvement of 10 or more points compared to
9 baseline, which was tested against a 30 percent performance goal. In 91 patients, the primary
10 endpoint event rate was 46.2 percent, with a lower 98.75 percent confidence limit of 34.3
11 percent, which exceeded the performance goal. Thus, the primary endpoint was met.

12 CEC adjudicated adverse event rates through 12 months are shown in Table 3, which is
13 on this slide. The rates of all-cause mortality, cardiovascular mortality, and heart failure
14 hospitalization were approximately two-fold higher in the single arm cohort than in the TriClip
15 group of the randomized cohort. Other event rates were comparable to the TriClip group of the
16 randomized cohort. And then this table continues on the next slide. And the question here is,
17 please discuss the clinical significance of the single arm cohort results, their value added to the
18 randomized cohort results, and the implications on defining the TriClip intended use population.

19 Dr. Lange: Dr. Friedman, your thoughts?

20 Dr. Friedman: I think the safety aspect is still there, a little bit higher with the major bleeding.
21 I'm honestly not sure what to make of that. If it's single arm, I mean, they're not comparing it to
22 anything. Am I wrong?

23 Dr. Lange: Correct. That's correct.

1 Dr. Friedman: But I still think it's a safety issue that is in the range of within reason, as I see it.

2 Dr. Lange: Dr. Krucoff, Dr. Yuh, do you have your hand up?

3 Dr. Krucoff: I have it up.

4 Dr. Zuckerman: If I could just interject one thing, Dr Friedman, it is a single arm registry, but

5 both the safety and effectiveness had performance goals that the results were measured against.

6 So, you can say what you want regarding the validity of the performance goals, but they did meet

7 the hypotheses for safety and effectiveness in this single arm trial.

8 Dr. Lange: Dr. Krucoff, Dr. Yuh, Dr. Shanker, and Dr. Selzman.

9 Dr. Krucoff: Yeah, so, to me, I got a lot of reassurance because we had so many additional

10 randomized patients we could add to the 350. That's not what I take from the single arm in this

11 case. What, to me, the single arm is most striking for is how much better, how much higher the

12 percentage of reduction to moderate or less TR actually occurred, than was expected or

13 predicted. So personally, I would see this as ground to go back to the drawing board and look at

14 the criteria of why did you expect it to have very limited effect, in these sorts of more torrential

15 patients, and try and leverage that. Either with, again, potentially in a post-market label

16 extension, or in a device design. But that to me, it was the most striking thing about the single

17 arm, was how much higher a percentage of patients had with more TR reduction. I think it was

18 said earlier that no surgeon would leave the OR with moderate regurgitation. And the reason for

19 that, I think it was Craig was saying that, is that it's because there's a price to pay long-term. And

20 I do think that our whole frame shift in this particular patient space, is that these are not patients

21 who die fast, gasping for air, like left heart failure patients. These are patients who die a long,

22 slow, and as we heard, agonizingly cruel and uncomfortable kind of death. So, leaving behind

23 anywhere where we get more performance, more reduction of TR than expected, I would take a

1 deep dive into that. Because ultimately, any TR left behind, probably there is a price to pay. It
2 just may be later, rather than earlier. With relief of symptoms being more the immediate benefit.

3 Dr. Lange: Dr. Yuh.

4 Dr. Yuh: Yeah, I echo Dr. Krucoff's impressions. I was just struck that the device performed
5 better than they expected, and informs, I think, study design in terms of the post-market trials.

6 Dr. Lange: Thank you. Dr. Shanker.

7 Dr. Shanker: Yeah, I echo what both my colleagues have said. And of course, have to throw in
8 there as an electrophysiologist that there were five patients who had CIED related tricuspid
9 regurgitation. It was encouraging to see when Abbott brought up that data, that the TR was
10 effectively treated, even in those patients where the lead was, the lead entrapment was a cause of
11 the-- contributed to the tricuspid regurgitation.

12 Dr. Lange: Thank you. Dr. Selzman and then Dr. Bart.

13 Dr. Selzman: You know, I'm focusing on the last part of the sentence, implications on defining
14 the TriClip intended use population. You know, Dr. Adams mentioned there's two ways that can
15 creep. This is a very high-risk patient population. I can't find all the demographics associated
16 with the single arm, but clearly, they were thought to not be the greatest candidates. But
17 nevertheless, they did so well. I think, as the FDA thinks through this, you know, I'm not sure
18 we're going to have an upper limit on who this patient population could be, because these are no
19 option patients that you could try. It would be interesting with the transcatheter valve
20 replacement, that's going to set up a study, I don't know. Nobody will do that study probably, but
21 to compare these two patient populations in that study-- but, as it goes to the intended use, I think
22 this sets that there is probably no bar to not try it. These are no option patients. It's more, what

1 I'm interested in is the other side of the intended use, as we get lower and lower down in terms of
2 risk and suitability for clipping.

3 Dr. Lange: Okay. Dr. Bart, and then I'll summarize.

4 Dr. Bart: Yes, I view the results as mixed in this single arm cohort. It's true that the technical
5 success rate was very impressive. But the selection committee who decided to put these patients
6 in the single arm study actually did a pretty good job of defining a group that did not do so well
7 clinically. The heart failure rates were much higher. The death rates were much higher, than the
8 randomized cohort. So, there's something about these patients that it is worse. CEC, maybe I
9 missed, yeah, hospitalization for heart failure rates were quite high, and death rates were higher.
10 So, a mixed result, and I think we need to keep that into perspective when we're thinking about
11 which patients would qualify for a study like this.

12 Dr. Lange: I'm going to summarize. As you mentioned, this group did meet their end point.
13 There is no comparison group with regard to quote hard end points, like heart failure or death.
14 But what we do have is, even though they were not predicted to have moderate or less TR, 80
15 percent did. And now, again, these were a selected patient population. They were selected to be
16 considered for it, even though it wasn't thought that they would be quite successful. But in fact,
17 they were, and most of these people had torrential TR. So that shouldn't be a contraindication to
18 its use. And we may even need to consider encouraging those patients, because, as was
19 mentioned, they're not typically surgical candidates.

20 Dr. Zuckerman: Good. I think we're ready for the next question.

21 Dr. Lange: Okay. Number five.

22 **Question Five**

1 Mrs. Naber: Okay. Question five is about the indications for use statement. The sponsor has
2 proposed the following indications for use statement. The TriClip G4 System is indicated for the
3 improvement of health status in patients with symptomatic severe tricuspid regurgitation, despite
4 being treated optimally with medical therapy, who are at intermediate or greater risk for surgery,
5 and in whom tricuspid valve edge to edge repair is appropriate, as determined by a heart team.

6 The three questions here are, please discuss whether the available clinical data support the
7 proposed indications for use. Please discuss whether the phrases “improvement of health status”
8 and “as determined by a heart team” should be modified or further defined, and please discuss
9 other indications for use modifications if recommended.

10 Dr. Lange: Let’s start with A, and I’ll just ask the group, and I’ll just ask for a show of hands.
11 Discuss with the available clinical support for the proposed indications for use. Actually, I see
12 some hands up. Brindis, and then Dr. Vidovich. Ralph.

13 Dr. Brindis: A, yes, I think that the available clinical data supports the proposed indications. In
14 terms of the phrases, “improvement of health status,” I’m comfortable with that. You know, that’s
15 consistent with KCCQ. And maybe over time we’ll learn more and you could even change the
16 indication, but that’s what we have at the present time. Determined by heart team, if I’m not
17 mistaken, our expert consensus documents like to use the term “multidisciplinary team,” so I
18 might suggest that it be changed to “determined by a multidisciplinary team” or “a
19 multidisciplinary heart team,” to get all the comment of making sure we have all the appropriate
20 players involved in the decisions for who’s best suitable for this procedure.

21 Dr. Lange: Terrific. Thank you, Ralph. I’m going to call on Dr. Vidovich and Dr. Shanker, Dr.
22 Blankenship, and Dr. Cizik.

1 Dr. Vidovich: Yeah, so this is Mladen Vidovich. I agree with A. I think this data supports this
2 indication for use. For B, I would probably wordsmith “improvement in health status,” a little
3 bit. It probably is legitimate that the three correlates with KCCQ, but it looks a little bit, I don't
4 know, brushed with broad strokes, I would say. So I would wordsmith that a little bit. And then
5 C, I don't think there would be other indications I could come up with right now, based on this.

6 Dr. Lange: Okay, thank you. Dr. Shanker.

7 Dr. Shanker: Thank you. In line with what I had discussed before, roughly 97 percent of patients
8 that were studied had NYHA class two or class three symptoms. I do think that should be
9 included to prevent this device being used in very sick class four patients, which may not have
10 great outcomes. The second consideration for the FDA is about 93 percent, 94 to 97 percent of
11 the patients had AFib. They weren't in sinus rhythm, and I think that should be considered in the
12 IFU.

13 Dr. Lange: Okay, thank you. Dr. Blankenship.

14 Dr. Blankenship: I'm a little uncomfortable with the improvement of health status language, in
15 that we really lack the more objective measures of it. So, perhaps improvement of patient's
16 perception of health status, or improvement of perceived health status, might more accurately
17 reflect what we've been talking about today.

18 Dr. Lange: Thank you, Jim. Dr. Cizik.

19 Dr. Cizik: Yes, I find this pretty generic. SF-36 is considered a health status measure. It's a pretty
20 broad term, in the PROMS world, so especially if there's concerns about data collection and post-
21 market, I think this could be more specific. I have ideas, but I don't want to force them on people,
22 but I think this is pretty broad.

23 Dr. Zuckerman: Okay, Dr. Cizik, you're not forcing them on anyone.

1 Dr. Lange: Please. I'm sorry, Bram, I was going to say. What are those specifics, Amy?

2 Dr. Cizik: Can you hear me okay?

3 Dr. Lange: Yes.

4 Dr. Cizik: Yeah. I mean, being specific to the measure itself, "a moderate to large improvement
5 in KCCQ." I know that's very specific. But I think, too, back to some of the baseline data, this
6 idea, too, and we see this in other PROMS measurement, right? If people already are functioning
7 higher, it's harder to get them to that higher state. And so, I think that was really important for
8 some of this data we saw, right? Like, you needed to be lower quality of life to see a bigger gain.
9 And so, I think being realistic, even from the patient, letting patients know, look, you got to be
10 feeling bad enough for this to make you feel better, you know. So, does that help?

11 Dr Lange: That was very helpful, Amy. Very helpful. Dr. Friedman, Hauptman, and Hirshfeld.

12 Dr. Friedman: Yeah. Dave Friedman. So, I agree with the panelists too about we have to be more
13 articulate about these comments. Improvement of health status is very vague. Trying to be more,
14 less ambiguous, maybe something along the lines of improving functional quality of life,
15 something or other, and as determined by a multidisciplinary structural heart team, would be
16 words that come to my mind.

17 Dr. Lange: Okay. Thank you. Dr. Hauptman and then Dr. Hirshfeld.

18 Dr. Hauptman: I just want to comment on the symptomatic severe. We heard about the five-
19 grade scale, severe three, severe four, severe five. Just throw out the possibility that the FDA
20 may want to limit it to, let's say, severe four and five. Massive and/or torrential, where, as I
21 mentioned before, I'm, you know, diuretic therapy, probably not really that effective, and it's a
22 mechanical problem with the valve that can't be fixed with diuretic therapy. People have
23 mentioned the word creep several times. I would be concerned that, you know, severe three could

1 be looked at as moderate by some, you know, could be moderate, but called severe three. I think
2 we really have to have some assurance that this is truly severe TR, and the patient is
3 symptomatic. Both.

4 Dr. Lange: Okay. And last word Dr. Hirshfeld.

5 Dr. Hirshfeld: Yes. Hey, my microphone's on this time.

6 Dr. Lange: Yes, sir.

7 Dr. Hirshfeld: Yeah, I came back to advocating improvement of health status, and the reason is I
8 think we had to be careful to try to micromanage indications in the IFU. We can get too far into
9 the weeds trying to micromanage it. The other is that I think we don't really know yet who the
10 optimal patients for this device are. We've seen this heterogeneity in the response of the
11 individual patients. And so, I think that it's probably better to leave this in a more general
12 framework and leave that to the intuition of the clinicians, rather than do something that might
13 tie people's hands or, you know, make people try to fudge the echo data or something in order to
14 justify doing this.

15 Dr. Lange: Okay. So, I'm going to summarize some suggestions, and I appreciate Dr.
16 Hirschfeld's dissenting view to keep it general. I personally agree with Dr. Cizik that health
17 status for a patient, that doesn't mean that they live longer. They run hospitalizations-- and I think
18 being a little bit more specific will help the patient understand what the benefit is, and whether
19 that's called improvement in health status as noted by KCCQ, or by symptoms, I think will be
20 helpful to the patient. You've heard people say a multidisciplinary structural heart team. And
21 you've also heard that this should be applied to people that have severe TR and symptomatic TR
22 as well. Other considerations are to say that it's not been assessed in New York Heart Association
23 class four patients. And then, again, Amit raised the point of, is there any way to mention that

1 most of these patients had AFib? That's the totality of opinions. But I think they do provide a
2 framework for you all.

3 Dr. Zuckerman: I would agree. We're ready for the next question.

4 **Question Six**

5 Dr. Lange: The next question is regarding the safety and effectiveness of the device, the benefit
6 risk profile. Do you want to do that here? Because we're soon going to be doing that with regard
7 to the questions, and the voting. Do you--

8 Dr. Zuckerman: Yes, the point of this question is just to get people thinking about a benefit-risk
9 decision in a general context. Because once the voting starts, it's very quick and you don't have
10 time. If we can spend a few minutes just talking about some of the general ideas here, Dr. Lange.

11 Dr. Lange: I'd be happy to do that. Dr. Yuh, let me start with you. Then we'll go to Dr. Bart and
12 Dr. Selzman.

13 Dr. Yuh: Yes, in terms of the safety of the device, I think the data is pretty obvious and I'm very
14 comfortable with the safety of the device. In terms of the efficacy, in terms of what the patient is
15 really experiencing, I still do put a put a lot of faith in the KCCQ data, even though there is a
16 potential placebo effect in that it's in that methodology. It is still the reality to the patient. And to
17 discount that, I think, does a disservice to the patient. And I think this a new initiative by FDA, to
18 be more interactive with the patient population, is laudable, and I think this goes along with that.

19 Dr. Lange: Okay. I've got Dr Bart.

20 Dr. Bart: Yes, I agree. I think that the safety profile is adequate. And I think that it's important to
21 consider what the alternatives are for these patients. And their alternatives are quite limited. So, I
22 think overall, the totality is favorable.

23 Dr. Lange: Thank you. Dr. Blankenship and then Jennifer Schwartzott and Dr. Katz.

1 Dr. Blankenship: Yep. Just very briefly, because the safety profile looks good compared to a lot
2 of the things that many of us do, I have a lower bar for efficacy. And even if it's only helping
3 symptoms, you know, that's what total hip replacements do, they help symptoms. And if we can
4 help symptoms with this at a low cost in terms of risk, I think it makes a lot of sense.

5 Dr. Lange: Well said. Okay, Jennifer.

6 Mrs. Schwartzott: I'm always going to root for the benefits of a medication, but I'm also not a
7 risk taker. I really don't see high risks for this. I think longer studies need to be done, but if we
8 can present an option that's low risk and minimally invasive, I mean, that's a game changer for all
9 the patients out there that can benefit from this. Heart failure is not fun. I have been there. It is
10 not fun at all. I'm lucky that the medications work on me. But if they were to stop working on
11 me, or my disease were to progress, I would want to have something like this on the market and
12 available. And the patients deserve that.

13 Dr. Lange: I appreciate that comment and insight. Thank you, Jennifer. Dr. Katz and then Dr.
14 Selzman.

15 Dr. Katz: Marc Katz. So, I mean, I think we all agree on the safety, that we didn't hear about any
16 really bad untoward effects with the clips. And I'm a big fan of clips on the left side. However,
17 from the benefits, I mean, we didn't hear anything about it decreasing the need for paracentesis,
18 decreasing the amount of peripheral edema. I think the place that this is going to find its
19 usefulness is, most patients will end up getting a transcatheter valve replacement, but patients
20 with really severe RV failure, in whom a transcatheter valve replacement will actually lead to
21 worsening RV failure because of no pop off, those are probably the patients that might benefit
22 the most, where you can decrease at least the amount of regurg (phonetic) some, but leave some
23 pop off for a very weak RV.

1 Dr. Lange: Appreciate that comment. Thank you, Marc. Dr. Selzman.

2 Dr. Selzman: So, I'll just go back. Of course, my vote is going to be positive, positive. But I
3 have the asterisks to it, which is when we take the patient population from the average age of our
4 two presidential candidates down to something that's a little bit lower, I don't know if... That
5 concerns me. It also concerns me that when we put these clips in, we're putting a lot of faith in
6 the surgical arm of the treatment team. One of the things that wasn't mentioned in the big STS
7 study that gave surgery a less a favorable view, was the fact that patients that got a tricuspid
8 valve repair did a lot better than those that got a tricuspid valve replacement. And when you put a
9 clip on, and we've seen this with the MitraClip, it's hard to re-repair those. So basically, once you
10 put this clip on, if there is a surgical option, it takes it away, and it demands that it would be a
11 replacement. Having no experience because I've never operated on a TriClip. But I've operated
12 on a MitraClip. So, as we think about this and the indications, I'll just state yet again, somehow,
13 some way, and perhaps it's in the post-market study as the creep goes down to lower ages and
14 less risk, that there be some way to hold the therapy accountable.

15 Dr. Lange: Thank you, Dr. Selzman. And Dr. Hauptman, I'll let you have the last word on this.

16 Dr. Hauptman: I'll be quick. I'll just thematically back up what Dr. Selzman says, and I would
17 encourage the agency to work with the sponsor to evaluate post-implant deployment of the
18 defibrillator leads, and pacemaker leads, because safety, periprocedural safety, I think everybody
19 agrees on. But what happens a year or two or three down the road, if the patient needs a lead or a
20 lead revision? So hopefully there's enough data in the European experience that can inform the
21 agency on that. Dr. Lange, I think you're muted.

22 Dr. Lange: I'm sorry. Thank you. I think what you've heard is people consider there to be little
23 risk in its current use. Benefit with regard to symptoms. And again, some concern about whether

1 it closes options in the future. But, again, we'll address this-- I appreciate this, it's thought
2 provoking. We'll be voting, and by the way, after everybody's vote-- and please don't reveal now
3 how you're going to vote. But after the vote, everybody will have a chance to explain why they
4 voted as they did. This is a thought-provoking question. I'm going to move to seven because I
5 think this goes into the proposed post-approval study that some people have referenced already.
6 So, let's get to that question.

7 **Question Seven**

8 Mrs. Naber: Okay, question seven is about the post-approval study. Patients enrolled under the
9 TriClip IDE, including those enrolled under the continued access protocol (enrollment is limited
10 to 450 patients, 360 patients were enrolled as of January 5th, 2024, and no study results are yet
11 available). All these patients will be followed through five years. Additionally, Abbott Medical
12 proposes to conduct registry-based post-market surveillance of the TriClip device, through the
13 STS ACC Transcatheter Valve Therapy, or TVT registry, including linkage of the TVT registry
14 with the Centers for Medicare and Medicaid services, or CMS claims data. Patient outcomes will
15 be analyzed annually through five years post-procedure. Patient demographics and baseline
16 characteristics, as well as outcomes during the first year post-procedure, including assessments
17 performed at the index procedure, discharge, 30 days and 12 months, will be collected through
18 the TVT registry. For years two through five post-procedure, outcomes including mortality,
19 repeat procedure for tricuspid valve-related dysfunction, and hospitalization will be collected
20 from the CMS claims data. So, the two questions here are, please discuss the strengths and
21 limitations of the proposed single arm registry-based study design for the post-approval study.
22 And please discuss whether sample sizes for specific subgroups or underrepresented minority
23 patient populations should be pre-specified and evaluated in the post-approval study.

1 Dr. Lange: I'm going to go to Dr. Krucoff and then Dr. Brindis. Dr. Selzman, Hauptman, I'm not
2 sure if your hands are up for this question or whether-- okay, so if you do want to address this,
3 keep your hands up, and if not take them down. Dr. Krucoff and then Dr. Brindis. Mitch, what
4 are your thoughts?

5 Dr. Krucoff: Yeah, so I think as a breakthrough device, the post-market actually takes on added
6 importance, because the job is not done with a point of approval in something this novel, this
7 new. I think there's also the challenge of having another breakthrough device that's now
8 approved. That would be a have been a total game changer, as a comparator, potentially, if it had
9 been available, you know, seven years ago when planning for this sort of started. But I think as
10 we go into the post market, the real imperatives that come out of today's discussion, are first of
11 all, the main event, the main benefit that every patient who testified testified to, and that the data
12 support, have got to be extended in the post market. And that includes-- that's primarily the
13 KCCQ, so finding a way to make that efficient, doable, working together with the NCDR, as Dr.
14 Brindis mentioned earlier, who's interested in more than a 50 percent completion, rate. Or
15 through some other mechanism. But whatever the mechanism is, I think Bram Zuckerman's
16 emphasis on the importance of following through on the main impact of this therapy, on quality
17 of life, has got to be carried through into the post market. And that needs to be clear from the get-
18 go. The other thing that I think out of today's discussion, that would be a point of emphasis, from
19 my perspective, in the post market, is to better understand the role of rhythm and LV function in
20 these patients where atrial fibrillation has such a high presence, and where AV synchrony has
21 such a key role in how people feel. Being married to an individual who has had atrial fibrillation
22 off and on, she knows she's a different person energy-wise when she's in rhythm or not. So, I
23 think putting those pieces together, the left heart, the heart rhythm, and the TR regurgitation, and

1 how TR makes people feel, is a different animal than most of us are used to. Or most of the
2 cardiology community is used to dealing with. Rather than ignoring the right side, we focus on
3 the left side. That's not what we're talking about here. We have to understand what patients
4 experience, whether that's volume overload, whether you don't need to increase diuretics if the
5 valve is made competent, but you do get rid of volume. I think those are the kinds of questions
6 that I would hope this post market would carry forward, and a breakthrough device. And really
7 concentrate on-- I think that can be done single arm. I do think that clearly will be a better, faster
8 way to understand the important questions, that we have unanswered here today.

9 Dr. Lange: Thank you, Mitch. Dr. Brindis, Dr. Cizik, Dr. Yuh and Dr. Vidovich. Ralph.

10 Dr. Brindis: Yeah, thanks. Ralph Brindis. First, a little background, in the year 2021 and 2022,
11 off label in the TVT registry, we had about 360 to 370 tricuspid procedures entered. And those
12 are basically the ones that were actually entered. In terms of under underrepresented minorities,
13 in those two years about 11 percent were African American, and eight percent were other than
14 Caucasian. The strengths of course, of the registry is not only would you be following the TriClip
15 IDE patients described, but you'd also be following patients that are being done, not from these
16 studies. We'd be having that data. We'd have the strengths of a huge patient cohort to follow over
17 time. The other strengths are related that most of these patients are in the Medicare aged. And so,
18 we have that ability to use CMS claims data, not only for death or hospitalization, but maybe
19 even answering some of these questions related to utilization of pacemakers or other procedures
20 downstream. Some of the limitations are, I think, discussed and obvious. The most important one
21 is making sure that we can improve our KCCQ one-year results. Data entry.

22 Dr. Lange: Great, thank you. Dr. Cizik.

1 Dr. Cizik: Yeah, I think I just want to echo the importance of the two-year and five-year KCCQ
2 data. I know it's harder to get patients. Believe me, I work with trauma patients at these longer
3 time points. But I think that's where we'll see some really interesting data. And also echoing, just
4 some clinical, as to whether it's a PROM or some clinical value for things that we heard from
5 the patients today in the public hearing. Shortness of breath, edema, fatigue. Maybe a little more
6 specific symptom data collection might be helpful for indications as well.

7 Dr. Lange: Thank you, Amy. Dr. Yuh.

8 Dr. Cizik: And, just, I'm sorry--

9 Dr. Lange: Oh, okay.

10 Dr. Cizik: I have had success. So, it's not to ask for something and then not provide a solution. I
11 do find registries are a good place to partner and get patient-reported outcome data. If that's not
12 already going on, hopefully that's something that can be helpful.

13 Dr. Lange: Thank you. Dr. Yuh.

14 Dr. Yuh: I think this construct and its duration over a five-year span presents an opportunity to
15 see if this intervention can help physicians manage a tricuspid disease, right heart failure,
16 because I think it speaks actually directly to part B, in terms of minority patient populations,
17 underrepresented groups who don't have the access to the close medical follow-up that other
18 groups have. And so, I think it's an opportunity to see how this not only impacts the
19 management, but also advantages those that are represented that don't have the same access to
20 health care.

21 Dr. Lange: Good point, David. Thank you. Dr. Vidovich.

22 Dr. Vidovich: Yeah, I think this is a great strength. The only question I have is, do we have
23 enough granularity, to follow up the rhythm issue which was brought up, the atrial fibrillation,

1 and do we have enough granularity to see the procedures that will be done for implantable
2 devices that caused TR, you know, TR caused by the leads. Could this be a signal we could pick
3 up later on? Again, I don't know if there's enough granularity to look into that.

4 Dr. Lange: Okay. Dr. Schwartzott. I mean, Jennifer Schwartzott. My apologies.

5 Mrs. Schwartzott: Oh, no problem. Jennifer Schwartzott. I've seen firsthand how well registries
6 can work in collecting data, so I think that's a wonderful idea. Patients are more than willing to
7 share when they've had positive or negative experiences. They want to spread the knowledge out
8 there to other patients. I also think, that when we talk about these subgroups, you know, as we
9 said in the last question, some of the doctors said, we should be looking at the younger
10 population if that's going to become more prevalent. And look at five-year studies, but also
11 maybe even further down, because those people are going to have to live with this device longer
12 than the population that's currently really receiving it and being studied.

13 Dr. Lange: Okay. Bram, I'm going to summarize here two things. One is I do believe the registry
14 data carries value. A large number of patients, we already have some enrolled, and as Ralph
15 suggested, already have some minority patients in there. As Bram, as you have highlighted,
16 Ralph mentioned, and Abbott has conceded, the collection of KCCQ data has not been very
17 robust. And since this particular study, the value of it, or the major endpoint in which we're
18 basing this, the effectiveness is the KCCQ. It's going to be pivotal that they collect that data and
19 continue to collect the data in the current patient population for two to five years. And
20 importantly, if we're going to try to tie this to hard endpoints, like decreased hospitalization,
21 decreased mortality, that they continue to collect this data in this particular group for two to five
22 years. We've heard a couple of other things. People are interested in LV function, baseline LV
23 function, making sure we collect that data. Atrial fibrillation, is it paroxysmal or chronic? And

1 what happens after the device is placed with regard to atrial fibrillation? I think Amy's suggestion
2 about getting specific about right heart symptoms, so we can see how it affects ascites, edema,
3 fatigue, those kinds of things, I think are also valuable. So I think I've summarized most of the
4 information that we've got. Does that give you sufficient guidance for now?

5 Dr. Zuckerman: Yes, that's very helpful. We can go on to the next question.

6 Dr. Lange: Okay. Question number eight.

7 Question Eight

8 Mrs. Naber: Okay. Question eight is about the training program. Please discuss key elements
9 recommended in the operator's training program for the TriClip procedure.

10 Dr. Lange: Okay. For interventionalists, Jim. Key elements.

11 Dr. Blankenship: Yeah, okay. I think one of the biggest questions coming out is, is how much
12 training and you know, run in is going to be necessary. We saw that there's maybe a benefit to
13 higher volume operators and teams. And so, I think one question is, how many procedures should
14 be done with a proctor involved. So, I guess one of the key things-- and I think that the program
15 they outlined that involves visiting a center of excellence and watching some procedures and
16 then getting started with proctors, is going to be important. And I think probably requiring prior
17 MitraClip experience is going to be important. And then recalling that it's not only the individual
18 operators, but it's the entire team, taking care of the patient before, during, and afterwards is also
19 going to be very important. So, building up the experience of the team as well as the experience
20 of individual operators is going to have to be an important part of it.

21 Dr. Lange: Okay. Mitch, other comments?

22 Dr. Krucoff: Yeah, I basically agree. I think that, again, the backdrop of having a lot of

23 MitraClip experience tells you how to operate the device. But I think the tricuspid valve is

1 clearly different than the mitral. But I think the training program, learning curve is something
2 that was done pretty well with MitraClip, and I think a lot of those same principles probably
3 apply. The point that's been made repeatedly is, after the procedure, the technical procedural
4 success, I think that the next part of training, and whether this is part of a multidisciplinary team
5 or something you go after the interventionists about, but I think you have to pay attention, that to
6 really benefit, somebody who understands right heart failure has to take care of the patient.

7 [unintelligible]

8 Dr. Lange: Great. I've got Dr. Vidovich, Dr. Brindis, Dr. Shanker, and Dr. Friedman.

9 Dr. Vidovich: Yeah, this is Mladen Vidovich. What confuses me is that experience with
10 MitraClip didn't translate in high volume sites and better outcomes. So I suspect it is the heart
11 failure team that probably is the key element here. Why did it better in the high-volume team? As
12 an interventionist, I don't know, I'm not a heart failure doc, but how would you follow up with
13 that and train them? I'm at a loss here. But I think that is the secret here and did better outcomes.

14 Dr. Lange: Okay. The secret sauce, okay. Dr. Brindis.

15 Dr. Brindis: Yeah, I'm not concerned about the mechanical aspects of the training program for
16 the TriClip per se. We have good models related to MitraClip. I think the big issue here is in
17 patient selection, and being able to make sure that the training program really works hard in
18 helping centers figure out who's the right patient to have the procedure.

19 Dr. Lange: Thank you. Dr. Shanker. And then Dr. Friedman.

20 Dr. Shanker: I agree with everything that everyone said before me. The one thing I do want to
21 throw in there, as an electrophysiologist, in my personal experience, when I'm ablating right
22 sided versus left sided accessory pathways, a tricuspid valve is a lot more — it's a little bit more
23 difficult to maneuver the catheter along the tricuspid valve annulus to get to where you want to

1 get to. The experience that folks have had with the mitral valve annulus will possibly be different
2 than on the cuspid side. And also, how you approach the tricuspid valve annulus, a transeptal
3 versus a retrograde, versus having to advance up into the IVC and down into the right atrium,
4 requires a little bit more — different skill set. That requires experience. So, it doesn't surprise me
5 that that the folks that were very well trained in MitraClip did initially have some issues on the
6 tricuspid side, but I suspect that that learning curve can be overcome.

7 Dr. Lange: Okay. Dr. Friedman.

8 Dr. Friedman: Yeah, Dave Friedman. Thank you. I think the unsung heroes are also the advanced
9 imagers. I think you need to have a credentialing team who are well versed in actually getting
10 proper echocardiographic data, so you can have a suitability analysis. And that comes down to
11 the core echo lab. And I think that's part of the training. And it's again, the structural team in
12 cahoots with the operators. The technicalities of the actual deployment of the TriClip, right,
13 what's been said, is relatively easily done compared to the suitability assessments. So that's part
14 of the equation, I think, too.

15 Dr. Lange: Great. Bram, I've heard four key components. First of all, a large experience with
16 mitral clip, as everybody in this study has. Second is patient selection. Third key element is
17 imaging and having credentialing with that imaging team. And then the last I heard is, I'm going
18 to call a management of a heart failure. And since most interventionalists aren't particularly
19 experienced or talented in that, as I would say, probably a multidisciplinary heart failure team to
20 help with the management. So those are the four elements I've heard.

21 Dr. Zuckerman: Great. I think we've finished this question, and we're ready to go on to the
22 voting, Dr. Lange.

1 Dr. Lange: Great. Alright, at this time, and I realize we've gone over a little bit. I appreciate
2 everybody's patience. I think the discussion has been very robust. At this time, we have an
3 opportunity to hear summations, comments, or clarifications, from the FDA and from the
4 sponsor. Both have a total of 15 minutes. I'll turn it over to the FDA first, and then we'll allow the
5 sponsor to provide summation.

6 Mrs. Naber: Okay, I'll just very briefly thank the panel on behalf of the FDA review team. We
7 really appreciate your time today. You gave us a lot of helpful insights and we really appreciate
8 all of the discussion regarding the TriClip device. I think I will, in the interest of time, turn it
9 over to Dr. Lange and the sponsor for other comments.

10 Dr. Lange: Okay. The FDA, again, I want to thank you for an excellent presentation and your
11 responsiveness to the questions from the panel. With that said, Erin, let me turn it over to you, for
12 final comments or summation.

13 Dr. Spinner: Yes, thank you. So, we'd like to thank all the panelists for all of the great discussion
14 today. And really letting us share and showcase our data, and really provide further discussion
15 and clarification for the questions. And lastly, we'd like to thank all the patients that participated
16 in bringing this data to light. Thank you.

17 Dr. Lange: Thank you for those brief but I'm going to say important comments, Erin. Thank you
18 very much. We're about to proceed to a panel vote, but before we do, I'd like to ask our non-
19 voting members to provide comments. Rachel Brummert, our consumer rep, Elijah Wreh, our
20 industry rep, and Jennifer Schwartzott, our patient representative, to see if they have any
21 additional comments. Rachel, I'll start with you. Ms. Brummert, any comments you'd like to
22 make? Alright. Not hearing any. Mr. Wreh, I'll turn it over to you. Any comments you have?

1 Mr. Wreh: Yes. This is Elijah Wreh, and I want to thank the panel members as well, and the
2 sponsor and my colleagues at the FDA for a successful, interactive, robust FDA panel meeting.
3 Just a few things I would like to emphasize before the panel takes a vote on the TriClip device. I
4 would like to remind members of the panel that the TriClip technology is not a new device. It is
5 based on the MitraClip device and it's not a novel technology. I think the sponsor results
6 demonstrate that the primary safety endpoints were met. And they state that, you know, I would
7 like to highlight for the panel members that, based on the FDA presentation today, the FDA noted
8 that the study had a low major adverse event rate at 30 days. And there were high technical and
9 device success rate at 30 days, as well, compared to other clinical studies that I've seen in the
10 past. So, the study sustained TR reduction and significant KCCQ improvement as well. So, I
11 want to highlight that the FDA agreed that the sponsor designed without shamming wax
12 (phonetic), and in addition the sponsor has good supporting evidence on the proper benefit.
13 Another important thing I would like to point out, Dr. Lange, is I want to highlight that the
14 KCCQ, with TR imaging as well, I also want to bring to the panel attention that the rates of
15 intervention, in the sham study as well. So, I want to thank you all for this discussion. Thank
16 you.

17 Dr. Lange: Elijah, thank you for hanging with us this whole time. I appreciate your sage
18 comments. Thank you. Jennifer Schwartzott, let me turn it over to you.

19 Mrs. Schwartzott: I'd like to thank the company for doing this study, recognizing the need. I'd
20 like to thank the FDA for hearing this, and for all the panelists who have shared all this
21 information and debated the facts. When it comes right down to it, the patients need options. This
22 is an unmet need. It's, you know, a set of very painful and uncomfortable circumstances. And to
23 have something that shows such promise, that is minimally invasive, that tackles a lot of these

1 issues. My mother went through open heart surgery. She did not do well with it and did not
2 survive. This wasn't available to her. Hopefully, for me in the future, if I were to need it, it would
3 be there. I wish I was voting today on this, because it's just so necessary. Take that into account. I
4 do think that the risk is low, and the benefit definitely outweighs the risk. Thank you very much.
5 Dr. Lange: Thank you, Jennifer, for those comments and your perspective. We're now ready to
6 vote on the panel's recommendations to the FDA. The panel will vote on three questions relating
7 to the safety, the effectiveness, and the benefit-risk profile of the device. Dr. Akinola Awojope
8 will now read two definitions that will assist us in the voting process.

9
Vote

10 Dr. Awojope: The medical device amendment to the Federal Food, Drug, and Cosmetic Act, as
11 amended by the Safe Medical Device Act of 1990, allow the Food and Drug Administration to
12 obtain a recommendation from an expert advisory panel on designated medical device pre-
13 market application PMAs that are filed with the agency. The PMA must stand on its own merits,
14 and your recommendation must be supported by safety and effectiveness data in application, or
15 by applicable publicly available information. The definition of safety and effectiveness are as
16 follows. Safety, as defined in 21 CFR section 8607D1. There is a reasonable assurance that a
17 device is safe when it can be determined, based upon valid scientific evidence, that the probable
18 benefit to the health, from use of the device for its intended uses and condition of use, when
19 accompanied by adequate direction and warning against unsafe use, outweigh any probable risk.
20 Effectiveness, as defined in 21 CFR Section 8607E1. There is a reasonable assurance that the
21 device is effective when it can be determined based upon valid scientific evidence, that in a
22 significant portion of the target population, the use of the device for its intended uses and
23 condition of use, when accompanied by adequate directions for use and warning against unsafe

1 use, will provide a clinically significant result. The panel members will now begin the voting
2 process. I will read each of the three voting questions and send each of the voting members an
3 email to respond to. The voting members, please vote for each question and remember to add
4 your name to the ballot. Once I read all the three questions, we will tally the votes and read them
5 into record. Thank you.

6 VOLi: Akinola, do you want to go ahead and read the questions in, or Dr. Lange, before we take
7 a break?

8 Dr. Awojope: Hello. Do you want us to move to the backstage?

9 VOLi: : Yeah, I guess if everyone can, we can go ahead and — Dr. Lange, can we go ahead and
10 take that little break now, so we can tally the vote? You're on mute.

11 Dr. Lange: We have not voted yet. And what I was thinking, Akinola would read the question,
12 allow everybody to vote on question number one, two, and three, and then we would take a five-
13 minute break to tally those.

14 Dr. Awojope: Okay. I'm going to read the question right now.

15 Voting Question One

16 Dr. Awojope: Question one. Safety. Is there a reasonable assurance that the Abbott TriClip G4
17 System is safe for use in patients who meet the criteria specified in the proposed indication?

18 Please vote.

19 Dr. Lange: Hold on, Akinola.

20 Dr. Awojope: Yes?

21 Dr. Lange: Hold on just a second, Akinola. Let's make sure that everybody has access to it. And
22 Jim, when you have the full tally, let me know and then we'll go to question number two.

23 Dr. Awojope: Okay. Please vote now, yes, no, or abstain.

1 VOLi: And we can move on to question two. We'll go through the questions and then we'll take
2 a five-to-15-minute break to tally.

3 Dr. Lange: Sounds great.

4 Dr. Zuckerman: Thank you.

5 Dr. Awojope: Okay.

6 Dr. Hirshfeld: I'm sorry, I didn't get the email, or...

7 VOLi: I'll send it in the chat. Everyone should receive it in the chat.

8 Dr. Hirshfeld: Okay.

9 Dr. Lange: Hold on just a second, before we go to question number two. Let's make sure Dr.
10 Hirshfeld can open up the chat, and vote.

11 Jim: Akinola, you can move on to question two.

12 Dr. Awojope: Okay, thank you very much. I'll now read question number two.

13 Voting Question Two

14 Dr. Awojope: Is there a reasonable assurance that the Abbott TriClip G4 System is effective for
15 use in patients who meet the criteria specified in the proposed indication? Please vote now. Yes,
16 no, or abstain.

17 VOLi: Okay, we can move to number three.

18 Dr. Awojope: Thank you very much. I will now read the question number three.

19 Voting Question Three

20 Dr. Awojope: Do the benefits of the Abbott TriClip G4 System outweigh the risk for the use in
21 patients who meet the criteria specified in the proposed indication? Please vote now. Yes, no, or
22 abstain.

23 VOLi: Dr. Lange, if you can take us to a break now, we'll go ahead and tally it up.

1 Dr. Lange: Absolutely. I was going to tell everybody that's watching, we're going to take a five-
2 to-10-minute break just to tally the votes. We'll go backstage. If you wait, we'll come back and
3 provide the results of that tally.

4 Vote Results

5 Dr. Lange: I want to welcome everyone back. The votes have been received and Dr. Awojope
6 will now read the votes into record.

7 Dr. Awojope: Thank you very much, Dr. Lange. Question one, the panel voted 14 yes, zero no,
8 and zero abstain. For question two, the panel voted 12 yes, two no, zero abstain. For question
9 three, the panel voted 13 yes, one no, zero abstain. The three voting questions are now complete.
10 I will now turn it back to Dr. Lange. Thank you very much.

11 Summary of Panel Recommendations

12 Dr. Lange: Thank you very much, Akinola. I'll now ask the panel members to discuss their
13 votes. I'll call you by name. If you answered no to any question, please state whether the changes
14 to labeling, restrictions on use, or controls would make a difference in your answer. Again, please
15 state your name, how you voted for each question, for the record. We'll start with Jim
16 Blankenship.

17 Dr. Blankenship: Thank you. So, for safety, I did not mention it before, but I tried to compare
18 the one-year adverse events for TriClip to those for the EVOQUE valve and MitraClip, and
19 they're in the same ballpark. I think that there was consensus that the safety of it is pretty well
20 established, so I voted yes on safety. In terms of efficacy, again, I think, an improvement in
21 patient-perceived outcomes is very important. That's why we do lots of other procedures. And so,
22 I think it's a very important end point. And it was proven to be statistically significant, fairly

1 beneficial there. And so, I think that since the safety, it seems proven, and the efficacy is
2 definitely positive, that the benefit-risk ratio favors approving it.

3 Dr. Lange: So, Jim, when you offer this to your patients, are you going to offer them a hip
4 replacement too?

5 Dr. Blankenship: No, I think the risk-benefit is better than hip.

6 Dr. Lange: Thanks, Jim, for those comments. Ralph Brindis.

7 Dr. Brindis: Ralph Brindis. I voted yes for all three. I agree with Jim's comments, and if the FDA
8 approves this device I think it will be an important armamentarium for the management of
9 tricuspid regurgitation. And it will be very interesting for me to see, if it is available, how our
10 structural clinicians will make decisions, whether to use an EVOQUE valve or a TriClip, in
11 which patients. And I think, also, will be very important to see how patients are managed
12 afterwards, with TriClip, should any needs for pacemakers and so forth, or even EVOQUE valve,
13 in the future, become necessary.

14 Dr. Lange: Thank you, Ralph. Dr. Bart.

15 Dr. Bart: Yes, Brad Bart here. I voted yes for all three. I thought the safety data were compelling.
16 I think that patient-related outcomes are important. And although there definitely is a placebo
17 effect, I think the sponsor provided enough information that the benefit was not related to
18 placebo alone. And so, risk-benefit balance was favorable.

19 Dr. Lange: Thank you, Brad. Dr. Cizik.

20 Dr. Cizik: Yes, I voted yes to all three. I did struggle a little with effectiveness. I was waffling,
21 just in the sense of the correct population. I think, to Dr. Shanker's point, I think when things get
22 generalized out into the real world, there's creep. People want to add patients on the lower end or

1 the upper end. So, I think there was a little concern for me there, but again well presented by the
2 sponsor. The data was very compelling and so thank you for all the hard work you did.

3 Dr. Lange: Thank you, Amy. Dr. Evans.

4 Dr. Evans: Yes, I voted yes to all three. I voted for the safety based on the discussion of the of
5 the committee. I think that, composing and decomposing the various outcomes for patients, both
6 of them are a must. And, in some ways, I think we need to do a little bit more of thinking about
7 how to use the outcomes to analyze what happens to the patients, rather than the other way
8 around. We tend to use the patients to analyze the outcomes. So, the way you compose
9 information, I think, is an important step in the future. I did have some concerns with parts of the
10 analyses, you know, the win ratio I think is a step forward in the composition of various
11 outcomes. But it doesn't incorporate ties which can complicate interpretation. It's on a relative
12 risk scale, which can make it very volatile, which is one of the reasons you're seeing volatility for
13 different subgroups, based on the sites of enrolling 10 or more or less than 10. And non-
14 comparability of the win ratio in those circumstances. The issue with relative risk is, you know,
15 you can increase risk of one in 10 to two in 10, and that's a relative risk of two, and very
16 important. It could also increase risk of one in a thousand to two in a thousand. That's also
17 relative risk of two, but they're very, very different. And particularly when you're composing
18 information from multiple outcomes, those aren't comparable. Because they're not trading off or
19 they're not adding up. So, I was able to reanalyze the data, more on a risk difference scale, which
20 will take out some of that volatility and will enable you to analyze things in a more comparable
21 way, without that volatility. And allow you to analyze all the out individual outcomes, as Dr.
22 Zuckerman pointed out, the importance of looking at each outcome individually, on a similar
23 scale, and also enable you to look at this sort of ordinal nature, also sequentially dichotomizing

1 on an individual level. I think all of the signal is in the KCCQ. You cannot completely get rid of
2 the placebo effect. However, the KCCQ, at least in the primary analysis that was presented, is
3 really only given credit when there's a 15-point improvement. And, given the magnitude of that,
4 that necessary improvement and the durability and the magnitude of response overall, I thought
5 that that made the result more robust. There was talk, you could redo the analyses, actually
6 replacing KCCQ with the TR severity, if you would like to do that, and that may be worth
7 looking at. But the analysis that I was able to do made me more confident that the result was
8 robust enough, particularly given the importance of quality of life for patients in this situation
9 and stage of life. Thanks.

10 Dr. Lange: Scott, thanks for those comments. If I serve on a panel with you again, I'm not going
11 to let you wait until the end to make those comments. Okay? Alright, it'd be appreciated during
12 the discussion part just as well. So, thank you. I do appreciate those comments. Thanks. Dr.
13 Friedman?

14 Dr. Friedman: The tricuspid valve has been mentioned as the forgotten valve, except, of course,
15 in this study, and I'm very heartened by the trial data information. I voted yes to all three
16 questions, and I was very comforted by the data that we've reviewed all day today. And I do have
17 some shared concerns about the future of what happens when a valve is clipped. What do we do?
18 How do we pass through a valve? How do we get by with a PA catheter? What do we do for the
19 EP guys who need to implant a device? These are unanswered questions. We need more time to
20 discern where these patients go in the future, which lends to the post hoc analysis that's been
21 discussed. But pleased to help.

22 Dr. Lange: Thank you. Dr. Hauptman, your votes?

1 Dr. Hauptman: Thank you, Dr. Lange. I voted yes on safety. I think that was very, very clear. I
2 voted no on question two. I just felt the need to pull back a little bit on unbridled enthusiasm.
3 Because I think we have a responsibility to better understand who's going to benefit, and that
4 needs better definition. We don't know anything about patients in normal sinus rhythm, at least
5 not in the U.S. study. Or the whole issue with low volume centers or patients with significant LV
6 dysfunction, 25%, 30%. Because the indication is written, it is agnostic on that. So, from that
7 standpoint, I might have voted otherwise with a somewhat different indication statement. I still
8 am troubled by the fact that there was no change in diuretics. There was no consistent story with
9 biomarkers. The imaging data is encouraging. So, at the end of the day, I ended up being the sole
10 dissenting vote on number three. I would encourage the agency to take a very critical look at the
11 continued access protocol, at one year, because I suspect that those data could tip the scales, at
12 least in my mind, and shore up what we know from the main cohort in this study. But the
13 sponsor, I think, did a wonderful job in presenting the data. I think this is a step forward in the
14 sense that, if we're going to rely on KCCQ, this is really, truly important to patients, we want
15 them to feel better.

16 Dr. Lange: Thank you, Paul. Dr. Hirshfeld?

17 Dr. Hirshfeld: So I voted yes, yes, and yes. And I would have liked to have seen more rigorous
18 data to support efficacy. But, lacking the rigor, it still seems fairly clear to me that there is
19 individual patient responsiveness, which is heterogeneous. And so, while I'm convinced that the
20 device doesn't universally help all patients who have severe TR, I think it does highly effectively
21 help a subset of these patients. And, accordingly, I think it's important that it be available as a
22 tool for interventional cardiologists to try to help these people. They need this potential option. I

1 think the clinical community and the sponsor will have an ongoing responsibility to try to
2 determine more precisely which patients are going to derive gratifying benefit from this device.

3 Dr. Lange: Thank you, John. Dr. Katz.

4 Dr. Katz: This is Marc Katz. I voted yes for safety, no for effectiveness, but then caved and
5 voted yes for the benefits outweighing the risks. And I base that on that I have experience
6 implementing both MitraClips and MitraClips in the tricuspid position. I think there will be-- or
7 is a role for it, in a limited population. It's going to have to find its niche between, you know,
8 valves and leaflet modification. I think another big part of this is the heart team. I think it should
9 be specified that a cardiac surgeon be part of the heart team, not just a quote multidisciplinary
10 group. I think that's actually been one of the best things that's happened in medicine in my career,
11 is the collaboration between those structural cardiologists and the cardiac surgeons. And I also
12 think that training on imaging is going to be crucial for this, because imaging the tricuspid valve
13 is not as simple as imaging the mitral valve. The technicalities of placing a clip have been taught,
14 during the rollout of the mitral clip, and I suspect will continue here. But you know if you can
15 see it, you can clip it. If you can't see it, it's very difficult.

16 Dr. Lange: Thank you very much, Marc. Dr. Krucoff.

17 Dr. Krucoff: Yeah, thank you. Mitch Krucoff. So, I voted yes on all three. I think the safety side,
18 for a breakthrough technology, this has the advantage of emerging from a very mature platform,
19 MitraClip and the mitral valve. And I think that experience, hopefully nationally and
20 internationally, will also translate into the commercial rollout of this, without major technical
21 complications, like many breakthrough technologies have to weather. On the effectiveness side, I
22 think it's very clear to me that there is an unmet need at the end-- when the beneficial effects of
23 optimal medical therapy hit the end of the road. We have to step back a little bit in the

1 cardiovascular community and recognize that what our expectations of what benefit looks like,
2 clinically, that the short term and long-term versions of what does it mean to save a life, may be
3 really different. And in the near term, saving the quality of life, may be, as we heard testimonials,
4 and as I think the quality of life, the KCCQ data indicate, that there's an impact in the first year at
5 a very high level. And then hopefully if over a longer term, mortality is physically at risk, that we
6 may see as those data emerge, some benefits, in saving a classical death the way we usually think
7 of saving a life. The benefit-risk balance, I think we have to come back to the ground that this is
8 in every way a breakthrough technology, and we have a lot to learn. A lot has already been
9 mentioned, the heterogeneous population, responders, non-responders. Do we set people up for
10 catastrophes later, by putting a clip in now? All of those things, and how this intervention plays
11 with regard to rhythm and LV function. But I think that's the work, and that's what, in my
12 opinion, the breakthrough technology process is for, is to get it into a post-market evaluation
13 period, where we're very serious about the quality and the information that needs to be collected,
14 as this becomes part of the practice of medicine.

15 Dr. Lange: Thank you, Mitch. Dr. Selzman.

16 Dr. Selzman: I voted yes on all three. I'm not sure I have anything eloquent to say that hasn't
17 been said thus far. I think, despite some of the less strong evidence of efficacy, having this in our
18 toolkit is going to be very vitally important, and we're going to learn a lot in the next five years.
19 So, thank you.

20 Dr. Lange: Thank you, Craig. Dr. Shanker.

21 Dr. Shanker: I wanted to, first, thank the sponsor and FDA for great presentations and for
22 inviting me on the panel discussion. I did vote yes to all three. I felt that the device hit the safety
23 aspect, low rates of MAE versus other structural heart therapies. Certainly, the data did

1 emphasize the importance of procedural training, image training, and also training the heart care
2 team in terms of post-procedural management of right -sided heart failure. An effectiveness
3 perspective, although it was largely symptom-driven in this open label study, it was verified by
4 the PRO [unintelligible] and also the improvement that was seen was early and sustained and
5 corroborated by hemodynamic and anatomic parameters. Going forward, in terms of patient
6 selection and labeling, the hope is that the patients that are selected will be class two, class three
7 patients, and as we pivot towards to the post-market phase surveillance aspect with this device,
8 I'll be really eager and getting more insights in terms of how AF plays a role in this disease.

9 Dr. Lange: Thank you very much, Amit. Dr. Vidovich?

10 Dr. Vidovich: So, Mladen Vidovich. Again, thank you for the FDA for a great meeting, and for
11 the sponsor for providing excellent data. I think the study was well done. I voted yes on all three.
12 I'm-- as it was mentioned, it was a forgotten valve, but I think forgotten no more. And I'm
13 actually pretty optimistic about the future of this device. I think we'll learn about atrial
14 fibrillation, and timing of this device with atrial fibrillation. We need to learn about leadless
15 devices with this clip and implantable leads, you know, how they will interact. There was
16 inadequate data on SGLT inhibitors, and I think the heart failure community will, I think,
17 welcome this to tailor the device drug interaction with this clip, because I think it's quite
18 important. And then again, also, I see a great opportunity for our imaging community to develop
19 better metrics, because the MRI data was actually very encouraging to me, to see how the
20 ventricle remodeled after the clip. So, I'm actually pretty optimistic in a very well-done study.

21 Dr. Lange: Great. Thank you, Mladen. Dr. Yuh.

22 Dr. Yuh: David Yuh. I'd like to thank the FDA and the sponsor for excellent presentations. I
23 think the safety data speaks for itself. I think the device performed very well. Oh, by the way, I

1 voted yes on all three categories. Not only did it perform well in the randomized group, but in the
2 single arm study as well. And these translated into what I think are meaningful subjective
3 improvements in patients' symptomatology. I think this technology represents a meaningful
4 advance in the treatment of right heart failure. And as a reformed heart failure surgeon, I
5 certainly appreciate and sympathize with those that have to deal with right heart failure. So, I
6 think this is a significant advance. And although not definitive, it's still a move in the right
7 direction and a lot can be learned from the post-market studies going forward. Thank you.

8 Dr. Lange: Thank you, Dr. Yuh. I'd like to thank the patient industry and consumer rep. I want
9 to thank the FDA and the sponsor, both of whom gave excellent presentations. I appreciate the
10 clarity of the presentations. For the sponsor, I know how difficult it is to do human subject
11 studies. This is a well-conducted study. You've been congratulated on that. Your collaboration
12 with the FDA in bringing this to this point where we can deliberate on it. And again, for the
13 responses. And so, with that, Dr. Zuckerman let me turn it over and see if you have any final
14 remarks before I close the meeting.

15 Dr. Zuckerman: I would just like to thank you, Dr. Lange, for your excellent leadership today,
16 and for all the panel members who did an outstanding job with this challenging file. Thank you
17 all.

18 Adjournment

19 Dr. Lange: Thank you. At this time, in El Paso, when we have a successful meeting, which has
20 gone very well, we call it "ita" time. That's fajita and margarita. And so, it's "ita" time. At this
21 point, the meeting of the Circulatory System Devices Panel is now adjourned. Thank you all very
22 much. I want to express my appreciation to you all for serving on this panel all day. Thank you.

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