which were done by the surgeon that performed the initial sternotomy?

And the second question was is that I can appreciate the randomization and kind of testing procedure that was carried out and it kind of raised a question in my mind, given the sponsor's presentation, where I believe they indicated that they used a block randomization within center. And was there an examination of the size of that block size in this type of a trial? And maybe the sponsor can come back and address this after lunch.

But if a small block size was used, for example, there is the potential for un-blinding and pre-selecting patients to receive the device and control. And was that part of FDA's assessment?

DR. XU: Let me answer that second question first. For the second one, you mean the randomization test. You see for us, it was done just as complete randomization.

DR. NEATON: So you didn't take into

account the blocking?

DR. XU: Oh, we take it in the second one. Let me go to the second. The results are shown on this slide that is actually the randomization of the test as each was done actually that is within center randomization.

DR. NEATON: And did this test take into account the restrictions on the block size pin center?

DR. XU: Yes, correct.

DR. NEATON: And what was that block size?

DR. XU: You mean the block size?

DR. NEATON: For the randomization.

DR. XU: Oh, you mean, actually let me -- my understanding is, okay, the randomization is within center, one by one. No block within one center anymore.

DR. NEATON: I understood the sponsor to indicate that blocks were used within center for the randomization.

CHAIR YANCY: We'll take that answer

this afternoon.

Dr. Blackstone, I think you had a question.

DR. BLACKSTONE: Yes. This goes back to the post-market approval to clarify something that perhaps is not clear to either the FDA or the sponsor.

STS data is reliable for in-hospital events, for some centers to four weeks, for zero centers to eight weeks. So the idea that the STS data can be used for up to eight weeks is false.

CHAIR YANCY: Thank you for that insight.

Are there any other questions? I don't think we had a chance to hear from our industry member, nor our lay person.

DR. YAROSS: I don't have any questions at this time or comments.

CHAIR YANCY: Well, if I can summarize what I have heard this morning, again, I want to thank the sponsor for a very learned

presentation, very thorough. And I thank the FDA for a very solid presentation as well, and the panel members for their questions both to the sponsor and to FDA.

The issues that we want to be certain the sponsor addresses at our next opportunity, has to do with any metric of clinical benefit, a focus on transfusion requirements. Give us a re-visit, if you will, of the assessment of adhesion, how exactly was that done? A statement about the study design, vis-a-vis the power calculation, both for the primary endpoint and any safety issues and any additional thoughts you have about the definitions of mediastinitis and the incidence of mediastinitis.

Thank you very much. We will reconvene at 1:00 p.m.

(Whereupon, at 11:59 a.m., a lunch recess was taken.)

CHAIR YANCY: We will now resume our panel discussion of this PMA. As per the norm,

the panel has two reviewers, Doctors Blackstone and Hopkins. We will begin with Dr. Blackstone's opening remarks. The panel may ask the sponsor or the FDA questions at any time, as we go forward this afternoon.

Before I yield to Dr. Blackstone, just one point of clarification for the panel. There is a new document at your table. That document represents a transcript of comments you will hear later during the open public forum.

Secondly, FDA has one slide that they would like to show to answer one specific query. We'd like to do this very quickly and allow just one or two brief questions.

MR. HILLEBRENNER: Thank you, Dr. Yancy. There were a couple of questions regarding the slide that we had presented on dissection times earlier. That slide included median dissection times. I believe the question was regarding standard deviations. And this slide does shows the means for the grade three no severe adhesions and then all patients. The

standard deviations are shown for the first two categories.

I believe the sponsor had included the overall patient means with standard deviations in their presentation earlier. I don't have those on hand necessarily. So, there is an example of that. And we also have information on the confidence interval, as well as a slide to show the distribution of the data, which is why we ended up using the medians in our original presentation.

But I'll leave that, in case there are additional questions.

CHAIR YANCY: Are there brief questions from the panel regarding what you see before you?

(No response.)

CHAIR YANCY: Thank you very much. Dr. Blackstone.

DR. BLACKSTONE: Some of what I will say may be repetitive of what we have heard this morning, but it perhaps may focus our attention

in some summary fashion on this device.

First the nature of the clinical problem. As we have heard, although under some circumstances it may be desirable to close a pericardium after a cardiac operation, conduits, grafts, and even compromised human dynamics may preclude doing so. The scaffold of fibrin remains on the anterior surface of the heart on which humeral and cellular processes generate adhesions between it and the surrounding tissues. In particular, retrosternal adhesions of varying density form when the operation has been performed through a sternotomy, the typical surgical approach.

If it is necessary to re-operate, these adhesions and scar formation increase complexity of every part of the operation, increase operative time, increase risk of inter-operative adverse events at sternotomy during dissection, during cannulation for systemic perfusion of myocardial protection, and even during the heart operation itself, and increase

inter-operative bleeding, leading to increased use of blood products. Thus, for more than a quarter century, various innovations are being tested to make cardiac re-operations easier and safer.

Perhaps simplistically, we might say there have been four general approaches to solve this clinical problem. One, a permanent sheet of various materials placed between heart and sternum; two, use of irrigating solutions intended to retard fibrin formation and less adhesions; three, bioresorbable membranes; and four, scaffold for autologous neopericardium regeneration. Walther and colleagues and Sukihara and colleagues recently reviewed progress in developing techniques in all of these areas for facilitating sternal re-entry. And these are being well referenced also by the SyntheMed folks.

Briefly in the 1970s and 1980s, permanent sheets of silicon rubber, PTFE and other polymers, as well as xenograft pericardium

were introduced for this purpose. By far, the most commonly used product in the past and at present is a PTFE sheet sown into place. However, use of permanent sheets and xenografts takes a little fussing and extra operative time and they have not been widely adopted by the cardiac surgical community. They are perhaps more widely used in neonates, infants, and young children who undergo stage reconstruction of those congenital heart lesions that require one or more re-operations.

In the 1990s, various topical solutions were introduced. Some of these were pharmaceuticals directed at reducing fibrin scaffold and reducing inflammatory response. Bioresorbable membranes were also introduced, either as a sprayable film, or as an absorbable membrane with various rates of resorbtion. This is a category into which REPEL-CV fits.

To complete the picture, I ongoing experiments and clinical trials that began in the 1990s introduce a scaffold or a matrix on

which an autologous neopericardium might form. This technique attempts simultaneously to reduce early adhesion formation and to regenerate a pericardium.

Now, there are problems with these approaches well documented. In enumerating these, I hope to form the basis for a lively discussion of what outcomes should be considered in assessing safety of this technology.

One, both permanent and temporary sheets are foreign bodies that can themselves incite an inflammatory response, leading at times to encapsulation, obliteration of dissection planes, and dense scar. Anecdotally, Dr. Gosta Pettersson a Scandinavian surgeon now at Cleveland Clinic recalls a clinical trial in the 1990s in Sweden that was stopped prematurely when a bioresorbable membrane was studied and found to incite a severe inflammatory response that resulted in rapid formation of a dense scar, making entry extraordinarily difficult.

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Needless to say, all the materials that are being used and tested today are ones that surgeons expect will not incite an even worse situation than does unaided healing.

Number two, both permanent and temporary sheets may stimulate scar formation on the surface of the heart which, at re-operation, obscures underlying cardiac architecture and structures such as coronary arteries. This was not assessed in REPEL-CV studies.

Permanent sheets do not grow. So, when placed in babies, the possibility exists for them to distort surrounding growing tissues. Presumably, this would not be the case for REPEL-CV. Most permanent sheets are opaque, so when they are placed over the anterior surface of the heart, the heart is no longer visible during sternal closure. An advantage of many resorbable membranes such as REPEL-CV is that they are transparent.

Five, both permanent and resorbable sheets are sutured to surrounding tissues to

prevent their migration. The necessary sutures are foreign bodies, as noted by SyntheMed.

Six, not all materials are long-term biocompatible and they require the extensive material testing that REPEL-CV has had to endure. However, the data before us cannot be considered long-term.

Seven, above all, the presence of a foreign body, either permanently or temporarily is a nidus for mediastinal infection. Perhaps more than anything else, this has prevent widespread adoption of these products, particularly, given the relative infrequency of re-operation.

With that background, we examine the efficacy and safety of REPEL-CV, a bioresorbable membrane intended to reduce occurrence, and I refer that word to incidence, which implies for me per unit time, severity and extent of substernal adhesions in patients undergoing cardiac surgery via sternotomy.

Four human trials are being

conducted. A short-term randomized, essentially single center pilot trial in adults; a small random trial in neonates requiring staged operations and having planned delayed sternal closure, so that both very early prevention of adhesion formation and later adhesions present at re-operation can be examined; a small open label trial in Europe in neonates undergoing staged re-operations, focused on the re-operation at two to eight months after index operation. And unlike study two, the sponsor did not tell us in the packet if a new piece of REPEL-CV was used if a delayed sternal closure was necessary. They tell us it was not. And four, the multi-center randomized trial whose details you heard this morning. The pivotal trial also is in neonates who are undergoing staged reconstructions so, predictably, required re-sternotomy.

From the trial in adults, comes the one contraindication to REPEL-CV. It is not to be used for LVADs. Interestingly, a synthetic

neopericardium has been said to facilitate explanting such devices. Movement of the connecting grafts was said to disrupt the REPEL-CV membrane. As we all know, we are entering a new era of temporary and permanent mechanical circulatory support devices, and tomorrow's LVAD may well be a completely intravascular device. Thus, the language of the contraindication needs to be more clearly chosen.

Efficacy. Trials two and three show an evolution in grading of adhesions from coarse to finer and a quantitative estimate of the surface area occupied by each grade of adhesion of what is called the investigational site. The extent of which may be open to interpretation, but we have had a couple slides on that this morning.

For the pivotal trial, percent of surface area occupied by severe adhesions was a primary endpoint. There is no mention in the materials provided how this endpoint was quantified for each patient, but I surmised it

was coarse visual estimate and I think that is now true. The percents in each grade added to 100 percent.

What we do know without question is that the distribution of values for these four additive grades demonstrated a quite non-Gaussian property. As evidence, the standard deviation of most summary mean statistics is larger than the mean. This was corroborated when the FDA showed us that these probably were closer to U-shaped distributions. Thus, I do not know if this product did or did not meet the predefined 20 percent clinically meaningful difference.

Thus, in section seven, table 17, page 38, figure one on page 40, table 2 on page 42 are completely un-interpretable by me. True, Wilcoxon tests of differences in medians are given, but is this appropriate test, given the U-shaped distribution and does it address the pre-defined 20 percent reduction?

Further, given the additive nature of

the scale for adhesions, are independent grade-by-grade analysis analyses of this ordinal scale appropriate as a secondary endpoint? Are there more meaningful methods of analysis?

The secondary dichotomous endpoints are perhaps easier to understand. Severe adhesions occurred at a substantially lower frequency in REPEL-CV patients, than in control patients. But what is clear from the data is that REPEL-CV is not a panacea. About a third of the patients still develop severe adhesions and either the same patients, or at least a similar percentage, develop the same fibrous capsule with focal foreign body giant reaction, as is typical of permanent sheets. This is found on page 51 and 52 in Section 7.

Perhaps the most perplexing secondary endpoint results are those of dissection time. A reason to use products to reduce adhesions is, in part, to reduce dissection time. Although not commented upon by the sponsor, in patients with either no severe adhesions or severe

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adhesions, dissection time was systematically longer in the REPEL-CV patients than in control patients. Why was this? The assessment time? Did it include both dissection time and the assessment of the REPEL-CV patients? We don't know.

Unmeasured in this trial was inter-operative blood loss which also is an important reason to prevent adhesion formation.

Now, safety. These are difficult patients with high expected mortality, complications of preoperative ischemia, with increased risk of enterocolitis and tricky balance of pulmonary and systemic blood flow in the interim between Norwood and cable pulmonary and Fontan procedures. So, it is important to set aside all these well-known predictable complications and focus on the most relevant safety issues, presence of the temporary foreign body in the mediastinum that may harbor infective agents, leading to mediastinitis.

Here again, I am confused by the

initial data, the adjudicated data, and the raw data. In description of various adverse serious events in Section 9, I think there is definite or possible mediastinal complications in six patients in the REPEL-CV group and four patients in the control group. Now, as I look at these six and four patients, I am struck that it appears as if the mediastinal complications are more severe in the REPEL-CV than the control cases. However, for this study and with FDA agreement, only the most serious mediastinal complication, namely mediastinitis, as defined by a surgical not necessarily a CDC definition was used.

Now admittedly, there are more foreign bodies in the mediastinum in these cases than REPEL-CV, so it is important that we have control patients to ascertain this background noise. This can be said of all other complications, which are important to these babies and their parents, but have little or no importance in assessing the safety of this

product.

Finally, are there other unknowns? Yes. We do not know long-term safety effects that might become evident were this product used for adult cardiac surgery, such as patients receiving biological prosthesis, that will eventually require replacement, if the patient survives long enough.

So in my opinion, there is clear incremental benefit of the product, in terms at least of reduced substernal adhesions. I do not understand why this is not being translated, however, into saving dissection time and, in fact, seems to prolong it. The product does not perfectly protect against adhesions. And why this is true probably cannot be ascertained from this sample.

Is it safe? We find some mediastinitis and some evidence of mediastinal inflammatory response. Probably it is more nearly equivalent to control patients than is portrayed in the tables. But this is something

that should be monitored, including degree of seriousness of the complications.

And I think I'll stop there, rather than going into my critique of the post-approval study because we have seen multiple versions of that and perhaps we ought to comment on what the real version is, than the comments I made on it very preliminary.

CHAIR YANCY: Thank you, Dr. Blackstone.

Protocol now is for the panel to interact with Dr. Blackstone for any points of clarification from his presentation.

(No response.)

CHAIR YANCY: If there are no questions for Dr. Blackstone, we will then take Dr. Hopkins' comments. And then we'll ask the sponsor to react to both sets of comments.

DR. HOPKINS: Thank you, Dr. Yancy. I think you will find that many of my comments will be parallel to Dr. Blackstone, but just kind of looking at it from a slightly different

perspective.

As a cardiac surgeon who operates primarily on congenital and reconstructive cardiac disease, both in adults and in children, I would agree that the significance of the development of such a product that if it works and if it were safe, would be a very good thing. To reduce adhesions to an insignificant level would likely a priori result in easier surgeries for the patients and the surgeon and better outcomes. However, this study doesn't necessarily give us a perfect device of this type.

In terms of the pre-implantation data, it seems very extensive and does appear adequate, but does suggest that there is an element of a foreign body reaction. The proposal suggests that this will reduce complications by reducing misadventures, in other words, entering the heart before you plan on it, and reducing the overall risk of redo surgery.

From that standpoint, the choice of hypoplastic left hearts in neonates is a very good choice, for the reasons outlined by the sponsors. There are planned staged surgeries that, over the course of the first year, there will be at least three surgeries planned in these patients. We all know as surgeons that the inflammatory phase of adhesions is at its worse between about three months and three years. Prior to two to three months, they are not a problem. They are not well formed. And as the patient, as was noted by a number of people, as the patient gets beyond three to four years, they begin to mature and become less of a problem.

In addition, current mortality rates, as a consequence of the re-operative status alone, for the first re-operation is really much lower than suggested in the proposal and, in most centers, certainly the quality of the centers enrolled in this study, mortality rates due to re-operation alone for the first or

second redo is between 0.5 and 1.0 percent, in my experience. And thus, makes this kind of a study with a mortality outcome difficult to power.

The suggestion that the STS database provides good control data, I would agree with Dr. Blackstone that that data is good for the in-patient data, but wholly inadequate for anything other than that. The Congenital Heart Surgeon Society has a better database and would be perhaps a better comparison.

Now let's talk about efficacy and then I'm going to talk about safety. I think I have less of a problem with the efficacy outcome that was pursued in this study than I perceived from some of the questions. I think that in fairness to the sponsor and to the principle investigators, this is a very difficult study to get your hand on. As has been pointed out, it's very difficult to quantitate adhesions. There is no imaging that can do it. And of course, there are surgeons that all of us know that

every case is the worse case they have ever had and then there are surgeons who say this is duck soup. So actually in the zero to three grading system, the only one I really believe is the no adhesions to minimal adhesions. And unfortunately, only three patients fell into that category. So this product clearly does not reduce the problem to zero. If in fact there had been ten or fifteen patients that had essentially no adhesions, that would have been a very, very significant finding and one hard to dispute, even by qualitative assessments.

In terms of efficacy, no difference in reentry misadventures were noted. No difference in mortality, although there was a trend to worse mortality in the study group. There was no change in operative time, which reflects, I believe, the fact that we as surgeons have come to other solutions to deal with re-entry into the re-operative mediastinum that are now fairly effective.

In terms of safety, there was minimal

information that I could discern on the bleeding differences. The mediastinitis issues we have raised and I think is one that, again, I think we have revisit as a panel as to whether mediastinitis or all mediastinal complications were adequately explored.

While it is not our job at this panel to rewrite the investigation, one that has been going on for nine years, I did note that there were no systemic inflammatory markers measured, such as c-reactive protein, TGF beta 1, TNF alpha, etcetera, that might have given a handle on differential mediastinal information.

The three excess deaths in the intention to treat analysis, there were three more on the REPEL side, if I believe correct, did not seem related to the mediastinitis, although I could not draw a direct line to that.

And finally in the labeling issue, if this were to be approved, is there significant or is there adequate data, and I think I would like the panel to think about this and this is

what I think about as a surgeon, is there sufficient data for us to suggest that we should leave it to the clinical judgment of every surgeon as to pick the patient for which this would be applied, or are there parameters that we can establish from the extensive amount of work that have been done by these investigators suggests that there are subgroups of patients for whom the risk benefit ratio might favor its use in other patients for whom the benefit would be vanishingly small. And by that I mean, patients for example, coronary patients who, in today's world, who are treated with statins and aspirin starting on the morning after surgery, the re-operative rate within about eight years to ten years is really becoming quite small and intervention is the application of choice for failure. So would coronaries, would bioprosthetic valve patients who have a replacement expectation at say age 50 of 15 to 20 years from now, should they receive such a device or should it be reserved for patients who

have an expectation or a planned re-operation within say three to four years?

I think I'll stop there and raise other issues as we go forward in discussion.

CHAIR YANCY: I'd like to thank Dr. Hopkins and Dr. Blackstone for very clear and thorough comments.

Again, per protocol, the panel can now pose questions to either Dr. Blackstone or Dr. Hopkins.

Let me just raise one question, since both of you commented on outcomes that were not pre-specified as either primary or secondary endpoints, specifically mortality, operative time, and mediastinitis and in fact, mortality was a safety variable. From a pragmatic standpoint, respecting what Dr. Hopkins just commented on about the difficulty of doing this and the unique characteristics of this patient population, are some of the absences in this outcome database preferable to the study size and design or are these considerations that are

likely intrinsic to the method itself and really are of significant substance and we need to consider this?

DR. BLACKSTONE: Well, as I said in my remarks, I think mortality in this group of patients is so related to the disease itself and to the first stage of the operation, once you get to the second or third stage, there is basically no mortality. So that it relates to the physiology of these patients, which is highly unstable while they are waiting. And so I've really discounted mortality as a meaningful endpoint for this group of patients.

CHAIR YANCY: I think that's important information.

DR. HOPKINS: Yes, clinically I think, first of all, this is probably the only population that made sense to do this study. But as suggested, the signal-to-noise ratio is extraordinarily high. I would hate to have been the clinical monitor on this study, because every patient is going to have adverse events.

The secret to doing this study is really tracking those serious adverse events that are in any way potentially device related. And those are the only ones that I focused on.

CHAIR YANCY: Thank you. Dr. Page, please.

DR. PAGE: Thank you. Dr. Hopkins, I thought you mentioned something that's interesting and new to me, and that is the time course of maturation of adhesions. And you commented that they really are at their worst in years two to four and then after that they tend to mature and become less of a problem.

DR. HOPKINS: Right.

DR. PAGE: Did you generate any opinion as to what the effect might be in the two to four year range of having this device in place for where it would be truly potentially active and just the 28 days post-operatively?

DR. HOPKINS: The data, of course, does not speak directly to that. But it does seem reasonable to me that if it functions as a

barrier and does seem to provide protection against dense fibrous adhesions at eight weeks, three months, six months, which is what you would see in the hypoplastic population, that that benefit should extend out again.

But then, is there really any, I mean, we had trouble discerning any real benefit at what should have been the peak conflict time, in which there should have been the most difference. So how far out does that benefit extend is a question that can be debated.

CHAIR YANCY: Dr. Domanski.

DR. DOMANSKI: Well, you know, I want to thank both the reviewers for a very carefully thought out discussion. I would like to ask Dr. Hopkins, who does a lot of these procedures, you know, this is a way of sort of integrating, how frequently, if this device were available to you, would you use it in these patients, knowing what you know now and what we do?

DR. HOPKINS: That's an unanticipated question and may or may not be a fair one.

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I would probably use this device if I were convinced of its safety, in other words, there was no difference in the safety with or without it, in patients in whom I was convinced that I was going to come back in a relatively short period of time. And that would probably represent -- well, I don't do babies anymore so I concentrate on the older folks. But when I was doing all of it, I would say less than ten percent of the patients.

DR. DOMANSKI: Well of course, the pith of my question was to try to get you to integrate the safety data for me.

CHAIR YANCY: I'd like for the panel to just recognize that's a speculative answer.

Dr. Hirshfeld?

DR. HIRSHFELD: Yes. One other safety dimension that hasn't really been discussed, and I think I'd like to hear what our surgical colleagues on the panel think about this, is that two important variables that affect mediastinitis in adult cardiac surgery

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are the presence of diabetes, which was not present in this population, and the presence of internal mammary artery harvest, which was also not present in this population. And I'd be curious to know whether our surgical colleagues feel that this is an important consideration in trying to generalize these data from children to adults.

CHAIR YANCY: Both of those would be variables in an adult population going forward.

DR. HOPKINS: Yes. I think that's a good question. I almost added that as a codicil to my answer. I probably, personally, would not use this in a diabetic or anybody else who had a higher risk potential of mediastinitis. Having said that, with the strict insulin control that all of us are now using, we're seeing that even the diabetic is having mediastinitis rates that are approaching one percent, instead of the old two, three, four percent.

The neonate is immunocompromised, but

as pointed out by my adult cardiac surgical colleague, the mediastinitis rates in neonates and young infants is very very low, even though they are immunocompromised and we leave their chests open for days. So they are a difficult population from the standpoint of the incidence of mediastinitis.

CHAIR YANCY: Dr. Somberg.

DR. SOMBERG: Well, this question is to either reviewer or the other surgical colleagues on the panel. And that is, that it seems to me that this device and your review suggests that we go from three dense adhesions to two, predominantly. And my concern is that, and sort of what Dr. Page brought out, but and you mentioned, Dr. Hopkins, that it's two to four years or something, but is there any literature that we know what will happen to if you take lesions where the barrier sort of diminishes their severity to go from dense to mildly dense, or moderate, or whatever that intermediate zone, over the prolonged period of

time? Could they not coalesce? Could they not continue to mature such that they might become just as severe over time?

So what I'm trying to ask you is, is there anything in literature, anything from the data that you saw presented today, that sheds light on this idea that if we move something back from a more severe to a moderate, that time will not correct that factor, like nature often does, and goes from moderate to severe again?

DR. HOPKINS: As far as I'm aware, there is no quantitative data, no study that addresses that. I'm not quite sure how it would be studied. In terms of the clinical impressions, there is a difference above and below the diaphragm. Below the diaphragm, adhesions tend to be progressive and get worse over time for reasons I don't know that anybody knows. And above the diaphragm and the chest, adhesions seem to get to be less of a surgical problem. They don't go away, but they become less dense and less inflammatory over time.

CHAIR YANCY: Dr. Blackstone, I want to emphasize the points you made about LVADs. I though that was very insightful. I think this LVAD experience described was from 1998 and certainly, in the last nine years, there have been a number of important developments and I would strongly support your statements in that regard.

Dr. Neaton.

DR. NEATON: I would like to ask Dr. Blackstone, I actually thought the FDA analysis this morning that we looked at that did the randomization test which makes no assumption about the underlying distribution, was very reassuring and kind of still pointed to a rather striking difference in the primary outcome between the two treatment groups. And I wondered if you factored that into your comments?

DR. BLACKSTONE: Well, the comments I wrote were prior to coming to this meeting, which is why I said given what we had in this

packet, face value of the packet. It wasn't until the FDA that I saw what I thought was the first real analysis of these data.

DR. NEATON: Maybe I can just ask a question. Kind of again maybe, given the discussion this morning for both of the reviewers, to what extent should we factor in the lack of blinding that was considered at least for the surgeons that repeated the sternotomy, but also the potential kind of un-blinding that may have occurred just from viewing the second procedure?

DR. BLACKSTONE: That's why I was happy to see that the FDA had actually figured that into a multi-variable analysis because that would be one of the things that I would have suggested.

Let me go one step further beyond what the FDA did, though, because the FDA still focused on the distribution of values in just the severed group. As you know, we actually have four grades of these that all sum up to 100

percent. And I wonder if that might actually be taken further and look at this ordered group of variables with their distribution and more meaningful analysis with all the data, as opposed to just the data in a single grade.

DR. NEATON: I would agree with that. I think one analysis that might be useful doing it, although I guess I am convinced personally that the different analyses that were done for the secondary outcomes that would support this would be some type of ordinal regression, which takes into a case the ordinal scale on which this was graded.

CHAIR YANCY: So I'll put this in English. We're agreeing that the FDA supports the primary endpoint being a statistically significant outcome. Okay.

If there are other questions from the panel, I would like to yield to the sponsor, so they can respond to the reviewers. But I would like for the sponsors to have the input of any remaining questions the panel has.

(No response.)

CHAIR YANCY: Sponsors?

DR. PINES: Eli Pines. What we would like to do is systematically go through the various questions that were raised either in the morning or now and address all the questions.

CHAIR YANCY: We have approximately 15 to 20 minutes or less. Will that be possible for you?

DR. PINES: We're going to try.

DR. BACKER: While they are hooking this up, I want to thank the panelists. I'm very impressed with the questions and the analysis.

Speaking as a pediatric cardiac surgeon that does take care of these patients, I really would like to go back to the airplane analogy. You know, airplanes don't crash very often, but when they do, it's an absolute catastrophe. And when you operate on a child and you get into massive bleeding with a ventricular fibrillation, that also is an

absolute catastrophe. And this, from my personal perspective, this is the reason that I got involved in this study, was the hope that we would be able to find a device that could help prevent these dense severe adhesions that make re-operation on these children occasionally very difficult and lead us to these complications that can lead to the death of these patients. And currently, there is no FDA approved device -- pardon?

(Off the record comments.)

DR. BACKER: Currently there is no FDA approved device that prevents these adhesions from forming.

So, I would like to go back to the problem adhesions and remind you of the 12-year-old patient who had the hole in the aorta required femoral bypass. The surgical planes are obliterated and this is what caused the complications that led to that patients' four week stay in the hospital.

Again, our primary effectiveness

endpoint showed a reduction in the percent area of severe adhesions from 47 percent to 21 percent. Again, speaking personally as a pediatric cardiac surgeon taking care of these patients, if I could achieve this goal in all of my patients, this would be a significant benefit.

Phil, do you want to come up and address the statistical analysis?

DR. LAVIN: Yes, Philip Lavin. I wanted -- this morning, several points were raised regarding the power of the pivotal study. And of course, this is retrospective power because the trial was planned around the primary efficacy endpoint. But the question was asked, so let's answer it.

In terms of the trial power to be able to detect differences, what we have here are four scenarios enumerated here, in terms of what you can do with 71 subjects per group. In the first scenario, if the control group incidence is one percent, then there is 80

percent power against a 12 percent alternative. In other words, could REPEL-CV be as high as 12 percent versus one percent? That's 80 percent power. You asked. That's what it is.

If it was two percent for control and for REPEL-CV, it would be two versus 14. And then it would ramp up to 10 versus 28 and 20 versus 41. So this is obviously gross, but it is not as fine as many larger trials that are prospectively planned to accomplish, but this is the answer of what you can do with 71 subjects.

The next slide I would like to show you is given that this is a post hoc endpoint, what would be necessary to achieve statistical significance? Statistical significance would be achieved by looking at a Fisher Exact Test, again with two groups, and again a superiority or an inferiority test, however you want to phrase it. The one percent, if the control were one percent and the REPEL-CV were 8.2 percent, that would account for a p-value of 0.05. Or two versus ten, or 10 versus 22, or 20 versus

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34. And again, that's getting a little bit closer but still, is that adequate? And that remains a question for discussion and it's not one I can immediately answer. But that is what the p-value would be and those are the affect sizes that would be detectable.

So with that, I'll skip over this for a moment. That's for future points. Another consideration that I would like to bring up here is, this morning, is the issue of the time that it takes to do the dissections. We saw this morning approximately 25 minutes for each of the two groups overall. No significant difference and attributed in part to the large standard deviation. We have a trial that was not again powered to look at this endpoint. We had one primary. That's the way that you play the game with FDA. You go with a single primary and you power it. You can have secondary endpoints. That's legitimate. But our trial, for what it was, was powered to be able to detect an endpoint with a percent grade three adhesions.

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A different endpoint, not this one.

We talked about this morning that there is no standard technique in the protocol for doing sternal re-entry. We also talked about the variable experience of the surgeon. We also talked about the anatomy and the different centers. Again, all of these are considerations.

Now let's try to hypothesize what we might be able to see with this trial, given working with a solid endpoint. Let's grant the following. That when a surgeon would go in and evaluate the patient, the distinction of whether or not a subject had severe adhesions or not, I think that would be something that if we were to have filmed it or we would have photographed it or been able to have had a second pair of eyes looking at it, the reproducibility of that measure would be well above 90 percent.

So let's use this endpoint for a moment. Let's consider this post hoc analysis of the adhesion percentages with severe versus

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not severe. Twenty-four, twenty-five minutes versus fifteen minutes. That p-value, just in taking all of the subjects, REPEL-CV and the controls put together, let's assume the null hypothesis of no efficacy is operating. All right? There we have a ten minute difference. Ten minutes shorter, if you could achieve a patient without severe adhesions.

And now let's think about for a moment what we saw this morning. What did we see? We saw 70 percent in the control group having severe adhesions. We saw 30 percent in the REPEL-CV having severe adhesions. Apply those numbers for a moment. Let's just work through on a marginal analysis. You know we don't have enough sample size to be able to dissect that out and you know our standard deviations are large.

So let's do a direct rate adjustment. If you go through and you do that adjustment, it would come through and you would conclude that there was approximately a five minute advantage

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for REPEL-CV that would be expected based on this more solid endpoint of a reduction in the incidence of severe adhesions. That's what the data would show, a five minute reduction. That's what a REPEL-CV has the potential to deliver on. And I think that's a very important point.

Now, let's take a look now at another point that was raised. Let's look at the investigators. Let's see if five minutes is even attainable or real. Well, we did this analysis. And this is looking at those who had three or more subjects per group. And there we looked at the mean time, this is the overall population again, restricted to those investigational sites that had three or more patients. And now we're looking at these data and we see it's approximately half of the subjects, 56 in total, 29 in REPEL-CV, 27 in control. And there we see 18 minutes for REPEL-CV and we see 22 minutes, 23 minutes for control. So maybe I just might be on to

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something, thinking that there is a five minute gain or a five minute expectation of benefit.

And so that's what I think is we're really facing. We have the power. We don't have the power in this trial to be able to deal with this endpoint. So what do we do? We deal with direct rate standardization. So I am conjecturing here and I'm offering you my advice as a professional statistician for 30 years that I would contend that down the road, this is the type of result that you might see.

And I think that at this point, you know, I would like to turn things over. Before I turn things over about the training on adhesions, I want to address a couple of points about the statistics and what we did here in terms of the analysis.

You know, when we do a statistical analysis, to follow GCP we create a statistical analysis plan. We do not un-blind the data to look at the data. We do not look to see if there are zeros and where the zeros occur.

Instead, what we try to do is to develop robust statistical methodology that will investigate the results.

So what did we do in our statistical analysis plan? What did we do in the document that was submitted to the FDA? Well, we did a t-test. And will the t-test assumptions work? Maybe yes, maybe no, just like the FDA statistician said. But we also did a Wilcoxon test. We also looked at the distributions of the means. And I submit that that is a non-parametric procedure, that is valid for any sample size. And we concluded the same result that we have statistical significance here. We also can do a randomization or a permutation test. The FDA statistician replicated the type of analyses that we did.

I would not be here today if I did not believe that the advantage for REPEL-CV was real and in excess of 20 percent. I stand by my conjecture and my belief, and my statements that there is a 26 percent advantage for REPEL-CV.

We saw it in sub-groups. We didn't need to result to the multi-varied analyses, but we did that. We also saw a 25 percent advantage.

So, correcting for blinding, correcting for sites, correcting for gender, correcting for Norwood, correcting for bypass, all of those results give us the conclusion that REPEL-CV is superior with respect to the primary efficacy endpoint.

And I said earlier this morning we had durability. We saw it carrying over to the patient level. We saw it carrying over to the worst degree level. And that I submit is an endpoint that is certainly more solid and quantifiable and reproducible than perhaps the endpoint that you were alluding to this morning that required training and standardization to trust.

So with that, let me turn things over to my colleagues to talk about the training for the assessment of adhesions and how we got to this point.

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DR. O'BRIEN: Again, I'm Jim O'Brien. I'm a cardiac surgeon from Kansas City. In terms of the assessment of the adhesions, as was mentioned this afternoon, the remarks from the panel, there is no pure objective way to measure this. There is no scanning method akin to, you have sometimes an histology or there is an imaging technique where you can grade the adhesions and apply a standardized technique based on technology, in order to say this is one, this is two, this is three. So we're going to be left with the subjective opinion of experienced surgeons.

In an attempt to standardize that as best we could, there was training that took place a priori before the study took place. And so all the sites and tall the surgeons were visited and there was training as to what the adhesion scoring system was and that that scoring system was based not just on the appearance, but also on the behavior of the surgeon in terms of what was required to dissect

that area.

The surgeons were also trained and specifically went to the perimeters of investigational surgical site, so they know exactly what are we're talking about, exactly where the REPEL had been placed.

And again, just to look at the cardiac adhesion grading system, it goes from none to severe. But at each step of the way, there was a difference in terms of what action the surgeon must take in order to dissect. And there was a comment made that you know, you can put a knife in a surgeon's hands and he's not going to put it down. But if you're involved in this study and you've had the specific training, then you know what you're supposed to evaluate in this regards.

And in terms of myself and the other investigators, you know, we're not into this because we all have a financial interest in the company. We realize that this is a problem and we deal with it every day. And these re-

operations, when we operate on these kids, it's very difficult. And the number of re-operations and the risk that these babies face is increased by the presence of these severe adhesions.

They paid me to come here today, meaning they paid me to stay in a hotel last night to be away from my kids. But that's not why we all get interested in this. We got interested in this because we're hoping that if there's something that makes these surgeries less risky, and there's nothing out there right now, that that's why we would be involved.

Currently, there is three adhesion prevention devices approved by the FDA and available world-wide. This study is typical of the adhesion prevention device studies in regards to size and the endpoints for all these studies were reductions of adhesions. And these adhesions were visually assessed in a similar manner by the surgeons at the time of surgery.

The surgeons filled out case report forms at the completion of the dissection of the

investigational surgical site, allowing at that time, that while it was fresh in their mind, what the percentages were.

Also mentioned this afternoon, you know, it's easy to say if there is zero. Well, I want to also submit that it's easy to say if they're severe. You know what the severe adhesions are. It's really stuck. The structures are welded together. And so this is an endpoint of the percent of patients that had severe adhesions. So either they are there or they are not. It's independent of the area assessment.

Here you see in the control group 72 percent of the control group had severe adhesions. On the REPEL-CV, only 30 percent had the presence of severe adhesions. So a little bit of a different endpoint, but nonetheless, maybe easier to accept than the estimation of area.

DR. BACKER: One of the other issues that came up was regarding the blinding of the

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evaluators. And I would repeat what Jim said. None of us really had a vested interest in the outcome of this study. And in fact, many people would come up to me and say, oh, how's the REPEL study going? What are you guys finding? I don't know. I don't know. We're not going to know until it's un-blinded because we never know when we're operating on these patients whether or not they got the REPEL device.

I had mentioned earlier that, you know, occasionally we saw what we thought might be little tags of tissue related to placement of the device, But I would emphasize that this was because of our hyperacuity regarding these patients and that when we operated on these patients, we had no interoperative clues as to whether or not the device had been applied, except that in some cases, we saw remarkably few adhesions and we would speculate maybe this was one of the patients that got the device. But there was no interoperative clue, there was no remnants from the Vicryl suture that would tell

us that there was something, a key that there was or a clue that there had been a REPEL placed at the time of the initial procedure.

A quick comment also about the masked versus the unmasked evaluation. Again, I said in my opening comments that many of our centers, our center, major center, we only have two cardiac surgeons, if one person is out of town and the child is scheduled for their bidirectional blend and it's five months, it is very difficult to reschedule that operation if the surgeon was not available. But the surgeon that was doing the evaluation, let's say it was me doing the evaluation and I had done the original REPEL, we had no system to know that that patient had received REPEL and, you know, in that six month time period, I may have done 100 or so open heart operations. I did not remember whether or not these patients received the device or not. Now, you can either believe that or not but we did not focus on keeping track of these patients. So even if we were

unmasked, it didn't necessarily mean that we were un-blinded and knew that the patient had received the REPEL device.

We did this post hoc analysis to look at the difference of the evaluations of the masked versus the unmasked, versus the total intention to treat and the difference in the percent of severe adhesions between control and REPEL-CV. And again, in this post hoc analysis, there was really no difference between these groups whether the evaluator was masked or unmasked.

I also wanted to address quickly again mediastinitis. Dr. Blackstone mentioned that we didn't use the CDC definition of mediastinitis. This is the definition of mediastinitis that we found throughout the three papers that we quoted that had the largest number of patients having treatment for mediastinitis. Again, our review of the literature and I hate to disagree with Richard, but in pediatric populations is between 1.4 and

6.7 percent. So I don't think that his statement that children with mediasternotomies have a lower incidence of mediastinitis than adult patients. And in fact, in that chop series, if you remember, 18 of 43 of the pediatric patients had hypoplastic left heart syndrome. And having an open sternum, which was 70 percent of our patients, was a nine-fold increase in the risk of mediastinitis. So again, I hate to disagree with you, but the facts are in that paper.

CHAIR YANCY: If we can begin to wrap up?

DR. BACKER: Sure, I'll wrap up. Thank you very much.

CHAIR YANCY: Thank you. Are there focused or specific questions now that can be answered by either FDA or the sponsors? Dr. Katz.

DR. KATZ: I was wondering, this is for the sponsor, since you had the pictures of the virgin heart postpericardiotomy, an the

patient with adhesions, do you have any pictures of the re-ops in the second sternotomy in the REPEL patients?

DR. PINES: We took no pictures throughout the study. Given the complexities of the operating room, as you know better than I, it was just not a setting to capture these pictures. Moreover, in the feasibility studies, we tried to capture those and those pictures were really not very meaningful. So we did not capture any photos.

CHAIR YANCY: Dr. Neaton.

DR. NEATON: I just want to make certain I understood Dr. Lavin's analysis of the dissection time. So is my take home of this correct that based upon kind of an analysis of dissection times by severity for both groups combined, one might project a five minute difference between treatment and control. And as such, the study that was actually done is under power to detect a five minute difference?

DR. LAVIN: That's correct.

DR. NEATON: And so, in the subgroup you showed, that was real data. That was not conjecture data.

DR. LAVIN: That's all real data.

DR. NEATON: Okay. So obviously, the compliment of that subgroup goes in the other direction.

DR. LAVIN: Well, no. The five minute advantage is confirmed by that data that I showed.

DR. NEATON: Right.

DR. LAVIN: So that was --

DR. NEATON: But there is another piece of that subgroup which is missing which must go five minutes in the other direction.

DR. LAVIN: Yes, I think that what you're describing is that there is another 50 approximately patients --

DR. NEATON: Right.

DR. LAVIN: -- and those are the early, those are the ones with zero or with one or two patients, per se.

DR. NEATON: Right.

DR. LAVIN: So, you're right. It is subject to potential subgroup analysis caveats.

DR. NEATON: Right. Okay, I just wanted to clarify.

DR. LAVIN: There is no question of it. But, in the situation where we have small end, we have to try to do something and this is what we're trying to do.

DR. NEATON: And just one follow-up question on the blinding, which I think the comments were helpful. Because as you indicated and several, it's a subjective outcome, I don't think there is any argument anymore about the consistency of the different ways of looking at your primary outcome, whether it's via a t-test or a randomization test, or the different components. At least for me, personally, things kind of fit together nicely there in showing a strong signal, no matter which way you look at it.

The issue is whether that signal is

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biased on all these cases. And that gets back to the issues around blinding. And is there, while I respect kind of the fact that the people here were kind of unaware of what was going one, but was the actual treatment recorded in the chart? Were there efforts made by the sponsor to keep the actual assignment from any written record that the surgeon might have upon re-sternotomy to kind of eventually un-blind this?

DR. LAVIN: Yes. The sponsor was perfectly diligent to guard that and did not have that recorded on the CRF. They were perfectly diligent in that respect.

DR. NEATON: What about recorded in the chart itself?

DR. PINES: What happened is just prior to chest closure, the person who was going to be randomizing the patients was given an envelope containing the randomization card. He opened the randomization card and it stated treated or controlled.

If it was treated, he applied REPEL-

CV. He captured the lot number and the sample number, put it back in the envelope, resealed the envelopes and that's the only record anywhere in terms of the patient treatment. That envelope was maintained closed throughout the study. None of the envelopes were opened until the study was complete and we unmasked the patients -- the randomization. Excuse me.

DR. NEATON: Thank you.

CHAIR YANCY: Dr. Page.

DR. PAGE: I'm not a statistician. I appreciate the input from the expert statistical minds here and I'll be asking Dr. Neaton his perspective on this. We've seen a couple times a slide that showed the difference or the lack of difference in time for dissection and then there are, I think, four bullet points of explaining a way why we're seeing that.

On the other hand, and in a randomized trial, shouldn't the randomization have taken care of that? So if there were a difference because of the standard deviation,

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the breadth of standard deviation, we might not see significance. But given a randomized trial, shouldn't we have seen a similarity in the times or a difference in the times for dissection?

Dr. Neaton, am I interpreting that correctly?

DR. NEATON: From my point of view, you are. That's the reason I made the point earlier that the issue in the standard deviation is one point that plays into the history of power, but the fact is here, the point estimate is slightly in the wrong direction.

And so what I heard Dr. Lavin say is that after looking at their data, they would project a difference in time of five minutes. And given the variability that they observed in this trial, it would have been unlikely, given the sample size, to pick that up. Am I correct?

DR. LAVIN: That's correct. Basically, you know, with a trial like this, you can have a five minute advantage and not see it. That's a statistical event. That's what you call the power

of the trial. The power for this comparison is approximately 20 to 25 percent, given the standard deviations that we have in the sample size. So it is very possible, under that scenario, for their to be a five minute advantage and still miss it.

DR. NEATON: The other related point I can say here, however, is that if this is considered a clinically relevant outcome, then the solution to this problem, of course, would have been to have a greater sample size with which to kind of hone in on that outcome and make it more finite.

CHAIR YANCY: We need to do this. We have at our seat a number of predetermined questions from FDA. Everyone should have a document in hand that has five questions.

Dr. Zuckerman? I'm sorry.

DR. ZUCKERMAN: I'm sorry, Dr. Yancy. Before we begin the question session, Dr. Domanski and others had asked the FDA to do a lunchtime assignment. Also, we would like to show one slide for clarification purposes. I should say the FDA

would like to show one slide for clarification purposes.

CHAIR YANCY: Please proceed.

DR. ZUCKERMAN: Dr. Gerry Gray from the statistics unit will be showing the slide and offering our interpretation.

DR. GRAY: Good afternoon. My name is Gerry Gray. I am the Associate Director for the Division of Biostatistics at the CDRH.

We just did some calculations over lunch and I wanted to make a few comments about the mediastinitis rates.

First of all, what we had here in the trial, as far as we saw was a control rate of 1.4 percent. That's one out of 69 patients. In the REPEL arm, it was four out of 73, 5.5 percent. And what really we can say from this trial is the difference of 4.1 percent was observed and the confidence level for that ranges from minus three to positive 12 percent.

So, from the evidence that we do have from this trial, the mediastinitis rate for the

REPEL arm could be as much as 12 percent greater than in the control arm. But you will also note that that confidence interval spans zero, so we don't, we really can't make a definite conclusion. The study was not powered to detect this kind of difference.

So then the question came up about okay, how big of a sort of a post hoc power calculation similar to that done by the sponsor, how big of a trial would we have needed to detect the difference?

And so the first thing we did was go through some calculations of supposing that we wanted to detect a difference from a control rate of two percent, where the true rate for the treatment was anywhere from four to eight percent, how big of a sample would we need to have? And as you can see, the sample size is quite large, ranging from several thousand to at least two to four hundred patients. That's to detect differences of two, four, or six percent over and above control-rated two percent. And by detect, I

mean, to reject the hypothesis that the rates are the same.

Another way to look at this, and the last thing I want to show is what you might want to do is design a study to demonstrate non-inferiority. And that is to demonstrate that the treatment arm is no more than some delta worse than the control arm. And this is probably more appropriate in this case. And we did some calculations for that based on an assumption that the rate in the control and the treatment arm were both two percent and the objective is to show that the treatment arm is no more than some delta percent worse than the control. And those deltas that we have done are four, six, eight, and ten percent. In order to do that with 80 percent power, you would have sample sizes, total sample sizes for both arms, ranging from 400, 200, 140, to 102.

So depending on the clinical opinion about what constitutes an acceptable delta in a non-inferiority trial, we can say here's the sample

size that you would need going forward in a trial to demonstrate non-inferiority. And this is only, the rates of two percent were chosen because that seemed to be a sort of consensus for the mediastinitis rate that we might see.

Thank you.

CHAIR YANCY: Thank you. We can take one brief comment from the sponsor in the context of this or one brief question from the panel.

DR. NEATON: Can I just ask --

CHAIR YANCY: Is that a question that we should hear, please?

DR. LAVIN: I just wanted to comment these are the sample size calculations that we had presented earlier, and this is basically here, a randomized trial, just as the one that we had.

CHAIR YANCY: Dr. Neaton?

DR. NEATON: I just wanted to kind of verify that your sample sizes there are the sample size, combined sample size for two groups with equal allocation or sample size per group?

DR. GRAY: The total sample sizes that

I showed, and I'm trying to get them to come back up, of 400, those are total sample size for both arms combined. And that's assuming equal allocation for the two arms. There is all kinds of, as you know, I mean, we could have allocated them equally or whatever, but this is total sample size, just with the basic assumption that we are going to allocate patients in a randomized trial one to one in the two arms equally.

CHAIR YANCY: Thank you very much. We need to proceed with our predetermined questions.

Briefly. Microphone, please.

DR. WEINSTEIN: Just a brief clarification about dissection times and the question, I think, relates to methodology. The tremendous amount of variables involved in trying to evaluate dissection times for surgeons, the variables are almost immeasurable, depending on how many surgeons you have that you have as many separate techniques. Some surgeons will dissect right through the sternum. Some will dissect going under the sternum, before they divide it. Those

timeframes are quite different. Some surgeons will use the saw from the top down or the bottom up. Some will use Metzenbaum scissors, some will use cautery. Depending on the amount of artificial tissue used on these patients, they all receive, or most receive either some form of GORE-TEX or homograft or both, the amount of adhesion formation they will form will be different, depending on who your assistants are, the experience of the surgeon we mentioned. Also any injuries themselves created while entering the patient can add five or ten minutes. This shift one way or the other, considering that the busiest surgeon in the study, in the pivotal study, did eight patients maximum can sway the numbers, I feel, a great degree either way.

As well, some patients will go on bypass early in the dissection and some patients will do a maximum dissection before going on bypass. So, I believe that we felt that section times here, while calculated, were relatively statistically meaningless.

CHAIR YANCY: We are going to begin the predetermined questions. I want to be certain that everyone on the panel has had a chance to raise any significant question to FDA or the sponsor. Before we go into this, are there any questions? Have we not addressed anybody's concerns?

(No response.)

CHAIR YANCY: We can go ahead and place the first question up. This is the part of the panel meeting where the discussion is now amongst panel members and FDA and sponsor will not be commenting. So this is amongst us. We are an advisory panel and we are commenting on specific questions that FDA has about this PMA. And our intent is to give them at least some direction and guidance on these questions.

Question number one is at your place and it refers to the information in tables 1, 2, and 3. For the second time, I won't read the tables, but I will read the question.

"The sponsor collected and provided data on several adverse events that occurred in the

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pivotal study, including mediastinitis and mortality. Other than for mortality, there were no pre-specified performance criteria or statistical hypotheses for the safety endpoints. A summary of the observed adverse events is shown in Table 1. Table 2 and Table 3 show the incidence of mediastinitis documented during the course of the study," I might add, as per the study definitions, "and after readjudication, respectively."

Let me pause for a minute or two and let you peruse Tables 1, 2, and 3 and then we need to answer the following question.

"Please provide your interpretation of the safety data collected in the REPEL-CV study."

You're a quick reader, Rick.

DR. PAGE: Dr. Yancy, just to frame the discussion, my question is, are we specifically addressing the study data or addressing data to support the proposed indication? Because the two, in my mind, are very different.

CHAIR YANCY: For this question, and I'll let Dr. Zuckerman comment, my understanding is

that we are specifically addressing the information on Tables 1, 2, and 3. Is that correct?

DR. ZUCKERMAN: That is correct. And that is why the tables are included with your question one.

CHAIR YANCY: Dr. Blackstone?

DR. BLACKSTONE: I've already voiced my opinion and that is that the tables may not reflect all the mediastinal issues here. And also the general question that we have even raised this morning, and that is, in a way, it's unfortunate that the adverse events that are directly related to reentry that second time, were not recorded.

CHAIR YANCY: Please note Dr. Blackstone's comments.

Dr. Somberg?

DR. SOMBERG: My opinion is that the data is such, and we've heard discussions of this by both sponsor and the FDA, and I agree with them, is that there is no significant difference between the two groups. With that said, the study, as we also heard, was not powered to be able to show a

significant difference in some of these single toxicities. So the panel has to be aware, and my colleagues have to be aware, that we have safety data from the study, but is that safety data enough to generalize to all the re-operation patients in pediatrics, let alone, two adults. And the answer there is probably not conclusively. And the panel has dealt with that in the past.

CHAIR YANCY: For each of these of these questions, it is very important that we have input from as many panel members, preferably all panel members. Dr. Domanski?

DR. DOMANSKI: You know, I pushed the business of power pretty hard this morning. I have to say though, that in fairness, you know, just in general fairness not just to the sponsor but to the enterprise, you know, one could be very arbitrary in deciding what represents a sufficiently small difference to detect, if you will. So I guess I'm persuaded that at least there is no real safety signal here. I guess the only -- I mean, there is no significant, there is no statistically

significant difference.

We can argue about how the trial should have been designed and how much difference we ought to be able to see, but there isn't any here.

The only thing that troubles me and I would like to go back to your comments if I could, is have we captured, if we have failed to capture the mediastinal complications, I mean, I want to understand the significance of that statement by you. Because here there is no statistically significant safety signal. So can you tell me what you feel we failed to capture?

DR. BLACKSTONE: In the case-by-case reports, there are reports of other mediastinal wound infections, some treated by antibiotics and so on. I count six in the REPEL group and four in the other group. What we -- mediastinitis is one end of the spectrum of severity. There are milder ends of that and it seemed to me that if that were graded, one might find that the grade of severity in the REPEL-CV group is a worse grade than those found in the control groups.

CHAIR YANCY: Dr. Zahka.

DR. ZAHKA: I do think that the safety issue is really the primary issue for that first stage. And I think that there should be concerns about mediastinitis and bleeding. The amazing number of complications that each of these babies have, I think makes it very difficult, unless there is a dramatic effect on safety of this device, to tell anything from other than a very very large study.

I'm a little bit concerned that the issue of bleeding may not be totally addressed by this study. And remember I'm a cardiologist, not a surgeon. But my recollection is that most of the babies, when they go back for sternal closure and they have this device placed, are two, three, four, five days out and have actually already stopped their bleeding.

So it's not exactly the same as putting in this device into a fresh post-op. So I think we'll be able to conclude from these data that there doesn't seem to be excess bleeding when its

used in exactly this way, but perhaps not be able to conclude that there is no excess bleeding if it's used in what may be a more standard way.

But I think the real key issue is there are so many complications for this group of babies, that it would probably take an enormous number of patients to tell.

CHAIR YANCY: I just want to be certain I get everyone to comment on this issue. I'll come back to Dr. Blackstone.

Dr. Hopkins.

DR. HOPKINS: I want to thank the FDA for skipping lunch and doing those calculations because I specifically wanted that demonstrated that the effect here would take an enormous study to evaluate. And in fact, Dr. Backer, if we went down to a one percent mediastinal rate, the end would go up to 4,000 or so. So, it's almost impractical to design a study that could factor in that safety. So from that standpoint, I'm convinced that there is no difference in the safety factors that we've seen, as evidenced by this study

in its current form.

CHAIR YANCY: So we need to continue. We haven't heard from several other panel members.

Dr. Katz?

DR. KATZ: The only comment I wanted to add with all the discussion about mediastinitis is, I think it's a little bit unrealistic to add in the episodes of mediastinitis after the second sternotomy and relating that back to the initial procedure with an absorbable device and some cause and effect relationship. Obviously it needs to be taken in context. But that's --

CHAIR YANCY: So I need to understand your input on this question. Your interpretation of the safety data then are no significant signals?

DR. KATZ: Correct.

CHAIR YANCY: Okay. Dr. Jeevanandam.

DR. JEEVANANDAM: I think, if you look at this from a truly statistics point of view, yes there is no difference. There are some trends. And I think and I reiterate my point that we have been looking at infections, which is mediastinitis

but we haven't looked at hematomas and hemorrhage, which on the other tables do tend to again, tend to be higher.

Now why one would have a hematoma if the chest were open, and then you go back in after theoretically the bleeding stops, I don't know. And I don't know if those were patients who had primary closure and not have their chest open. And if that's true, then was there a sub-analysis on those patients?

It seemed to me that the hematoma and bleeding in the first operation were things that just were not considered and everybody focused on mediastinitis as the primary safety point.

CHAIR YANCY: Dr. Weinberger, I haven't heard from you.

DR. WEINBERGER: I'm sort of satisfied in a very narrow context. I think that within the population of little babies who need to be operated on because primarily they have hypoplastic left hearts, were incredibly sick, that in that population you're not causing a major increase in

morbidity. In that regard, I can buy into the data.

I am very uncomfortable about generalizing to a population that doesn't have a high background of comorbidities and expected complications because I think that you would see a very major, you might see a major signal if you took out the background of comorbidities.

CHAIR YANCY: Dr. Hirshfeld?

DR. HIRSHFELD: I don't have anything to add to what's already been said.

CHAIR YANCY: Dr. Yaross?

DR. YAROSS: I'll leave the clinical assessment to the clinicians who I think have addressed this fairly thoroughly. But I will point out that in terms of reasonable assurance of safety, one has to consider the implications of trying to do a perfect study in the sample sizes that have been discussed.

CHAIR YANCY: Ms. Mottle?

MS. MOTTLE: Thank you. I agree that the safety data statistically looks okay but I am

concerned about the extrapolations to the general population because of the many concerns being expressed. We're not seeing enough data in other potential complications. We don't know enough with the adult population.

CHAIR YANCY: Doctors Blackstone and Neaton, I'll let you have the final word on this question.

DR. NEATON: I'll just say that I think there is, as a consequence of the sample size for this study, substantial uncertainty about the safety. And the p-values being not being greater than 0.05 give me no reassurance whatsoever. I mean, the absence of a difference in a p-value in a study like this is meaningless just because of the power issues.

And the power arises from two different sources that I think were kind of stated earlier by the reviewers. One is, when you throw all the adverse events together as of where you have the more common events here, there is so much noise relative to signal, you wouldn't expect to see

anything. And then for the events that we spent most of the time talking about out there, they are occurring with such low incidence, that one just can't be certain about kind of whether there is a difference or not.

So I don't think that we can say there is no evidence here of a safety signal. I think we have to say there is just uncertainty about whether there is a safety issue or not because of the size of the study.

CHAIR YANCY: So, Dr. Zuckerman, I think we've heard from all the panel on this first question. And I'm going to attempt to paraphrase what I heard. So don't throw anything.

But what I heard was that, in the context of what we've been provided and, I will take Dr. Weinberger's phrase, it is a very narrow context. And I will accept Dr. Neaton's phrase that there is at least some, if not substantial, uncertainty there at least doesn't emerge an overwhelmingly strong safety concern, but there are some issues that are unresolved and we remain

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tentative about the safety issues. Is that fair?

Well, is that acceptable to you, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. That's a very helpful summary. In fact later when we read the regulatory definition of safety, I think Dr. Weinberger's gestalt fits in with our standard regulatory definition of safety, which is helpful and you'll be reminded of.

CHAIR YANCY: We'll move on to the second question. The second question is on effectiveness. Again, to save time, please look quickly at Table 4. The question that we have to focus on is on the screen in front of us.

"Please provide your clinical and/or statistical interpretation of the results of the primary effectiveness endpoint analysis in the entire study population. Please provide your evaluation of the clinical benefit of the device."

We will start with Dr. Neaton.

DR. NEATON: I guess I just repeat what I said before. I guess I'm convinced about the

various ways this has been looked at. I do want to say that I agree with Dr. Blackstone's kind of fine point about the term incidence in the label that maybe the entire term, occurrence or incidence should be struck because, just to point out once again, a relatively small fraction of people had no adhesions.

So we're talking about a device that reduces the severity of adhesions clearly by these metrics.

CHAIR YANCY: That's very valuable input. I think Dr. Hirshfeld has a comment.

DR. HIRSHFELD: Well, I find the data convincing that the extent and severity of adhesions was reduced by the device. And I thought that particularly when we saw the histogram and we saw that there were 40 percent of the patients who received the device who have grade zero to grade one adhesions only, I thought that was fairly compelling data.

Where I am still in somewhat of a conundrum is that I don't see any, in the rest of

the data, I don't see any benefit to the patient of this particular endpoint finding, that there is, that we've talked about the dissection times. And also if one goes through all the litany of all the other serious adverse advents, if anything they trend in the direction of being more common in the REPEL treated group. And so, I'm a bit in a conundrum to explain why, although we have seen this measurable benefit in the endpoint, we haven't seen that in a benefit of the clinical outcome of the patients.

CHAIR YANCY: Other input? Dr. Hopkins.

DR. HOPKINS: Yes, I would agree that the effectiveness as defined as a reduction in the amount of adhesions has been proven.

I am less concerned about the blinding masking issue, for some of the reasons that were brought up. Knowing cardiac surgeons as I do, our tendency is to be hypercritical. There is nothing in it to, even if you were un-blinded, to be biased in favor of this. So I suspect the data is pretty

respectable.

At worst, the instrument used is a surgeon satisfaction survey, which is do you like what you just operated on or did you hate opening that chest? And to that extent, that's not an inappropriate survey instrument.

CHAIR YANCY: So, so far we have a consistent thought amongst the panel that the effectiveness is best represented as a decrement in the severity of adhesions, not a decrease in the incidence. Is that a consistent thought? Any contrary thoughts to that?

Dr. Page was first, I believe.

DR. PAGE: I think that's a fair summary, Dr. Yancy. My only concern is that again, that this is specifically focused for this indication in cyanotic infants with anticipated re-operation.

CHAIR YANCY: Dr. Somberg.

DR. SOMBERG: I agree with that and I would make the statement that I don't think we should expect to see from this small study a

clinical benefit. This study was not really designed for that purpose. And maybe it's to the sponsor's detriment that they even measured this dissection time. You shouldn't have done that because it was just not some endpoint that was well thought out and that could be measured that was trained for and that was standardized, like they did that small field.

So you know, I think those concerns should be left for potentially a labeling issue that this does reduce the severity of adhesions, but beyond that nothing has been demonstrated might be an appropriate statement.

CHAIR YANCY: Dr. Katz, you are next recognized.

DR. YAROSS: Yes, I just point out that that is precisely the indication that the sponsor appears to be seeking for the reduction, for reducing the incidence, severity, and extent of post-operative adhesion formation.

CHAIR YANCY: Dr. Katz, please.

DR. KATZ: I think you have to limit

that statement though for the severity of adhesions between the anterior or the plane of where the device was placed in the posterior sternum. Because I know in some barriers that are placed in the plane beneath the barrier can actually be worse. And we really don't have any information about that. So it's really just that very limited area that we could make that statement in.

CHAIR YANCY: Just as a point of clarification, if this PMA is approved, then the final language drafted by the FDA will account for the additional issues that you have raised.

Dr. Jeevanandam.

DR. JEEVANANDAM: There's actually two questions. The first question is about the --

CHAIR YANCY: Exactly.

DR. JEEVANANDAM: -- primary effectiveness. And I think if you look at just the way they graded the adhesions and looking through all the statistics, yes, they have attained their primary effectiveness.

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Now, --

CHAIR YANCY: So let me truncate your comments there because that's exactly the way I'm thinking about this. So again, what I'm hearing around the table is that the measure of effectiveness, that is a reduction in the severity of adhesions, was met. And we are comfortable with that? So, -- and not the incidence. And I respect that.

So let's now begin to deliberate on the clinical benefit. Dr. Jeevanandam, if you could go first, please.

DR. JEEVANANDAM: They have not demonstrated any clinical benefit in terms of time of dissection, in terms of, I don't think they, in terms of mortality, or bleeding, or anything that has affected their second operation.

So yes, it's, in their mechanism, has shown to have decreased adhesions, but without any clinical benefit as they have demonstrated.

CHAIR YANCY: Are there other comments regarding this question of clinical benefit? Dr.

Hirshfeld you were one of the first ones this morning to address this.

DR. HIRSHFELD: I don't have anything additional to say.

CHAIR YANCY: You agree?

DR. HIRSHFELD: Yes.

CHAIR YANCY: Dr. Weinberger?

DR. WEINBERGER: I think that I am convinced, not because of the intrinsic strength of the data, I think that I'm convinced really because of the strength of the statistical analysis. I'm particularly perplexed that the weakness of the methodology for gathering this information.

As an analogy, I hearken back to the days of coronary angiography before we did quantitation with some sort of objective measurement where intra-observer variability was huge. And I really have a small footnote or a small worry that the methodology where inter-observer variability or even intra-observer variability cannot be in any way measured that we could not possibly see anything other than a major

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difference.

So I think that going forward, some methodology should be garnered to try to have a more robust way of determining endpoints. And I think this might have just as easily been graded one plus two, plus three, plus four, plus, rather than assigning continuous variable numbers to that. That's the way I feel about the precision of the data.

CHAIR YANCY: Other comments about clinical benefit from either Ms. Mottle or others that haven't yet spoken?

MS. MOTTLE: Nothing more than what has already been said.

CHAIR YANCY: Thank you. So, is it fair for me to again paraphrase the answer on the panel's behalf to question two, is to take this as a two-part question. And with regards to the first part of our assessment of the effectiveness endpoint analysis, the panel believes that within the context of what was specified as a primary endpoint, that there is evidence is that is

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statistically acceptable that the severity of adhesions has been reduced, but we don't accept that the incidence of adhesions has been reduced.

Is there disagreement with that comment? Is that acceptable? Dr. Zuckerman.

DR. ZUCKERMAN: Okay. I think what you're trying to summarize is that we have three zeros with each p-value and we have statistical significance for a parameter measured. But, as you pointed out, the point of the question was two-fold. Even if there is statistical significance, the FDA would like to hear especially from the operating surgeons that are on the other side of the panel.

In the scheme of things, is this a clinically useful result? For example, as the discussion was going on a few minutes ago, if you had babies like this, would you want to use the device and why, given these results? Is it clinically useful?

CHAIR YANCY: Our surgical colleagues? Dr. Jeevanandam.

DR. JEEVANANDAM: I think if with the decrease in adhesions, for this indication, for a patient who you know you're going to have re-operate in six months and with the results that we've seen in this group of patients, the neonates on Norwood, I think, I would use this device. But I would not extrapolate this to the adult population, with the data that we have.

CHAIR YANCY: Dr. Katz?

DR. KATZ: The data we have makes it a very hard question to answer. My sense is that it may make it easier to do the sternotomy, however, I would have then thought there would have been a smaller, a decrease in the number of inadvertent enterotomies that occurred, which there wasn't.

So that leaves me really in a quandary as to whether I would use the device based solely on this narrow bit of data that we have there. I guess I'm not convinced from this that it significantly reduced, from a functional standpoint, what it would take, or what would have a clinical significant point there.

CHAIR YANCY: Dr. Hopkins.

DR. HOPKINS: Yes, I think I accept the fact that the reduction in severe adhesions is a priori a good thing. And at some level, it should be reflected in the overall outcomes and specifically, mortality or as was described, serious disastrous re-entry misadventures.

The incidence of that, however, is so low, even in the presence of severe adhesions, that to capture that in any kind of statistically meaningful way would take an enormous number of patients. But the logic appeals to me as a surgeon. So yes, there are subgroups of patients that I would, that I might use this in.

CHAIR YANCY: Do you need anymore input, Dr. Zuckerman?

DR. ZUCKERMAN: No, those were very helpful comments from the operating surgeons.

CHAIR YANCY: Let's proceed to question three, please.

Again, you have a table to peruse before you. It's Table 5. Hopefully we can

address this question fairly quickly, because it simply raises a question about the secondary endpoints. Let me remind you that the main secondary endpoints with a percent of patients with severe adhesions, a percent of patients by worse degree of adhesions, and the mean percent of investigational site by adhesion severity.

Our question is to provide our "clinical and/or statistical interpretation of the secondary effectiveness data."

Dr. Somberg.

DR. SOMBERG: Well, I think this goes back to the study size. And the issue is that right now we don't see a significant signal. Our statisticians has pointed out we probably wouldn't see a statistically significant signal and p-values don't matter here.

And I think what I meant when I said earlier that the committee has dealt with this in the past is that when studies are done and there are potential toxicities that haven't been seen, you can ask for further follow-up at a later date

but right now, there is no demonstration of a signal that we have to be concerned about. And the reason for that may be that the study was too small or that it may not be there. So we have to, in post-marketing, if this comes to that, that's always an if, you have to ask that there be more surveillance than there would otherwise be.

CHAIR YANCY: Trying to achieve some consensus here, I just want to be able to understand the language. So you are accepting the secondary effectiveness data, rejecting it or saying it's not interpretable? You can pass.

DR. SOMBERG: No, it not necessarily should be put in those terms. What I'm saying is that we do not see an adversity signal because you have to measure efficacy versus safety. So we don't see something that is adverse that would question the safetyness here, but we do not have adequate information --

CHAIR YANCY: Dr. Weinberger.

DR. SOMBERG: -- in regards to the sample size. And when we, you know, you can always

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speculate on any device, any drug, etcetera, that a large enough sample will show something that hasn't been seen here before. So what I'm saying is we have to be cognizant of that and take that into account when we deal with the issues of surveillance at a later date.

But right now, no, there are no secondary signals that would make me concerned about the safety of this device in the secondary analysis.

CHAIR YANCY: Let me just remind the panel that this is not about safety on question three. This is about effectiveness. And so we're looking at the secondary endpoints.

Dr. Weinberger?

DR. WEINBERGER: I think that I voiced my reservations previously. I think that the secondary endpoints by themselves have statistical problems. They have been pointed out both by the sponsor and by the FDA and don't, by themselves, make the argument convincingly. And as we've already said on multiple occasions, the clinical

benefit of these is far from clear in the context of the study and arguable, I think, by the clinical experience of cardiac surgeons.

So I think that what we're left with is accepting the primary data that there is a decrease in the severity of adhesions, together with the very clear clinical experience that reduction of severity of adhesions translates to a clinical benefit. That latter point in the logic was not tested in this study.

CHAIR YANCY: This specific question again, just to be clear, indicates whether or not we accept the secondary effectiveness data. And let me remind you that the first entry on Table 5 indicates that the percent of patients with severe adhesions in the control population was 72.7 percent and the percent of patients in the REPEL-CV population with severe adhesions was 30.4 percent in the p-values demonstrated there.

Dr. Neaton?

DR. NEATON: Well, I just was going to comment again maybe for the record, Table 5 is a

whole different ball of wax than Table 6. Table 5, in my mind, is pretty clearly interpretable and supportive of the overall primary outcome. Table 6 is un-interpretable from my point of view. And I was very pleased to see the sponsor show the overall results.

This is, essentially, an epidemiological investigation that requires a lot more thinking to make any heads or tails out of it. And so, I'm a little disappointed that the only outcome to assess clinical efficacy has been referred to as statistically meaningless. And so what we're left with is these other measure and with uncertain risk against a balanced risk benefit. And so I feel very differently about Table 5 than Table 6.

CHAIR YANCY: Thank you very much. Dr. Hopkins.

DR. HOPKINS: My response is 3A is arguable, 3B is un-interpretable, 3C is meaningless, and 3D is yes.

CHAIR YANCY: And I got all that.

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There was another hand on this side. Was there not? Dr. Hirshfeld.

DR. HIRSHFELD: At the risk of repeating myself, I'm bothered by Table 6. And we've heard a number of proposed explanations for why the data in Table 6 may be less meaningful than they are, but it still seems to me that the randomization procedure should have covered most of the explanations for why, or should have overcome the problems here. And the fact that we have longer dissection times in every subset of the REPEL group, is at complete variance with the data in Table 5.

But I think the data in Table 6 are perhaps actually the more important data in terms of clinical effectiveness.

DR. NEATON: Let me just say again, that Table 6 would be fine if the comparison was the overall for the device versus control. But if you look across in that table, those comparisons are not protected by randomization at all. And so you're comparing apples and oranges. And I think

it's highly problematic.

And even going up and down until you kind of understand how time relates to severity of adhesions, there is a number of other potential confounding factors that would explain that relationship. So that that's the reason I said that I just don't know what to make about this table. Perhaps the overall numbers kind of are, kind of generally kind of consistent with the idea that time is related to severity, but it needs a lot more analysis to be sure about it. But going across is what is problematic.

CHAIR YANCY: Dr. Katz.

DR. KATZ: I think just in the clinical context of how this works, the only thing that you can say from this is that there was less time to dissect the anterior part of the right ventricle from the posterior part of the sternum.

However, the remainder of the dissection of adhesions, and I guess maybe I'm not sure when the stopwatch started and stopped, if they were only measuring that segment of time, then