

1 most cases.

2 Remind me again of your second question.

3 DR. PAGE: Well, in terms of once you
4 had some experience with this device --

5 DR. BACKER: Oh, right, yes.

6 DR. PAGE: -- could you truly be blinded
7 as to whether it had been placed originally?

8 DR. BACKER: I think that, you know, at
9 our center, we did about 13 patients and we were
10 conscious at the time of re-operation as to whether
11 or not there was anything there. And we did, on a
12 few patients, see tiny remnants of kind of whitish-
13 yellow fibrocollagenous looking material at the
14 very edges of the pericardium, which I think we
15 were, you know, very heightened in our awareness of
16 whether something might be there or not. We sent
17 some of that to pathology. Dr. Anderson looked at
18 all of that and I think that's in your report. But
19 it was all, it was just minute amounts of
20 fibrocollagenous material with a foreign body
21 reaction.

22 The question we had was whether that was

1 related to the Vicryl suture that we had used. You
2 know, there's four Vicryl sutures at the corners.
3 So that could also have been part of the remnants
4 of the tissue. But we never saw anything unusual
5 or dramatically different in the sternal re-entry.

6 And I think it was really our heightened
7 awareness of whether or not there was something
8 abnormal that we even sent of some of these small
9 amounts of tissue to pathology.

10 DR. PAGE: And were sham Vicryl sutures
11 placed in the non, in the controlled patients or
12 not?

13 DR. BACKER: They were not.

14 DR. PAGE: So the Vicryl sutures alone
15 could have been --

16 DR. BACKER: Potentially, yes.

17 DR. PAGE: -- an indication to the
18 surgeon. Okay, thank you.

19 CHAIR YANCY: Before we got to our
20 break, I would like to entertain questions from
21 three different cohorts on the panel that haven't
22 been represented yet. Our consumer representative,

1 our surgical colleagues, and our statistical
2 representatives. So, Ms. Mottle, do you have a
3 question?

4 MS. MOTTLE: Yes. Thank you, Dr. Yancy.

5 Just a point of clarification. In study
6 two, you noted that the device was placed at the
7 time of initial surgery and then was replaced at
8 the time of delayed primary closure. I didn't note
9 that in the pivotal study.

10 So was that the same procedure
11 throughout all of the clinical trials? And could
12 that not have affected some of the results with
13 replacing the device in two to five days?

14 DR. PINES: Sure. What you said is
15 absolutely correct. The one difference between the
16 feasibility study and the pivotal study is in the
17 feasibility study at Children's Hospital LA, when
18 initiated that study, there was on-going
19 discussions with the FDA. And the concern was,
20 will placement of REPEL-CV lead to catastrophic
21 events prior to chest closure?

22 So all the patients enrolled at

1 Children's Hospital were patients who had undergone
2 the Norwood procedure with delayed closure. So at
3 the time of, at the end of the surgery, intra-
4 operatively, the patient was randomized to
5 treatment or control. If the patient was
6 randomized to treatment, a piece of REPEL-CV was
7 placed at the surgical investigational site, which
8 was exactly the same investigational site in all
9 the studies. Okay?

10 At the time of chest closure, if the
11 patient was randomized to REPEL-CV, well before
12 that, at the time of chest closure, the
13 investigator made an assessment whether the extent
14 and severity of the fibrinous adhesions, adhesions
15 formed in the zero to three day time period, if
16 there were less than, more than, or the same as you
17 would normally expect to see. And he made an
18 assessment. Okay?

19 Subsequent to that, he removed -- if the
20 patient was randomized to REPEL-CV, he removed the
21 REPEL-CV and applied a new piece of REPEL-CV. And
22 then at the time of the second sternotomy, we

1 assessed the adhesions and that was the data that
2 Dr. Weinstein reported.

3 In the pivotal study, because of the
4 safety concern, essentially, we have convinced the
5 FDA and the FDA agreed with us that there were no
6 events of concerns on the initial placement. So
7 the pivotal study and the European study,
8 essentially, not essentially, the patient was
9 randomized just prior to chest closure, if they had
10 delayed closure. If they didn't have delayed
11 closure, the patient was randomized and the
12 treatment applied at the time of chest closure in
13 the operating room.

14 CHAIR YANCY: Did you need a follow-up
15 question?

16 (No response.)

17 CHAIR YANCY: Surgical colleagues? Yes,
18 Dr. Katz? Press the button.

19 DR. KATZ: Three brief questions. The
20 first one may be addressed to Dr. Backer. I was
21 wondering, I realize that the area of study was
22 between the edges of the pericardium, but it looked

1 like you intentionally overlapped where the REPEL
2 was placed under the pericardial edges. Did you
3 get a sense of what the inflammatory reaction was
4 like between the pericardium and, for example, the
5 right atrium where the device was laid?

6 DR. BACKER: Unfortunately, we really
7 didn't because that was not part of the
8 investigational surgical site and we were blinded
9 as to whether they had had the REPEL or not. So it
10 was really hard to, you know, get any information
11 about that.

12 DR. KATZ: Okay. Secondly, was the
13 REPEL used in any of the second operations?

14 DR. BACKER: The REPEL was not used in
15 the second sternotomy, no.

16 DR. KATZ: Okay. And then lastly, the
17 comments that were made about not using this in
18 left ventricular assist device patients, was that
19 based solely on the two clinical cases that were
20 done, or was there other information involved at
21 that conclusion?

22 DR. BACKER: That was based on the

1 clinical cases from Baylor. And I think the, what
2 the information that I received from the
3 investigators who were there was that the, you
4 know, the device, this was a Thoratec device with
5 the long Dacron tube graft traversing the
6 mediastinum. And with each cardiac cycle, that
7 thing moves significantly and acted almost like a
8 hammer that was hitting against the REPEL.

9 And I think Eli was there at the time of
10 the actual looking at the REPEL graft after it had
11 been in place for a few days. Eli, maybe you want
12 to comment?

13 DR. PINES: Sure. I was in the case at
14 Columbia. And essentially, the patient was
15 randomized to REPEL-CV and REPEL-CV was placed
16 directly above the outflow graft. And
17 unfortunately, the patient crashed so the chest was
18 left open for an extended period of time, roughly
19 three to four hours. And as you look at the REPEL-
20 CV with the constant pulsating motion of the
21 outflow graft, probably I would say within an hour
22 to an hour and a half, you began to see the

1 material break down because all this pulsating and
2 sheer stresses against the material. That's really
3 the only case where we saw that. And it's really
4 unique, as Dr. Weinstein said, to the LVAD patient
5 population, because no other implantable device
6 gives you that kind of dynamic forces.

7 I would like to add another point with
8 regard to the inflammatory response. In the animal
9 studies that we did and the studies that I cited in
10 the canine, if you recall, we did the study where
11 we inserted the material and looked at epicardial
12 to pericardial adhesions. In that case, in those
13 dogs, ten dogs to be precise, essentially they were
14 free of adhesions, 12 percent of the area was
15 involved with adhesions. Histologically, there was
16 no sign of inflammatory response.

17 And likewise, in all the
18 biocompatibility studies, when the material was
19 implanted either in the pericardial cavity and
20 when you look at the histology at 28 days, it was
21 no different than the histology that you see for
22 the untreated, or in this case, rabbits.

1 And then the last point that I would
2 like to add with regard to adhesions in areas other
3 than "the investigational surgical site," in the
4 clinical study, we overlapped the material roughly
5 by one and a half centimeters to facilitate the
6 suturing to the pericardial edges. But we did not
7 capture or do we have any information on adhesions
8 between the epicardium to the pericardium in
9 humans.

10 But again, in dogs when we looked at the
11 epicardial, the pericardial adhesions and as the
12 data showed, essentially, they were free of
13 adhesions.

14 So the way REPEL-CV works, it's
15 mechanical barrier to minimize, if you will, the
16 fibrin bridges between two opposing surfaces. So
17 if you have two opposing surfaces and you have
18 fibrin bridges connecting them, if you place the
19 REPEL-CV, essentially you block or minimize the
20 formation of these fibrin bands. If you minimize
21 the formation of these fibrin bands, the fibral
22 base can't migrate into these bands, lay down the

1 collagen, and the other extracellular matrix result
2 in adhesions.

3 And that's why it's critical to have a
4 material in place at the initial time when you form
5 these fibrin bridges. If you can prevent or
6 minimize the formation of these fibrin bridges by
7 definition, and that's the whole principal behind
8 the barrier approach to adhesion prevention, the
9 sequence of events leading to fibrous adhesions is
10 minimized or blocked.

11 CHAIR YANCY: Thank you. Dr.
12 Jeevanandam?

13 DR. JEEVANANDAM: I would like to
14 congratulate the sponsor for this trial, actually,
15 because it's very difficult to look at things such
16 as pericardial adhesions. So I think it was a good
17 trial. But I have several questions.

18 First, in response to Dr. Somberg's
19 questions about adhesions, I think, there are other
20 factors that can cause immediate adhesions, such as
21 hematoma formation. I think blood can cause
22 adhesions. Deformed bodies cause a lot of

1 adhesions and mediastinitis, obviously, can cause
2 a lot of adhesions. If you have any of those three
3 factors on top of just physical barriers can cause
4 adhesions and I think adhesions do mature over a
5 period of time.

6 I think my question, I have several
7 questions, but one of the questions was, in your
8 measurements of how much area of severe adhesions
9 if they were, were pretty through numbers like 74
10 percent, 36 percent, etcetera. But we saw on the
11 video of Dr. Backer that a lot of times when you
12 start taking on these adhesions, you start from the
13 xiphoid and you just start taking down adhesions
14 almost blindly.

15 So if you start taking down adhesions
16 blindly, how can you go back and say what
17 percentage of areas had severe adhesions?

18 DR. PINES: Sure. I'm going to let Dr.
19 Backer and company address that.

20 DR. BACKER: Thanks for the question.

21 I think what I did was when I re-
22 operated on these patients was I tried mentally, in

1 my mind, to first decide what the biggest
2 percentage of adhesions I found was. So, were the
3 majority of the adhesions severe, were they
4 moderate, were they mild? And I think the video
5 showed at least what in my mind was the different
6 types of adhesions. And then I kind of backtracked
7 from that percentage of say, in this patient it
8 seems like about, you know, 80 percent of the
9 surgical site was severe, you know, 20 percent was
10 moderate, and then 10 percent was mild.

11 What I found typically was that the
12 patients tended to be kind of lumped at one end or
13 the other of the spectrum. And once you kind of
14 mentally categorize this, it was actually not that
15 difficult to decide, you know, what percent was,
16 you know, mild, moderate, and severe.

17 I think that the more patients that you
18 evaluated, the better you became at this. And I
19 think that the centers that had more patients
20 enrolled tended to have a little tighter standard
21 deviations on their evaluations.

22 DR. JEEVANANDAM: So what you're really

1 saying is that this, you didn't develop a grid or
2 a specific area and then mark out where you had
3 your adhesions. This was more of a judgment from
4 a surgeon taking the adhesions down.

5 DR. BACKER: That's correct.

6 DR. JEEVANANDAM: Okay. I guess my
7 other --

8 DR. O'BRIEN: Actually, we did develop
9 a defined area where we were measuring the
10 adhesions. So it wasn't like a gestalt of your
11 overall adhesiolysis that you did, but you looked
12 at that investigative site, where you knew the
13 REPEL was. And that's why we marked it by the
14 landmark, so when you go back in, you know
15 everything, you can't always identify the
16 appropriate anatomy. If you know you're measuring
17 the adhesions between the pericardial edges and
18 between the diaphragm and the great vessels, then
19 that gives you the grid. That gives you the area
20 where you are specifically looking at the
21 adhesions.

22 DR. JEEVANANDAM: But you didn't

1 actually map out that area for every patient and
2 then go back and draw where the adhesions were.
3 Again, it was the surgeons' gestalt of that area
4 and how much adhesions there were in that
5 particular area.

6 DR. O'BRIEN: He would look at that area
7 and way 70 percent of this area, 40 percent of this
8 area, was severe, 20 percent was. But it was just
9 that area. You didn't, in terms of actually
10 drawing it, no, but in your mind's eye you know,
11 you were just there and you said okay, this
12 percentage of this area would contain this grade of
13 adhesions.

14 CHAIR YANCY: I think we need
15 clarification here because I'm hearing two
16 different answers. I'm hearing one answer that
17 seems to be very subjective and the other answer
18 seems to be semi-quantitative or semi-precise. So
19 was it protocol specified methodology to assess the
20 adhesion?

21 DR. O'BRIEN: Yes.

22 CHAIR YANCY: And what was that protocol

1 specified methodology.

2 DR. O'BRIEN: The methodology was that
3 you looked back at the investigative surgical site,
4 which was defined by the boundaries of the
5 pericardial edges which you can identify. And then
6 you applied that grading scale that was outlined
7 before, going from zero to four, which for surgeons
8 that do lots of re-operative cardiac surgeries is
9 pretty straight forward.

10 CHAIR YANCY: The grading scale is
11 fairly intuitive. But it's this percentage of
12 adhesions that Dr. Jeevanandam is getting at. And
13 I'm supporting his line of questioning in just
14 trying to understand what were the metrics
15 established so that there could be a fair
16 assessment in the control arm and the REPEL-CV arm.
17 So, you're telling me that there were boundaries
18 pre-specified.

19 DR. O'BRIEN: Correct. Yes, there were
20 anatomic boundaries that were identified. And
21 that's why it was also difficult to analyze any of
22 the adhesions between the epicardium and the

1 pericardium where the sheet went beyond that,
2 because that would be much more subjective.
3 Whereas, the discreet boundaries of the pericardial
4 edges could be objective from one surgeon to
5 another.

6 CHAIR YANCY: Dr. Jeevanandam, did you
7 need to continue?

8 DR. WEINSTEIN: I just have a very brief
9 comment, in case it helps clarify your point, that
10 the dissection of the adhesions isn't blind from
11 underneath the sternum and then the sternum is
12 opened and the areas assessed. In the pediatric
13 population, because of the increased percentage of
14 cartilage and the time it takes for the ribs and
15 the sternum to ossify, you can see all the way
16 under the sternum to take down the adhesions under
17 direct vision, which is why many of my students do
18 that in pediatrics. So that area is looked at
19 under direct vision.

20 DR. JEEVANANDAM: Right, I understand
21 that. But once you take down those adhesions, then
22 you really can't quantify what you have taken down.

1 I mean you can't say that you know, 33 percent of
2 this has severe adhesions because you know, you're
3 taking them down underneath the sternum, so you
4 don't know what percentage you are taking down
5 underneath the sternum.

6 CHAIR YANCY: Dr. Hopkins, you had a
7 question?

8 DR. HOPKINS: Actually I have a number
9 of questions, Mr. Chairman.

10 DR. PINES: Can I just quickly respond
11 to the question?

12 DR. HOPKINS: Yes.

13 DR. PINES: What you said is absolutely
14 correct, obviously, and that's why I think it was
15 critical to have masked observers making the
16 assessments because we knew the assessment was
17 somewhat quantitative, if you will. And that's why
18 you see the large standard deviation and that's why
19 we enrolled as many patients as we did, so that at
20 the end of the day, we would have enough masked
21 patients to be able to make a decision based on
22 blind assessments.

1 CHAIR YANCY: Dr. Hopkins, proceed
2 please.

3 DR. HOPKINS: Yes. I have one question
4 that has to do with the biology of your device and
5 the pre-implant studies. And then the rest of my
6 questions have to do with the data in the pivotal
7 study.

8 In the pre-implant and biological
9 rationale for this, you refer to this as a
10 bioresorbable device. In what sense is it
11 bioresorbable? Is it bioresorbable in that it
12 dissolves into water? Is it water or hydrophilic?
13 It is hydrophilic or does it degrade by foreign
14 body effect and, in effect, is a low grade
15 inflammatory response that removes this device?

16 DR. PINES: Thank you. I'm going to
17 have Dr. Cohn and Dr. Anderson respond to your
18 question.

19 DR. COHN: My name is Daniel Cohn. I
20 am Professor at the Hebrew University in Jerusalem,
21 Israel and I have a financial interest in the
22 company. I am inventor of the Polymers One.

1 Yes, this is a hydrophilic polymers, a
2 block of polymer which each of the components
3 brings to the part a specific chemical, physical,
4 and biological task property. The PLA brings the
5 hydrolytic cleavage ability whereby the polymer
6 degrades. The PEG being this hydrophilic
7 component, makes the degrading segments of the
8 chains to really be relatively rapidly water
9 solubilized, as opposed to many other hydrophobic
10 materials, PLAs, Vicryls, etcetera, which continue
11 to be hydrophobic until the molecular weight is
12 very low and then triggering continuously for a
13 response. In this case, early on, the fragments
14 are water solubilized, minimizing the foreign body
15 response, that is due to the chemistry of the
16 polymer.

17 Thank you.

18 DR. ANDERSON: And the question
19 regarding the foreign body reaction, any material,
20 even the Vicryl suture is a foreign body. And one
21 does have a small normal foreign body reaction,
22 which is what I call it.

1 Let me start with saying my name is Jim
2 Anderson. I'm at Case Western Reserve. I've been
3 doing clinical implant retrieval for 29 years. So
4 it's in that perspective that I evaluate these
5 sorts of things.

6 This was a normal foreign body reaction
7 that I saw. As far as the material is concerned,
8 itself, of course, the PLA is made up of a Krebs
9 Cycle intermediate and when that degrades, that
10 eventually goes into the Krebs Cycle and is
11 metabolized. The polyethylene oxide also can
12 undergo oxidative degradation and end up in a Krebs
13 Cycle intermediate. That's a hydrophilic material
14 and so, as such, it may be cleared renally at a
15 larger molecular weight than the poly-lactic acid
16 would be. But that's safe and efficacious, too.

17 So both components that go into the
18 material under hydrolytic, enzymatic, or oxidative
19 degradation are converted into the Krebs Cycle
20 intermediates and can be subsequently metabolized
21 into water and to CO2 for excretion.

22 CHAIR YANCY: Dr. Anderson, would you

1 identify, if you don't mind, whether or not you
2 have conflicts.

3 DR. ANDERSON: Oh, I'm a consultant. I
4 have no financial, I'm sorry, I have no financial
5 interest in the company. I have no stock.

6 CHAIR YANCY: Thank you.

7 DR. HOPKINS: For the follow-up question
8 to you, sir, for the surgeons in the group, we
9 think of PGA, which is the Vicryl ---B

10 DR. ANDERSON: Right.

11 DR. HOPKINS: -- material that was used
12 to fix this as being non-hydrophilic and, in fact,
13 by and large is degraded by foreign body reaction.
14 Would you say this device is more hydrophilic than
15 PGA and would be more solubilized by its water
16 affinity characteristics, as opposed the foreign
17 body reaction that Vicryl suture, for example,
18 often engenders?

19 DR. ANDERSON: Well, this material
20 certainly is more hydrophilic than the Vicryl
21 suture. It takes up water and thus, makes it more
22 susceptible for the rapid biodegradation or the

1 bioresorbtion. That's the molecular design that
2 went into this material. And so it was
3 deliberately designed to be more rapidly degradable
4 than the Vicryl suture.

5 DR. HOPKINS: And that's the basis of
6 the various ratios that you tested in the pre-
7 implant study?

8 DR. ANDERSON: Yes.

9 DR. HOPKINS: Okay, thank you. Now, a
10 series of questions on the pivotal study.

11 Presumably, the theoretical
12 complications of placing this device were captured
13 in your adverse events basket. Specifically, were
14 there any episodes of postpericardiotomy syndrome
15 that may or may not have been attributable to the
16 placement of the device? And in the low cardiac
17 output adverse events groups, would tamponade have
18 been picked up in that group? Because I did not
19 see tamponade specifically listed as a separate
20 SAE.

21 DR. PINES: I'm going to let the
22 investigators answer that question.

1 DR. BACKER: The question regarding a
2 tamponade, I don't believe there were any patients
3 that were thought to have tamponade related to the
4 REPEL device.

5 The REPEL device is somewhat, is very
6 permeable and very flexible and very pliable,
7 unlike say placing a pericardial membrane or other
8 pericardial type substitutes. And I did not see
9 any tamponade in my patients and I don't believe it
10 was reported in those SAEs.

11 DR. HOPKINS: Would that have been
12 captured in the AEs that were --

13 DR. BACKER: It should have been
14 captured as a re-operation for pericardial
15 tamponade.

16 DR. HOPKINS: Okay. The next question
17 while you're standing there, Dr. Backer.
18 Extrapolation of the LVAD data or the LVAD lack of
19 applicability of this device to LVADs, one of the
20 biggest issues on adhesions and re-entry into
21 congenital heart re-repairs and reconstructions is
22 the placement of a conduit and the often intimate

1 association of the conduit to the chest wall that
2 can cause misadventures. It is common practice to
3 use, in addition to the homograft material, Dacron
4 hoods, as well as there are numerous centers in the
5 country that have now gone back to Dacron and
6 porcine.

7 We all endeavor to place these conduits
8 away from the sternum or the anterior chest wall.
9 But in those patients in whom that is not possible,
10 would you think that this device would not be
11 indicated to prevent adhesion of the conduit to the
12 chest wall? Because the motion of the heart
13 grinding against the chest wall would probably have
14 the same affect, it would seem, as the Dacron
15 conduit in an LVAD device.

16 DR. BACKER: You know, I would be
17 speculating, because we didn't use the device in
18 any patients like that. The only patients that I
19 used the device in were the patients that had a
20 Sano procedure, where there was a GORE-TEX graft
21 from the ventricle to the pulmonary artery that
22 frequently did lie immediately beneath the sternum.

1 And at least what I saw at the time of the REPEL
2 application was that it had this hydrophilic effect
3 where you formed sort of a layer of water or
4 solution between the heart and the membrane and
5 then above the membrane. And what I saw was the
6 heart and the GORE-TEX graft moving nicely
7 underneath the membrane.

8 As to whether or not that same kind of
9 nice physiologically appearing occurrence would
10 occur with a Dacron graft underneath the device, I
11 couldn't say.

12 DR. HOPKINS: Well, Sano is a three and
13 a half millimeter, or a four millimeter GORE-TEX --

14 DR. BACKER: Correct.

15 DR. HOPKINS: -- whereas, a Dacron hood
16 and a suture line of a graft proximal osmosis would
17 be much more. It measures 20 millimeters and would
18 be much more mechanically correct.

19 Let me go back to one question that
20 wasn't answered. Would postpericardiotomy
21 syndrome have been picked up on your clinical
22 events monitoring post-operatively?

1 DR. BACKER: Yes, it should have been.
2 I mean, those patients would have been, that would
3 have been categorized --

4 DR. HOPKINS: But there was no category
5 in any of the listings that I saw for
6 postpericardiotomy. No, it was NC,
7 postpericardiotomy, zero.

8 DR. BACKER: Yes. Jim, why don't you
9 come up? Because you were in the design study.

10 DR. O'BRIEN: It would have been picked
11 up in terms of the presence of a pericardial fusion
12 or if they needed additional treatments outside of
13 the norm of the events common to that population.
14 And postpericardiotomy syndrome was not listed as
15 one of the events common to that population. So,
16 it should have been picked up.

17 DR. HOPKINS: There were a couple of
18 pleural effusions and things like that, though.

19 DR. O'BRIEN: Pleural effusions, which
20 again, would have would have been picked up as
21 that. But if they were going to be treated with
22 steroids or had a pericardial drain placed, then it

1 wouldn't have been picked up as that.

2 DR. HOPKINS: So, as far as we know, now
3 the STS database does have postpericardiotomy
4 syndrome as one of the follow-ups. As far as we
5 know, however, that specific question was not asked
6 in that form, postpericardiotomy syndrome. Yes,
7 no?

8 DR. O'BRIEN: Not as a specific yes/no
9 tick off.

10 DR. HOPKINS: Okay.

11 DR. O'BRIEN: It should have been
12 captured as an adverse event.

13 DR. HOPKINS: Okay.

14 CHAIR YANCY: We want to break in about
15 five minutes. So, --

16 DR. HOPKINS: I've just got one more
17 question.

18 CHAIR YANCY: Please.

19 DR. HOPKINS: Okay. Since the area of
20 coverage, and again, I'm just turning up the
21 magnification on the data that you've already
22 given. Since the area of coverage here was the

1 area of re-entry, presumably the primary benefit
2 was to prevent any misadventures, as so well
3 demonstrated by our clinical colleagues. Were
4 there any re-entry misadventures on any patients,
5 either in the control group or in the REPEL group?

6 DR. PINES: I'm going to let the
7 investigators speak to it, but in terms of numbers,
8 there were four what the investigators called minor
9 superficial entry in the control group and
10 likewise, there were minor entries in the treatment
11 group.

12 DR. HOPKINS: In the area of coverage?
13 Because the area for example, where we saw --

14 DR. PINES: That's the only --

15 DR. HOPKINS: -- the nip in the atrium
16 was not in the area of coverage of the device.

17 DR. PINES: We only addressed the area,
18 the investigational surgical field.

19 DR. HOPKINS: So there were four minor
20 misadventures in each group.

21 DR. PINES: Yes, sir.

22 DR. HOPKINS: No majors as discussed

1 that required going on bypass or --

2 DR. PINES: Oh, absolutely --

3 DR. HOPKINS: -- before establishing
4 full exposure --

5 DR. PINES: The most that they required,
6 and it's all documented, is one stitch.

7 DR. HOPKINS: All right. So no
8 difference in misadventures on re-entry.

9 DR. PINES: Correct. But we're looking
10 at a very small number of patients.

11 DR. HOPKINS: Okay.

12 CHAIR YANCY: Let's let the final line
13 of questioning come from Dr. Neaton. I think he
14 has some statistical questions for Dr. Lavin.

15 DR. NEATON: Actually, I want to go back
16 to the primary endpoint because I didn't quite
17 understand the explanation of it. And so, let me
18 just, can I give you a conjecture and tell you what
19 I thought I heard? That actually when you're going
20 in, you're counting the number of adhesions and
21 then you kind of keep track mentally within this
22 area what percentage of them are severe versus

1 moderate or mild. Is that, is my understanding of
2 that correct?

3 DR. PINES: No, it's not totally
4 correct. What we did is capture the surface area -
5 -

6 CHAIR YANCY: Speak into the microphone
7 please, so that we can capture your comments.

8 DR. PINES: Sorry. That's not totally
9 correct. What we captured is the area involved
10 with adhesions. So it's a surface area
11 measurement. It's not like measuring spaghetti
12 strings, if you will, because as the video showed,
13 you don't have discreet areas. I mean essentially
14 when you have severe adhesions, it's plastered to
15 the surface of the heart.

16 So we weren't counting adhesions. We
17 were really mapping out, if you will, the area
18 involved with the respective adhesion severity.

19 DR. NEATON: So when you, and as part of
20 the preparatory work for your pivotal trial, have
21 you done any work to understand how reproducible
22 that measurement is by surgeons?

1 DR. PINES: No, we did not do any kind
2 of standardization --

3 DR. NEATON: Okay.

4 DR. PINES: -- with regard to that.

5 DR. NEATON: Can I, just another
6 conjecture, perhaps.

7 So, and your film was very interesting,
8 the snipping going on there. So I'm trying to
9 understand the disconnect between your primary
10 outcome and the dissection time. And so you
11 presented data in the briefing document indicating
12 that people that had severe adhesions on a greater
13 fraction of the area, had longer dissection times
14 than those who didn't. And you have a treatment
15 difference which is pretty substantial, by looking
16 at a number of different measures.

17 Is it possible that people as a
18 consequence of using the treatment have a lot more
19 mild adhesions? From the data you presented in the
20 book, I didn't see it here today, there were very
21 few people that had no adhesions. So everybody had
22 some, it looked like.

1 DR. PINES: That's correct. I mean --

2 DR. NEATON: And so is it possible that
3 the difference in the dissection times is
4 attributable to the fact that there are many more
5 people with the device that have a lot of mild
6 adhesions?

7 DR. PINES: I'm going to let Dr. Backer
8 address that. But by definition, the total area is
9 100 percent involved with adhesions. So by
10 definition, if you have fewer severe adhesions,
11 you're going to have more either in the mild,
12 moderate, or non-category.

13 DR. NEATON: Yes, but the actual time
14 that it takes to dissect. I mean --

15 DR. PINES: We did not do an analysis,
16 nor do I think it can be done, where you look at
17 time to dissection as a function of the severity of
18 the adhesions.

19 Other than severe adhesions, one of the
20 assessments that we did is look at the dissection
21 time for non-severe versus severe adhesions. And
22 we can speak to that slide. I think it would

1 probably be more appropriate to do after lunch.
2 But I think more importantly, I think that would be
3 appropriate to Dr. Backer to speak to some of the
4 limitations associated with capturing the
5 dissection time.

6 DR. NEATON: Can I just ask maybe just
7 one other thing that perhaps you could look at
8 during the lunch that may, is you presented some
9 nice data in the pack in terms of the impact of
10 some surgeons being un-blinded. Did you look at
11 the dissection time for the patients that were
12 totally blinded, a different surgeon, the second
13 sternotomy?

14 DR. PINES: No, we did not look at the
15 dissection time as a function of the masked and
16 unmasked. We did look at the area involved with
17 adhesion for the masked and unmasked, but not the
18 dissection time.

19 DR. NEATON: Something that you could
20 look at?

21 DR. PINES: Sure. I mean, the database
22 is there. That's very easy to do. But I think the

1 bigger picture is the limitations associated with
2 the dissection time and what does it really mean.
3 And maybe it would be appropriate for Dr. Backer to
4 speak to it.

5 DR. BACKER: Again, as I mentioned in my
6 slide presentation, the standard deviation of the
7 dissection times was very large. They were
8 typically 25 plus or minus 20 minutes. And I think
9 this goes back to different surgeons using
10 different techniques to open the sternum.
11 Different levels of capability on sternal reentry
12 and the multiple different factors with our patient
13 population. You know, a patient with
14 transposition, the order is right underneath the
15 sternum. A patient with a Sano shunt can be
16 crossing the middle of the sternum. A patient with
17 dextrocardia of the heart sitting in the middle of
18 the chest. So, I think it was, the combination of
19 all those different things that prevented us from
20 having a tight standard deviation on the dissection
21 times.

22 DR. NEATON: I just want to point out,

1 though, that is true except that your point
2 estimate for the location was in the wrong
3 direction. And so there was no evidence of any
4 difference in dissection time at all between the
5 two groups, quite apart from the variability, which
6 would impact the power for the --

7 DR. PINES: What I'd like to do is have
8 Dr. Backer --

9 CHAIR YANCY: Excuse me.

10 DR. PINES: Oh, I'm sorry.

11 CHAIR YANCY: Let us do this. I think
12 that we've had a very good series of comments this
13 morning. I want to thank the sponsors for your
14 very scholarly and orderly presentation and very
15 thorough response to the questions. I'd like to
16 thank the panel for very good questions as well.

17 As I hear it, there are several things
18 that we hope that you would allow us to revisit
19 with you after the lunch, and that would be any
20 evidence you have of clinical efficacy. I accept
21 Dr. Hirshfeld's concerns that we would like to see
22 anything, whether it's ICU study, whether it's

1 total OR times, or anything that strengthens the
2 application with regards to clinical efficacy.

3 And I think the other issues regarding
4 the assessment of adhesions might be worth greater
5 clarification after lunch. But I want to thank you
6 for being so forthcoming with the answers.

7 We will go ahead and take --

8 DR. PINES: Thank you.

9 CHAIR YANCY: We will go ahead and take
10 a break now and will reconvene at 10:30. Thank you
11 very much.

12 (Whereupon, the meeting went off the
13 record at 10:18 a.m. and went back on the record at
14 10:34 a.m.)

15 CHAIR YANCY: While FDA is preparing for
16 their presentation and we're all getting settled,
17 one of the panel members approached me and wanted
18 to add one more item for the sponsor to consider
19 when we have a chance to address each other again
20 this afternoon. and that has to do with whether or
21 not you have any data regarding the need or
22 requirement for transfusions. Potentially, it's

1 the function of a clinical outcome that might be of
2 benefit with regards to the use of the REPEL-CV.
3 So if you can add that to your list, if you have
4 that information, it would be appreciated.

5 We'd like to resume our panel meeting
6 now and we will have the FDA presentation. The
7 first FDA presenter is Sonna Patel, who is a
8 bioengineer and is the review team leader for this
9 PMA. Dr. Patel.

10 DR. PATEL: Thank you, Dr. Yancy. Thank
11 you to the panel members for attending this panel
12 meeting and for putting forth your time and effort
13 in review of this device.

14 I would like to present the FDA review
15 of the REPEL-CV bioresorbable adhesion barrier. I
16 would like to acknowledge the following individuals
17 for their participation on the PMA review, and I
18 would further like to acknowledge the FDA IDE
19 review team, the Investigational Device Exemption
20 review team and thank them for their efforts in
21 getting this device to PMA.

22 The REPEL-CV is a single use

1 bioresorbable adhesion barrier. It is designed to
2 be resorbed in 28 days and is 52 percent by weight
3 poly-lactic acid and 47 percent by weight
4 polyethylene glycol. It is designed to prevent
5 interconnection as the result of the fibrin bands
6 that develop during the course of normal healing.
7 Typically this device, as we know in the pivotal
8 study, is used when re-operation is likely.

9 As was noted before, the proposed
10 indications for use for this device is as a
11 surgical adjuvant indicated for reducing the
12 incidence, severity and extent of postoperative
13 adhesion formation in patients undergoing cardiac
14 surgery via sternotomy. The contraindications for
15 this device are that it is contraindicated in
16 patients in whom a ventricular assist device is
17 implanted.

18 The preclinical review of this device
19 consisted of a biocompatibility and sterilization
20 review, review of the mechanical and chemical
21 properties, review of the animal studies. And FDA
22 has no major concerns regarding the preclinical

1 review.

2 The clinical studies for this device
3 consisted of three feasibility studies, as were
4 noted by the sponsor, and a fourth pivotal study
5 for study of safety and effectiveness and 144
6 enrolled pediatric patients at 15 centers.

7 The pivotal study design consisted of
8 neonatal patients undergoing a planned second
9 sternotomy. One continuous piece of REPEL-CV was
10 placed to the area directly below the sternotomy
11 site. It was placed directly over the heart
12 between the epicardium and the sternum and the
13 device was not studied for placement between any
14 pericardial surfaces. The severity of adhesions
15 were evaluated using a grading scale of zero to
16 three after the second sternotomy.

17 The adhesion evaluation occurred. The
18 patient had the first sternotomy before chest
19 closure and then was randomized to the REPEL-CV or
20 control group. At the second procedure, an
21 evaluator defined the investigational surgical site
22 and then graded the adhesion area with four

1 possible values, grades zero to three, consisting
2 of no adhesion, moderate, mild, and severe
3 adhesions.

4 The panel has raised a number of issues
5 regarding the investigational surgical site. FDA
6 recognized this as a concern and advised the
7 sponsor to take photos of the region. The
8 percentages of area with grade zero, one, two, or
9 three within that investigational surgical site
10 were recorded. Note that these percentages are
11 supposed to sum to 100 percent.

12 There are two types of data that are
13 available from this type of evaluation, the total
14 percentage, area covered by a particular grade, and
15 the total number of patients with grades zero, one,
16 two, and three adhesions. The statistical analysis
17 of this adhesion scoring and the other results from
18 the study will be discussed by Dr. Yunling Xu.

19 The FDA presentation will now consist of
20 the statistical, clinical, and epidemiology reviews
21 by Dr. Yunling Xu, Dr. Wolf Sapirstein, and
22 Mingdong Zhang.

1 I would now like to introduce Dr. Xu for
2 the statistical review.

3 DR. XU: Thank you, Dr. Patel for the
4 introduction.

5 Good morning. Today I am going to
6 present in the following sequence. First, I will
7 describe the pivotal study design, followed by
8 discussion of the primary effectiveness data. At
9 the end, I will conclude with a summary.

10 As mentioned by Dr. Patel, there were
11 three feasibility studies and the one pivotal study
12 in this PMA. My presentation will focus on the
13 pivotal study only.

14 The pivotal study was designed as a
15 randomized controlled clinical trial with the
16 REPEL-CV being the investigational device and the
17 standard of care being the control. Seventeen
18 study centers were planned to enroll patients. The
19 randomization ratio was one to one at each center.

20 The primary effectiveness endpoint is
21 defined as the percentage of area with grade three
22 adhesion measured at the second procedure. The

1 starting out hypothesis is that the mean percentage
2 of the area with grade three adhesion in the REPEL
3 arm is larger than or equal to that in the control
4 arm. Correspondingly, the alternative hypotheses
5 is that the mean percentage of area with grade
6 three adhesion in the REPEL arm is smaller than
7 that in the control arm.

8 For testing the hypothesis on the
9 primary effectiveness endpoint, two populations
10 were defined in the clinical protocol, evaluable
11 patients and the per-protocol patients. The
12 evaluable patients include all randomized patients
13 who had their adhesion measured at the second
14 procedure. Note that the sponsor refers to them as
15 "intent-to-treat" population. The per-protocol
16 population includes all evaluable patients who had
17 their adhesion measured at least two months after
18 the first one and had no major protocol violations.

19 Having shown the primary effectiveness
20 endpoint, the starting hypotheses and the analysis
21 populations, I will proceed to present the sample
22 size planning in the next slide.

1 Based on the primary effectiveness
2 endpoint, the planned sample size was 50 patients
3 per arm. This could provide a power of 80 percent
4 to detect a difference of 20 in the mean percent of
5 area with grade three adhesion between the repair
6 arm and the control arm. It was assumed that the
7 standard deviations was 35 for both arms.
8 Accounting for possible loss to follow-up, the
9 total approved sample size was 156 patients. This
10 slide concludes the description of the study
11 design.

12 Now let me present the study result,
13 beginning with patient accountability. After the
14 first sternotomy, 73 patients were randomized to
15 the REPEL arm and 71 patients were randomized to
16 the control arm. Before the second surgery, there
17 were nine deaths and eight emergent openings in the
18 REPEL arm, seven deaths and eight emergent openings
19 in the control arm. In addition, two patients in
20 the control arm were treated with other marketed
21 devices. These withdrew from the study before the
22 second surgery. In the end, there were 56

1 evaluable patients in the REPEL arm and 54
2 evaluable patients in the control arm.

3 First let's look at the t-test result of
4 the primary effectiveness data. The average
5 percentage of area with grade three adhesion is
6 21.3 percent for the REPEL arm and 47.3 percent for
7 the control arm. So the difference between them is
8 minus 26 percent. And a 95 percent confidence
9 interval for the difference is from minus 41
10 percent to minus 11 percent.

11 The operant of this interval is below
12 zero. So statistically, the mean percentage of
13 area with grade three adhesion for the REPEL arm is
14 significantly smaller than that for the control
15 arm, with a one study P-value of .0004.

16 Having said this, in the next few
17 slides, I would like to bring to your attention
18 some questions that may arise about the t-test,
19 followed by results from alternative tests.

20 This is a histogram of the primary
21 effectiveness data. As you can see, most of the
22 data points at the two ends of the range of

1 possible values for the primary effectiveness
2 endpoint. Is the t-test still appropriate for the
3 study hypotheses regarding the primary
4 effectiveness data? By the central limit theorem,
5 the answers seems to be yes, due to the moderately
6 large sample size of the study. Nevertheless, the
7 randomization test, with raw observations as the
8 scores, was performed to support the t-test result.

9 The randomization test is a type of non-
10 parametric statistical test. This is the
11 randomization test result on the primary
12 effectiveness data. The one side of p-value is
13 .0005, which is very similar to the t-test result,
14 supporting the conclusion that statistically the
15 percentage of area with grade three adhesion for
16 the repair arm is significantly smaller than that
17 for the control arm.

18 Now, let's turn the discussion to
19 several potential issues, including center effect
20 un-blinded evaluation and the missing primary
21 effectiveness measures.

22 Let's first look at the center effect.

1 This slide shows the treatment effect by a center.
2 The difference between the REPEL and the control
3 ranged from minus 50 percent to positive 15
4 percent. This indicates a possibility of center
5 effect. Note that 17 centers were approved to
6 involve patients and 15 centers did so. In
7 addition, center number nine had control patients
8 only and center number 12 had no evaluable patient.
9 That's why only 13 centers are shown on this graph.

10 To adjust for center effect, a
11 randomization test stratified by center was
12 performed. The one-sided p-value is 0.0013,
13 indicating that statistically the percentage of
14 area with grade three adhesion for the REPEL arm is
15 significantly smaller than that for the control arm
16 after removing center effect.

17 Now, let's take a look at the un-blinded
18 issue. The study was designed for the evaluator to
19 be blinded. During the study, however, the
20 adhesions in about 25 percent of patients were
21 measured by un-blinded evaluators. This may
22 potentially lead to confounding and a bias . To

1 address this issue, the FDA decided to perform a
2 covariate adjusted analysis.

3 After careful consideration of the shape
4 of the primary effectiveness data distribution, the
5 FDA chose to dichotomize the primary effectiveness
6 data to build a logistic regression model. Using
7 the logistic regression model, the treatment effect
8 could be assessed after adjusting for the effects
9 of various covariates. Since there was no pre-
10 specified cut-point, three cut-points which are 25,
11 50, and 75 percent were tried in order to assess
12 the sensitivity to choices of cut-points.

13 Dichotomization of the primary
14 effectiveness data was done in the following way.
15 If a patient's percentage of area with grade three
16 adhesion is greater than the cut-point, his or her
17 primary effectiveness endpoint of value is rated as
18 one, otherwise as zero.

19 Shown on this slide are two sided p-
20 values for the treatment effect. After adjusting
21 for blinding status in conjunction with four other
22 covariates, including gender, heart-lung bypass

1 machine usage, procedure type, and chest closure
2 delay. All three ways of dichotomization gave a t-
3 value less than five percent for the treatment
4 effect.

5 So statistically, patients in the REPEL
6 arm have significantly less grade three adhesion
7 than patients in the control arm under the models
8 used.

9 Lastly, let's look at the missing
10 adhesion measuring issue. About a quarter of the
11 randomized patients did not have their adhesion
12 measured, due to death or emergent opening. Those
13 patients were not part of the evaluable patients
14 and were not included in the statistical tests
15 presented so far.

16 Using a logistic regression model
17 mentioned on the previous slides, the FDA analyzed
18 all randomized patients with multiple imputation of
19 the missing primary effectiveness values.

20 This slide shows the two sided p-values
21 for the treatment effect from the analysis of all
22 randomized patients. The p-values are less than

1 five percent. So statistically, patients in the
2 REPEL arm have significantly less grade three
3 adhesions than patients in the control arm under
4 the models used. Note that the same set of
5 covariates including gender, heart-lung bypass
6 machines usage, and chest closure delay was used in
7 the multiple imputation model and the patient
8 analysis model.

9 With all that said, the primary
10 effectiveness data have been analyzed using
11 different approaches to address various issues,
12 such as the distribution of the data, center
13 effect, un-blinded evaluation, and the missing
14 adhesion measures. All the different analyses have
15 come to the same conclusion. Statistically, the
16 mean percentage of area with grade three adhesion
17 in the REPEL arm is significantly smaller than that
18 in the control arm for the pediatric population
19 studied.

20 Before I turn the podium to Dr.
21 Sapirstein, I would like to make the following
22 comment on secondary effectiveness endpoints

1 results. There were no pre-specified hypothesis
2 tests for secondary effectiveness endpoints in the
3 current protocol. And the p-values presented in
4 the PMA were not adjusted for multiple comparison.
5 Thanks for your attention.

6 I would now like to introduce Dr. Wolf
7 Sapirstein, who will present the clinical review
8 for REPEL-CV.

9 DR. SAPIRSTEIN: Thank you, Yunling.
10 Good morning. My name is Wolf Sapirstein and I
11 will be reviewing the clinical data provided to
12 support this marketing application for the REPEL-CV
13 adhesion barrier from an FDA perspective. And I
14 will try to be no too repetitive of the excellent
15 presentation by the sponsor.

16 Dr. Don Hagler, a pediatric
17 cardiologist at the Mayo Clinic and a consultant to
18 this division of the FDA participated in this
19 review and provided a balance to my cardiac
20 surgical background perspective.

21 My review will cover these aspects of
22 the pivotal study and briefly review the

1 feasibility data endpoints.

2 The sponsor undertook three feasibility
3 or pilot studies. The first in 1998 randomized 27
4 adults at two United States Centers in a short-term
5 safety assessment. Two ventricular assist device
6 implants for bridge of transplant were included in
7 the REPEL study and were assessed at re-operation
8 for cardiac transplant with reporting of unusually
9 exuberant adhesions.

10 A second study for safety and
11 effectiveness randomized 13 pediatric patients
12 scheduled for re-operation at a single center was
13 conducted and the REPEL arm had the device placed
14 retrosternally prior to closure of the first
15 thoracotomy. The intensity of adhesions at re-
16 operation was classified as more or less extensive
17 than usual or absent at the re-operation. In five
18 of seven REPEL patients and in one of six control
19 patients, adhesions were graded as less than usual.
20 Investigators reported severe mediastinitis
21 occurring in two REPEL recipients.

22 A single arm open-label marketing study

1 was conducted in Europe for CE labeling purposes on
2 15 pediatric patients undergoing planned re-
3 exploration in two French and one German center.
4 These studies were performed with a three scale
5 grading system.

6 This is the inclusion criteria for the
7 pivotal study. The preliminary studies provided
8 assurance of safety and possible benefit to allow
9 proceeding to this pivotal IDE trial. In
10 calculating the study sample size, the sponsor
11 proposed the study objective would be achieved with
12 a demonstration of reduction of adhesions by 20
13 percent.

14 All right, just go back to that. I
15 should add the pivotal study was block randomized
16 with 144 patients at 17 United States centers. Two
17 centers were subsequently removed from the study
18 for inadequate enrollment. The retrosternal
19 cardiac surface deficient of pericardial protection
20 was covered with the REPEL-CV barrier in the
21 investigational treatment area, prior to closing of
22 the first thoracotomy, but was left bare in the

1 control arm, allowing contact with the sternal
2 repair.

3 This is the assessment schedule used in
4 follow-up of these patients and their visit number
5 one captures the delay that occurred in primary
6 closure in many of these patients.

7 The grading of adhesions encountered at
8 re-operation was to be conducted by a masked
9 evaluator. A three grade scale employed in the
10 feasibility phase was modified to one with four
11 grades for the pivotal study. Grading was
12 determined by the ease with which adhesions
13 realized with grades two and three differentiated
14 by the extent to which sharp dissection was
15 required for this purpose.

16 This slide depicts the inclusion
17 criteria. Enrolled patients were infants and
18 children undergoing stage mediastinum exploration
19 to correct or palliate congenital cardiac lesions.
20 In 81 of the 110 evaluable cases, this was a
21 Norwood procedure for hypoplastic left heart
22 syndrome.

1 The FDA accepted that this restricted
2 enrollment was necessary, in order to ensure re-
3 exploration within a defined time frame in order to
4 assess device performance as an adhesion deterrent.
5 It was felt that the study outcome could be
6 extrapolated to other populations.

7 I'm sorry. This is again the
8 assessment schedule capturing the fact that there
9 was a delay in the first thoracotomy closure in
10 extremely ill patients under visit one. Indeed,
11 delayed closure was required in 83 of the 110
12 evaluable cases, a sort of measure of the critical
13 nature of the interventions conducted.

14 The assessment of the adhesion grade,
15 both severity and extent, was to be evaluated by a
16 member of the investigational site's surgical team,
17 masked for the arm to which the patient was
18 randomized. As reported by Dr. Xu, in fact for 13
19 re-operations in each study, an evaluation was
20 performed by the unmasked operators. The sponsor
21 and we have statistically demonstrated that this
22 balanced protocol deviation did not alter the

1 analysis of the device's performance, vis-a-vis the
2 control.

3 This slide, again, depicts the
4 randomization process. Seventy-three patients were
5 randomized to the treatment arm and seventy-one to
6 the control. A second operation, re-exploration
7 was not performed in 17 cases in each arm to leave
8 56 and 54 evaluable patients in the REPEL and
9 control arms, respectively. These are termed the
10 "intent-to-treat" cohort by the sponsor.

11 Patients explored in less than two
12 months were excluded for the protocol analysis of
13 54 REPEL and 49 control patients.

14 This slide summarizes the procedures
15 for assessing study safety, which the sponsor has
16 already discussed in great detail. All randomized
17 patients were included in this analysis. Two
18 randomization violations in the control arm were
19 excluded.

20 The primary effectiveness endpoint
21 captured both the extent and density of adhesions
22 in the retrosternal area of the heart, unprotected

1 by parietal pericardium. As previously noted,
2 study sample size was calculated for a projected
3 decrease in adhesion severity in the treatment arm
4 of at least 20 percent demonstrated with a power of
5 80 percent.

6 These are the secondary effectiveness
7 endpoints and these were not powered for a
8 hypothesis statistical evaluation. The percentage
9 of patients in whom the worst severity grade was
10 zero, or one, or two, and the mean of the areas in
11 each arm involved with a grade were captured as a
12 compliment to the primary effectiveness endpoint.

13 Additional secondary effectiveness
14 measurements were the time taken to lyse these
15 adhesions and the number of patients listed
16 according to the highest grade of adhesion
17 encountered.

18 I will now summarize the outcome of the
19 study. The adverse events recorded were consistent
20 with those encountered and reported for treatment
21 of these pediatric cardiac patients undergoing
22 several complex surgical intervention. The event

1 rates were essentially similar for the two study
2 arms and with a commendably low mortality. Events
3 were disease and intervention related, rather than
4 attributable to the device.

5 This, the adverse events here are those
6 we considered specifically related to the
7 procedure. The discrepant rate for the
8 mediastinitis and general concern on our part,
9 particularly, a severe mediastinitis was reported
10 for two REPEL cases in the second pilot study or
11 feasibility study, even those these were presumed
12 to be descriptive of inflammatory adhesions, rather
13 than infection.

14 The sponsor undertook additional
15 adjudication of these cases and claims the
16 incidence is comparable to that in literature
17 reports for multiple procedures in congenital
18 pathologies. The sponsor also maintains that
19 mediastinitis following the second sternotomy
20 should not be attributed to the REPEL-CV device and
21 that event rates for the two cohorts are not
22 statistically different, rather calculated only for

1 that occurring between the thoracotomies or when
2 that after the second procedure is also included.

3 The primary effectiveness endpoint
4 compared the mean percent area of myocardium at
5 risk that was involved with severe adhesions in the
6 two study arms. The 26 percent reduction in mean
7 percent of grade three adhesions for the treatment
8 group compared to the control statistically
9 achieves the projection for effectiveness used for
10 sample size calculation.

11 These graphs illustrate the secondary
12 endpoint that captured the distribution of patients
13 according to the highest grade of adhesion severity
14 that they exhibited. The distribution of grade
15 three adhesions is also included here. It should
16 be noted that when you combine grades two and
17 three, thus reverting to the three grade
18 classification as used in the feasibility study,
19 eliminates the substantial difference in adhesion
20 severity between the two study arms; 49 for the
21 REPEL case compared to 52 for the control patients.

22 The graphs in this slide depict the

1 means of the percentage areas for all the surgical
2 sites involved by each grade adhesion severity. As
3 shown, the areas of involvement with grade three
4 adhesions when it occurred was less extensive in
5 the treatment than in the control arm.

6 When mean areas for grade two and three
7 are once again combined, the REPEL arm maintains a
8 lesser surface area of adhesion involvement, 66
9 percent compared to 82.9 percent in the control
10 arm.

11 Another secondary effectiveness
12 endpoint is the dissection time. One would
13 anticipate that the extent and severity of
14 adhesions would be reflected in the required time
15 for freeing adhesions for surgical exposure. This
16 was not the case. The median time for the
17 dissecting the more extensive involvement with
18 grade three adhesions in the control arm did not
19 differ from that required by the less severely
20 involved REPEL patients. And we used a -- no, this
21 is correct. This was also the case for the
22 dissection of the less severe adhesions, as well as

1 the median dissection time for the entire cohort.

2 Now to go on with summary comments,
3 that was safety. The only safety issue to surface
4 was whether the mediastinitis encountered reflected
5 the possible adverse impact of introducing a
6 foreign body, the REPEL-CV membrane, to an
7 operative field, particularly one at heightened
8 risk for contamination for repeat interventions.

9 The effectiveness objective for
10 reduction in extent and severity of adhesions with
11 use of the device has been met. This however, did
12 not translate to a clear benefit in time required
13 for adhesion lysis and one may question if this
14 reflects on the discriminatory robustness of the
15 grading system or of the measuring instrument, that
16 of use of a sharp dissection.

17 In conclusion, here are some labeling
18 considerations that surfaced in the course of this
19 review. Can the results of a study restricted to
20 pediatric patients indeed be extrapolated to other
21 populations? The device has been studied as a
22 barrier for adhesions to myocardium unprotected by

1 parietal pericardium and not for other pericardium
2 applications, such as intrapericardial obliterative
3 adhesions. The label indication is all inclusive
4 for reducing post-operative adhesions for patients
5 undergoing cardiac surgery via sternotomy.

6 This concludes my review. Dr. Zhang
7 will now provide some epidemiological comments for
8 our post-market surveillance study. Thank you.

9 DR. ZHANG: Thank you, Dr. Sapirstein.
10 Good morning distinguished members of the panel and
11 members of the audience. I am Dr. Mingdong Zhang,
12 one of the epidemiologists in the office of
13 Surveillance and Biometrics.

14 As an epidemiologist in the PMA review
15 team, I am responsible for working with the sponsor
16 with the development of the post-approval study
17 protocol.

18 What you are about to see in my
19 presentation is based on the latest version of the
20 protocol we had. We continue to work with the
21 sponsor to develop protocol that both the FDA and
22 the sponsor will agree upon.

1 So first, I will describe the general
2 principles and objective for post-approval studies.
3 Then I will comment on the rationale for the
4 proposed post-approval study. I will follow with
5 a summary of the latest working of the sponsor's
6 study protocol and also present an assessment of
7 that protocol. I will conclude with the PAS issues
8 that we would like the panel to discuss in the
9 afternoon.

10 Before we talk about the post-approval
11 studies, we need to clarify that the discussion of
12 a post-approval study prior to your formal
13 recommendation on the approvability of this PMA
14 should not be interpreted to mean FDA is suggesting
15 that the panel find the device approvable. The
16 plan to conduct the PAS does not decrease the
17 threshold of evidence you required that you find
18 the device approvable.

19 The pre-market data submitted to the
20 Agency and discussed here today must stand on its
21 own in demonstrating a reasonable assurance of
22 safety and effectiveness in order for the device to

1 be found approvable.

2 These are the two general principles
3 for post-approval studies. The objective of a PAS
4 is to evaluate the device performance and potential
5 device-related problems in a broader population and
6 over an extended period of time after the pre-
7 market establishment of reasonable device safety
8 and effectiveness.

9 Post-approval studies must not be used
10 to evaluate unresolved issues from the pre-market
11 phase that are important to the initial
12 establishment of device safety and effectiveness.

13 Reasons for conducting post-approval
14 studies include gathering post-market information
15 on any of the following: (1) Longer-term
16 performance. (2) Data on how the device performs
17 in larger intended use populations who are treated
18 by average physicians as opposed to highly selected
19 patients treated by median physicians in clinical
20 trials. (3) Post-approval studies are also needed
21 to evaluate the effectiveness of training programs
22 for use of the devices. (4) Evaluation of the

1 device performance in sub-groups of patients,
2 since clinical the trials tend to have limited
3 number of patients which may not include all sub-
4 groups of general intended patient population. (5)

5 In addition, post-approval studies are needed to
6 gather real world experience and the monies for
7 adverse events, especially adverse events. (6)

8 Another reason for post-approval studies to address
9 issues and concerns that the panel members may
10 raise, based on their experience and observations.

11 These are the issues that we consider
12 as rationale for a possible proposed post-approval
13 study: Based on a review of the PMA and considering
14 that the REPEL-CV is the first of its kind of
15 device to be used in the U.S., if it gets approved,
16 we believe long-term safety profile, when used in
17 a larger number of individuals within the intended
18 population and conditions of general use, should
19 be considered in the post-approval study. One
20 specific issue the post-approval study could
21 address is the incidence of mediastinitis, as the
22 pre-market study was not powered to detect rare

1 events. Therefore, it is necessary to evaluate
2 what the incidence of mediastinitis is in the
3 larger patient population.

4 The pivotal study was statistically not
5 powered to detect the differences in the incidence
6 of mediastinitis between the REPEL-CV and control
7 groups.

8 This table presents an overview of the
9 latest study protocol submitted by the sponsor.
10 Currently, they propose a multi-center,
11 longitudinal, observational study with
12 historical/concurrent controls. There might be
13 some differences between what I had and the slides
14 the sponsor presented this morning because the
15 sponsor changed their presentation on PAS and we
16 didn't have that very latest version of the
17 sponsor's presentation.

18 The study population consists of
19 patients undergoing a single cardiac procedure.
20 The age group of the study population will be
21 defined by indication for use. Patients
22 receiving the device will be enrolled in up to

1 15 study centers in the U.S. The controls will
2 be gathered from the Society for Thoracic
3 Surgeons Registry, which is a U.S. and nation-
4 wide voluntary registry of cardiac procedures
5 in the U.S. The proposed sample size is 170
6 patients to be followed for eight weeks. And
7 the primary outcome is incidence of
8 mediastinitis.

9 Based on the information provided in
10 the protocol, the sponsor is believed to have
11 used of the following assumptions in the current
12 sample size calculations. A mediastinitis rate
13 of six percent in the REPEL-CV and two percent
14 in controls, a four percent non-inferiority
15 margin, and a one-sided test with alpha 0.05.
16 It should be noted that the REPEL-CV and the
17 control enrollment ratio is not specified in the
18 calculations.

19 The sponsor claims that 170 patients
20 provide 80 percent of power for the non-
21 inferiority hypothesis test. We, however, were
22 not able to replicate the calculation and to

1 verify the statistical power the sample size
2 provides. It should also be noted that
3 assumptions for the sample size calculations
4 were not clearly described in the protocol.

5 As I mentioned in the previous slide,
6 the sponsor proposes a non-inferiority design
7 with a four percent offset, with incidence of
8 mediastinitis in the controls at two percent.
9 The current protocol does not include clinical
10 justification for this non-inferiority margin.
11 Therefore, it is not clear if a four percent
12 difference is clinically significant.

13 In terms of the length of the follow-
14 up, the sponsor proposes eight weeks of follow-
15 up. There is no justification for this length
16 of follow-up. It is not clear if eight weeks
17 are sufficient to evaluate the long-term safety
18 performance.

19 And let me just ignore this slide,
20 since in this morning, the sponsor proposed to
21 not do an interim analysis.

22 As I said at the beginning of the

1 presentation, we continue to work with the
2 sponsor to develop an appropriate post-approval
3 study protocol. At this point, there are some
4 unresolved issues that we would like to have
5 panel members consider and make recommendations.

6 The first issue we would like the
7 panel members to consider is the primary study
8 endpoint. The sponsor agrees to use the
9 incidence of mediastinitis as the primary
10 endpoint in the PAS. We would like you to
11 discuss the advantages and disadvantages of
12 using mediastinitis as the main safety endpoint
13 versus using a composite safety endpoint in the
14 PAS.

15 The second is a non-inferiority
16 margin. The sponsor is proposing a non-
17 inferiority margin of four percent with the
18 incidence of mediastinitis in the controls at
19 two percent. We would like the panel members to
20 discuss if a four percent non-inferiority margin
21 is clinically relevant and an acceptable
22 difference margin to evaluate in the post-

1 approval study.

2 Finally, the duration of the follow-
3 up. The sponsor is proposing an eight week
4 follow-up of patients in the PAS. We would like
5 you to discuss what you think is appropriate as
6 a follow-up to assess long-term safety of this
7 device in the post-approval study.

8 This concludes my presentation, as
9 well as FDA's presentation this morning. We
10 welcome any questions you may have.

11 CHAIR YANCY: Thank you very much.
12 I would like to thank the FDA speakers for their
13 clear presentations and we would like to open up
14 questions for the panel. Let me advise the
15 panel that we have approximately 40 minutes
16 before we need to break for lunch.

17 There are two sets of issues that the
18 FDA has presented. The primary data that are
19 being used to support this PMA and then specific
20 questions about a potential post-marketing
21 study. So for clarify purposes, let's first of
22 all address any questions we have about the

1 primary data being used to support this PMA and
2 then we'll reserve time to raise questions about
3 the post-marketing study.

4 Dr. Somberg?

5 DR. SOMBERG: My question is for Dr.
6 Sapirstein. Maybe you could come up and fill me
7 in on the meeting between FDA and sponsor when
8 the primary, no, the pivotal study was put
9 together.

10 You said in your presentation that
11 the results of the pediatric population which
12 would permit a re-look within a reasonable
13 length of time could be extrapolated to a larger
14 population. At the end of your presentation,
15 you ask the question, is it extrapolatable to
16 the adult population. That's sort of like
17 taking both sides of an issue.

18 So when you met with the sponsor, I
19 take it you and the other members of the
20 clinical review team felt that it was
21 extrapolatable. And I was wondering, what
22 database do you base this on?

1 DR. SAPIRSTEIN: Well, this may sound
2 like a bit of an alibi. Our division became
3 involved with this at the PMA time frame, not at
4 the IEE approval time. But our feeling on
5 reviewing this was that based on the concept of
6 adhesions performance, we felt that this was not
7 related and could not be attributable to any age
8 differentiation and that adhesions occurring in
9 pediatric cases were very similar to adhesions
10 occurring in the adult environment.

11 We did not have the evidence for the
12 VAD, for instance, and the ventricular assist
13 device experience at the time, which showed an
14 adverse affect of prosthetic devices. In
15 adults, of course, is a possibility of large
16 amounts of prosthetic material, conduits, and so
17 forth.

18 So we may have been a bit too
19 presumptive at our initial acceptance of it.
20 We're not sure about it at this stage.

21 CHAIR YANCY: Dr. Zuckerman, please.

22 DR. ZUCKERMAN: I just want to

1 clarify with Dr. Somberg. He gave Dr.
2 Sapirstein an extremely difficult question to
3 start off with. Did you get a complete answer
4 to that relevant question? Dr. Patel is perhaps
5 in a position also where she can provide some
6 more information as to the history of this
7 application.

8 DR. SOMBERG: I was just trying to
9 fish out, as I asked the sponsor and I'm asking
10 the regulator as well, fish out what data there
11 exists on both sides to this issue of
12 correspondence between two to eight months worth
13 of adhesion development versus eight to twenty
14 or thirty years of adhesion development. And I
15 think we're here today to approve a device for
16 all comers and not just the pediatric
17 population.

18 So what I'm hearing is that the
19 review division really wasn't in on the planning
20 of the pivotal study. If that's what I heard
21 from Dr. Sapirstein, then that's a fair answer.

22 DR. ZUCKERMAN: The Division of

1 Cardiovascular Devices wasn't in, but we're here
2 to represent FDA today and we take
3 responsibility for the actions of FDA and
4 perhaps Dr. Patel, our lead reviewer and expert
5 on this file, can put things in the proper
6 context.

7 DR. PATEL: We did have a very
8 involved discussion with the sponsor regarding
9 their intent to request approval for the adult
10 populations. And we do acknowledge that we
11 approved the study for pediatrics. But the
12 sponsor was advised in a future concern that
13 their device would probably go to panel, or the
14 intent would be, they would go to panel if they
15 intended to ask for adult patients. So that was
16 a future concern to the sponsor.

17 CHAIR YANCY: Is that satisfactory?

18 (No response.)

19 CHAIR YANCY: Dr. Page?

20 DR. PAGE: Yes, my question also is,
21 my initial question was exactly what Dr. Somberg
22 questioned as well, but in terms of everything

1 hinges on the assessment of the degree of
2 adhesions. And specifically, the severe
3 adhesions. In discussions for developing this
4 study, was there any, what effort was made to
5 objectively assess the degree of adhesions?
6 Were maps, we saw one slide up of the surgical
7 field that we're specifically looking at.

8 Are there those maps to identify or
9 is this just kind of an eye-balling by the
10 surgeon? And my concern is, our decision as to
11 approvability hinges on the surgeon's
12 assessment, which as I see as extremely
13 subjective and I submit, I worry is not truly
14 blinded. Clearly a number were in an
15 acknowledged way un-blinded. But my concern is
16 that the surgeon operating there is, it was not
17 adequately blinded in terms of assessing whether
18 there had been intervention with this device.

19 And finally, in terms of this map, or
20 however the best effort to objectify what seems
21 to be a very subjective assessment is, are there
22 any data with regard to inter or intra-observer

1 variability of this?

2 And finally, this comes down to the
3 initial trial as it was being developed. Was
4 this issue discussed? Because subsequent to
5 those discussions, you went down a road and the
6 sponsor went down a road where I'm troubled by
7 the assessment for the endpoint, which is the
8 critical issue.

9 DR. SAPIRSTEIN: As you can probably
10 imagine, the FDA has had many trial designs come
11 in for adhesion barriers and adhesion protective
12 agents. And we have used many different means
13 of trying to assess the effectiveness of those
14 from imaging the adhesions at the time of
15 exposure, having separate evaluations, and
16 reviewing videotapes, and they have not provided
17 us with the robust diagnostic measuring
18 instrument we have sought. And we thought that
19 in this particular cohort of patients, would
20 prove a very accurate one, especially if
21 unmasked evaluations were to be conducted.

22 We realize, as some of our questions

1 have indicated, that it is indeed a soft
2 endpoint, a three grading changed to four
3 grading. You divided one grade into two, the
4 use of sharp dissection. And the surgeons know
5 here that once a surgeon picks up a scalpel,
6 he's unlikely to put it down. So, these are all
7 problems that have come up.

8 CHAIR YANCY: Let me remind panel
9 that even though I agree with this line of
10 discussion, this does have a longitudinal
11 history of about nine years. And so there have
12 been very, there have been quite a few
13 conversations held with the FDA between the FDA
14 and sponsor and involved a number of different
15 persons, all of whom may not be here. So, let's
16 keep that context.

17 Dr. Domanski?

18 DR. DOMANSKI: You know, I have, I
19 certainly agree that there are some issues that
20 relate to the primary endpoint, but I want to
21 address something else. You know, there are two
22 things that have to be done. One is, if

1 something is approvable, it should be approvable
2 based on the fact that not only is it effective,
3 but that it's safe. And I'm sort of, I'm
4 floating this also to think about. I'm not
5 saying, you know, I'm not trying to say that
6 this is the case yet, but I guess I'm a little
7 bit worried about the power to see safety
8 endpoints in this study.

9 I mean, it's clearly, it's a small
10 study. It's under power to see clinical
11 endpoints, clearly. But I'm worried that it may
12 be under power to see the clinical safety
13 endpoints, too. I mean, the only signal that we
14 see in the whole thing is mediastinitis. And I
15 know it's not statistically significant, but
16 could it have been?

17 I mean, I wonder what the power to
18 see a difference in mediastinitis was. And of
19 course, it's going to end up being very low, but
20 I'd like to hear the number. I mean, what would
21 we have to do to actually see something wrong
22 with this device, in terms of safety?

1 My concern is that in addition to the
2 efficacy endpoint being soft and all this kind
3 of stuff, that the safety endpoint is totally
4 inadequate to make this determination. That's
5 the question I'm raising. I'm not saying it's
6 so, but that's the question that I want this
7 learned group, including the FDA staff to
8 address.

9 CHAIR YANCY: So this question is
10 directed to the FDA and the sponsor can respond
11 this afternoon.

12 DR. DOMANSKI: It's key, by the way,
13 because our job is not to be fair to the
14 sponsor. Our job is to do the appropriate thing
15 for the public. And if one of the two has to be
16 sacrificed, it's clear who that is.

17 So, I'd like to know whether this
18 trial could have ever demonstrated a safety
19 difference.

20 CHAIR YANCY: So to put this question
21 in context, it's directed towards FDA and the
22 question is, can our FDA cohort comment on the

1 statistical power of the study design?

2 DR. DOMANSKI: And specifically for
3 safety. I mean we're seeing a small signal. I
4 mean, how big a signal would we have needed to
5 say the mediastinitis was too frequent? I think
6 that's a statistical question for the
7 statisticians from FDA first.

8 DR. XU: I'm not the original person
9 working on the IDE, but when I look at this kind
10 of a protocol, for the safety, there is only one
11 calculation for the power for the mortality.
12 For this size of this study have 80 percent of
13 a power to show non-inferiority is a risk back
14 to the mortality with a margin of 19 percent.
15 But there is no calculation on the others.

16 DR. DOMANSKI: Yes. What about, but
17 yes, and mortality would be important. So the
18 answer to, part of the answer to my question is
19 that for mortality, you know, they have
20 reasonable power is the way I'm hearing this.
21 But what about for other major complications?
22 For instance, mediastinitis? What was the power

1 in this trial?

2 DR. XU: Because I think, at that
3 time, I don't know for whatever the reason,
4 there is no actually pre-specified even primary
5 safety endpoint. There is only all their
6 adverse events, as they called it as appropriate
7 in those events. So no calculation for the
8 power to detect any clinical meaningful
9 difference in the adverse events.

10 DR. DOMANSKI: Okay. So, I'm going
11 to summarize my concern and then shut up. My
12 concern is that this trial was inadequately, may
13 have been inadequately, may have been,
14 inadequately designed to assess safety. And if
15 that's the case, then you know, you just don't
16 have a trial. That's what I want to talk about.

17 CHAIR YANCY: So we would appreciate
18 the sponsor giving us a response in the
19 afternoon when it's your opportunity to speak.
20 But the question that was posed has to do with
21 power and so there may be some other opinions
22 around the table to contribute here.

1 I think Dr. Zahka, do you have been
2 holding for some time.

3 DR. ZAHKA: I would just like to
4 change directions for a little bit and this is
5 a statistical question.

6 The real issue here is does this make
7 the operation, the subsequent operation safer
8 for the children? I think everybody in this
9 room has already figured out that this is the
10 ultimate high wire act in congenital heart
11 surgery. And so what we need to do is, I think,
12 focus on is there any statistical power to
13 figuring out why the time to dissection, why the
14 event rate at the subsequent operations was
15 comparable in both groups. And one of the
16 things that the sponsor presented was that there
17 was a lot of variability from institution to
18 institution. And is there enough statistical
19 power left to break it down by institution to
20 look at, for an individual surgeon, whether in
21 fact this device proved beneficial for the
22 individual surgeon.

1 CHAIR YANCY: And so again, that is
2 a question for the FDA to attempt to address and
3 the sponsor can follow later.

4 DR. XU: As I just said, I mean, this
5 study is not powered to detect any difference
6 within centers. It is only powered to detect an
7 overall difference, as specified in the slide.

8 CHAIR YANCY: So what I'm hearing is
9 that as best as FDA can determine, the study was
10 powered presumably for the primary endpoint,
11 which is looking at the percent of adhesion.
12 And these other questions that have come up
13 regarding power for safety or for an individual
14 surgeon or by site, remain questions that have
15 to be resolved. Is that fair?

16 DR. XU: Yes. I mean, that is not a
17 consideration, I believe, at that time.

18 CHAIR YANCY: Okay, thank you.

19 Dr. Jeevanandam.

20 DR. JEEVANANDAM: I have three
21 questions. When Dr. Patel put up her slides,
22 she showed us a picture of what appeared to be

1 a map. Were those maps actually done? Were
2 pictures taken of the chest and was there a
3 percentage of adhesions that was done? Because
4 that's not unreasonable to do. I mean, once a
5 surgeon takes down the heart's adhesions, you
6 can take a picture and you can map out where the
7 intense adhesions were and that would be a
8 little bit more objective than the
9 subjectiveness that we have right now.

10 DR. PATEL: To our knowledge, that
11 was our interpretation of the investigational
12 surgical site. And as I noted before, we did
13 request photos from the sponsor for that region,
14 but to our knowledge, there was no mapping of
15 the area or photos.

16 DR. JEEVANANDAM: Okay, thanks.

17 I guess my other question is, you
18 know, we were focused on the safety issue of
19 mediastinitis. But I'm looking through this
20 folder which is, I guess the folder that we all
21 have, and I'm going to page 27. So if you look
22 at all the adverse events, you know, other than

1 mediastinitis, I think another adverse event
2 that we need to pay attention to is mediastinal
3 bleeding and mediastinal hematoma and need for
4 re-ops.

5 And I know this isn't powered, but
6 there are these trends that a little bit
7 worrisome. There is a trend towards
8 mediastinitis and if you look at respiratory
9 thoracic and mediastinal disorders, you know,
10 again, there is more mediastinal hemorrhage,
11 there is mediastinal hematoma, there is
12 mediastinal disorder NOS, I don't know exactly
13 what that stands for. But again, there are more
14 trends towards it on this side.

15 So that may be an other signal. You
16 know, you put a foreign body in the chest and
17 then you kind of close and there is potential to
18 have more hemorrhage because you prevent the
19 blood from being sucked out of chest tubes,
20 etcetera. So I think from a safety point of
21 view, that's another thing that one needs to pay
22 attention to.

1 My third point, and I just bring this
2 up, you know, we're doing a study here in
3 neonates. Neonates have a totally different
4 immunological system. They have very very
5 little fat on their hearts. Their hearts are
6 extremely, I mean, you can almost do anything
7 you want to their heart and they'll do okay.
8 You cannot apply that, I think, to a 70 year old
9 heart.

10 CHAIR YANCY: There was a bit of a
11 shudder in the room.

12 (Laughter.)

13 DR. JEEVANANDAM: And you know, I've
14 operated on both sides of the fence there and,
15 you know, the only data that we have right now
16 is that they have had two LVAD patients who have
17 had a lot of adhesions. And that was actually
18 reported as an adverse event. And those are the
19 only two adults that we actually have data on.

20 Now, I understand that around where
21 the graft is, maybe the REPEL broke apart
22 because of the graft pounding against the chest

1 wall. But that doesn't mean that the REPEL
2 didn't exist outside the chest wall as well. So
3 you should have had at least less adhesions
4 there and it shouldn't be reported as an adverse
5 event.

6 So again, you know, the only data
7 that we have with adults is not great and so
8 we're really extrapolating a lot to go to an
9 adult. And that would be my concern.

10 CHAIR YANCY: So we will continue to
11 save those perspectives for the afternoon.

12 Dr. Blackstone?

13 DR. BLACKSTONE: Yes, I'd like to
14 amplify the comments on mediastinal problems by
15 giving the FDA or the sponsor the list of four
16 patients in the control group and six patients
17 in the REPEL-CV group that, according to section
18 nine, have some mediastinal problems.

19 My interpretation of those problems
20 is that the six that I see in the REPEL-CV, as
21 opposed to the four that were presented, are
22 systematically more severe than the four that

1 are listed in the control patients; which
2 includes, for example, in the control patients,
3 some superficial, perhaps superficial,
4 mediastinal problems. But nevertheless, it's
5 the mediastinum where this foreign body is and
6 where we need to be thinking.

7 And perhaps during the lunch break,
8 someone can look at those total of ten cases and
9 tell us a little bit about why they were or
10 weren't counted as mediastinitis. We had a
11 slide that gave a surgical definition of
12 mediastinitis, not a CDC definition of
13 mediastinitis and sort of swept under the rug,
14 just as you say, a number of mediastinal
15 problems that may be pertinent.

16 CHAIR YANCY: Does FDA have a
17 comment? If not, we can go to the next
18 question.

19 DR. SAPIRSTEIN: We reviewed the line
20 listing for patients and the adverse events that
21 you have mentioned, Dr. Blackstone, we did not
22 consider to be mediastinal infections, i.e.,

1 mediastinitis. We found them to be related to
2 the procedure where there was bleeding from a
3 suture line or bleeding or some such thing, or
4 poor performance of a conduit, or something like
5 that.

6 And that's our basis for agreeing
7 with the listing of mediastinal involvement.

8 CHAIR YANCY: Dr. Hirshfeld and then
9 Dr. Weinberger.

10 DR. HIRSHFELD: We have been puzzled
11 by the lack of the difference in dissection
12 times in the two groups. And I'm wondering, it
13 appears that the answer may be in Dr.
14 Sapirstein's slide number 53, where he showed
15 that in the cohort of patients who received the
16 REPEL-CV who had grade three adhesions, that
17 they had the longest dissection times by far.
18 They had an average dissection time of 38
19 minutes, whereas the control population, who had
20 grade three adhesions, had a dissection time of
21 23 minutes.

22 And then in the cohorts who had the

1 lesser grade of dissections, both had short
2 dissection times at 13 and 14 minutes.

3 So, I think that raises the question
4 as to whether if one receives this device and
5 has the bad fortune to develop grade three
6 adhesions, whether they're actually worse and
7 technically more difficult to lyse than the
8 grade three adhesions that occur spontaneously
9 without the device.

10 CHAIR YANCY: Dr. Hirshfeld, let us
11 put that slide back up and if FDA can perhaps
12 tell us what the standard deviation is on those
13 numbers, that would be helpful.

14 DR. SAPIRSTEIN: These are the median
15 times for dissection. I don't have the standard
16 errors or the standard deviations. I'm sorry.

17 CHAIR YANCY: Okay. That's
18 acceptable. If there are not any other
19 questions along this line of thought, we'd like
20 to spend a few minutes discussing the post-
21 marketing study.

22 Dr. Hopkins?

1 DR. HOPKINS: One quick question for
2 FDA statistical analysis. During the lunch
3 break, would it be possible using a four percent
4 difference as recommended as the delta and a two
5 percent difference as an optimal to in fact
6 calculate for us a sample size to establish
7 power, so that we have some idea of the
8 disparity between what was feasible in this
9 study and what would be required to actually
10 power up to show a difference in mediastinitis,
11 or have you done that calculation?

12 DR. XU: Let me just clarify your
13 question. Are you asking for, you mean for the
14 post-approval study or the regional study?

15 DR. HOPKINS: No. I'm saying we have
16 data in which you can make estimates of the
17 means and the standard deviations. And we have
18 a delta proposed of four percent. You have all
19 the data that you would need to calculate a
20 power sample size population for a 0.05 alpha
21 and an 80 percent beta. So, could you just tell
22 us how many patients it would take to show that

1 difference?

2 DR. XU: Oh, you mean for a
3 randomized controlled trial?

4 DR. HOPKINS: Yes, absolutely. Just
5 call it up on the computer and plug the values
6 in and tell us.

7 DR. DOMANSKI: Could I just, since I
8 brought that up, can I just add one thing to
9 that? I recognize also that where complications
10 are relatively rare, you can reach a point where
11 it's very hard to climb the hill for a specific
12 one. What in addition would be interesting to
13 see is if you combine, you know, when you do an
14 endpoint like this, you usually try to put
15 together all of the serious things, death,
16 mediastinitis, and perhaps, you know, we should
17 come up with a couple of others, because it
18 would be interesting to ask the FDA.

19 I don't want to make the hill so high
20 to climb that no one can climb it. I'm just
21 wondering about if you look at serious things, -
22 -

1 DR. HOPKINS: That's my point in
2 terms of the charge.

3 DR. DOMANSKI: Yes.

4 DR. HOPKINS: If we're going to focus
5 on mediastinitis, we have a preliminary study
6 and we also have data from the STS database that
7 gives us the means and standards deviations, the
8 variability. We need to know what is feasible
9 to ask the sponsor to do. If it's 2000 patients
10 per arm, that's one thing. But if it's 175,
11 that's a calculation that can be done.

12 CHAIR YANCY: So --

13 DR. HOPKINS: But you have to --

14 DR. DOMANSKI: You have to tell him
15 one other thing, though. You have to tell him
16 what is a clinically significant difference if
17 you're going to ask him at all.

18 DR. HOPKINS: Well, they picked a
19 delta of four percent.

20 DR. DOMANSKI: Oh, okay.

21 CHAIR YANCY: So, gentlemen.

22 Gentlemen.

1 DR. HOPKINS: The delta is four
2 percent.

3 CHAIR YANCY: Gentlemen. Where we
4 are right now is that we have proposed a
5 theoretical question to FDA about looking at the
6 original data submission and giving us a
7 retrospective view of whether or not the power
8 that was anticipated reflects what we would
9 calculate in light of the event rate that we now
10 see. And we all understand that that's a
11 compromised approach. But nevertheless, if you
12 have the time and can provide that, we accept
13 it. But if you don't, we understand that.

14 But this is an important segue. You
15 can have a seat, thank you. It is an important
16 segue to get to the post-marketing study. But
17 I want to recognize Dr. Weinberger, who has been
18 holding a question, and then see if we can
19 discuss the post-marketing study.

20 DR. WEINBERGER: One of the recurring
21 themes has been the issue about extrapolating
22 from the pediatric population to the adult

1 population. And the very modest data that we
2 have was all in the feasibility studies. And
3 throwing away the LVAD patients, there were
4 patients who get typical adult operations there,
5 the CABG patients.

6 I would like to know if any analysis
7 was done by the FDA on the safety issues that
8 emerge from that very meager cohort of adult
9 patients. I saw that the sponsor reported that
10 two of the deaths were in CABG patients. As an
11 adult cardiologist, I wonder if putting a
12 membrane there will kink graft, will cause any
13 graft problems that are new or novel that would
14 not occur in the pediatric population.

15 So, is there any information from the
16 FDA's analysis of the feasibility studies, of
17 the adverse events in the feasibility studies?
18 Was attention paid to that? I know we didn't
19 discuss anything at all about an analysis of the
20 feasibility studies. We sort of posited that
21 they showed feasibility. But was there any
22 analysis done on those studies? Do we have

1 information? Because the FDA bought into this
2 pediatric to adult shunt in past years.

3 MR. HILLEBRENNER: Hi. My name is
4 Matt Hillebrenner and I am Chief of the
5 Circulatory Support and Prosthetics Branch where
6 this file was reviewed. And I just wanted to
7 clarify a couple of things. I think based on
8 our review of the feasibility data and some of
9 the safety concerns that were outlined with the
10 adult patients, in addition to some of the
11 practical concerns which, I think everyone here
12 agreed with designing a trial like this and
13 needing that second surgery, we recognize that
14 doing a study like this in this specific
15 pediatric population may have been the only way
16 to have finished that study. However, at the
17 time, we did make it clear to the sponsor that
18 there may be concerns raised with extrapolating
19 that data to an adult population.

20 So I don't, I mean, I think that's
21 one of the, as you know, from our panel packet,
22 that's one of the big questions that we're

1 looking for your help with because it is
2 difficult for us to make that extrapolation,
3 since we don't have the data in our hands. But
4 I don't want you to misinterpret that the
5 willingness to go forward with the study as
6 saying we think we can make that leap.

7 And to answer your specific question,
8 I don't believe we have any very detailed
9 analysis of the feasibility data. I think we
10 share some of the concerns regarding some of the
11 events that we're seeing and we don't
12 necessarily know what the effectiveness of the
13 device would be in that population, nor
14 applicability to a patient population that may
15 not be undergoing another surgery.

16 CHAIR YANCY: Dr. Somberg.

17 DR. SOMBERG: Well, I'm going to make
18 you happy, Dr. Yancy, I would like to go to the
19 second part of your sequence here and that is to
20 talk about the post marketing study. If that's
21 what -- that's my question for --

22 CHAIR YANCY: I actually think Dr.

1 Weinberger helped us introduce that.

2 DR. SOMBERG: Okay, good.

3 CHAIR YANCY: Because a post-
4 marketing study would be all ages.

5 DR. SOMBERG: I just wanted to know
6 if that's okay to move on to that.

7 And my sort of question observation
8 is that exactly what has been addressed here is
9 that I do not know why both the sponsor and the
10 FDA immediately gravitated to mediastinitis
11 which, at one point, is not significant, but
12 another point is yes, let's power a study to
13 look at that in a very small study.

14 So I would think, and I would put
15 this in the form of a question. Wouldn't it be
16 sort of optimum from a regulatory point of view
17 to look at number one a large enough population
18 to yes, you have a point estimate on a number of
19 important areas of toxicity, blood loss,
20 surgical time, and adversities like
21 mediastinitis and death as well.

22 And I wouldn't necessarily want to

1 combine them in a composite endpoint, because I
2 would like to be able to look at each
3 individual one. And then I would say, is we
4 have to have some sort of safety and hopefully
5 some efficacy in the adult population.

6 And I think we have to grapple at
7 some point today. And there are certainly many
8 more people who are expert in cardiothoracic
9 surgery than I here to address that. But all
10 patients are not the same. And I've seen
11 patients with constrictive pericarditis, or
12 constriction after surgery that needed re-
13 operation, etcetera, and then what do you do at
14 that point? You know, do they come to another
15 operation sometimes? There are some people who
16 are more aggressive in their inflammatory
17 response to a sternotomy. I have had one
18 patient that had multiple.

19 So could we not find, and this is a
20 question once again to the FDA and to the
21 sponsor, could we not find in a post-marketing
22 environment, a sub-section of the total universe

1 of patients that might be applicable here that
2 for some reason or another have unusual
3 responses and we could get, number one an
4 efficacy signal, and could we not define a study
5 in adults where we at least have a safety signal
6 for the first operation and for the first year
7 following it, when troubles can develop with
8 this type, as Judah said, with kinking of grafts
9 or pericardial constriction, etcetera.

10 So I'm saying is we need a larger
11 study. We need a study in adults and we need to
12 be able to look for a safety signal and, if
13 possible, an efficacy signal.

14 CHAIR YANCY: I respect your
15 insights. Let me just remind panel that the
16 post-approval study is an issue that we will
17 deliberate and it is not a foregone conclusion
18 that we have decided what the primary endpoint
19 will be. And so there is an opportunity to
20 discuss whether it will be mediastinitis alone,
21 a composite safety endpoint, or some other
22 metric, as FDA has already prompted us. And

1 we'll also have to discuss margins we use a non-
2 inferiority endpoint.

3 Let me also remind panel that this
4 application has to be approved based on
5 available evidence with regards to reasonable
6 safety and efficacy in what we already see. We
7 can't presume that the post-approval study is to
8 provide the additional comfort. It needs to be
9 a stand alone initiative. And so if we can keep
10 our trains of thought clear in that regard, that
11 would be, I think, most appropriate.

12 We need to have a statistical
13 statement from Dr. Neaton.

14 DR. NEATON: Actually, I have a
15 question for the FDA statisticians who looked at
16 this. They relate to the, again, going back to
17 the primary endpoint in the pivotal study. I
18 share the concern that was mentioned earlier
19 about how well was the blind maintained? Is
20 there any data that you were provided or that
21 exists on the maintenance of the blind, quite
22 apart from the analysis of those assessments