

U.S. FOOD AND DRUG ADMINISTRATION

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CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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MEETING

+ + + + +

WEDNESDAY, SEPTEMBER 19, 2007

+ + + + +

The meeting convened at 8:00 a.m.  
at the Hilton Washington DC  
North/Gaithersburg, 620 Perry Parkway,  
Gaithersburg, Maryland, Clyde W. Yancy, M.D.,  
Acting Chairperson, presiding.

PRESENT:

CLYDE W. YANCY, M.D., Acting Chairperson

MICHAEL J. DOMANSKI, M.D., Voting Member

JOHN W. HIRSHFELD, M.D., Voting Member

RICHARD L. PAGE, M.D., Voting Member

JOHN C. SOMBERG, M.D., Voting Member

JUDAH WEINBERGER, M.D., Voting Member

EUGENE H. BLACKSTONE, M.D., Consultant

RICHARD HOPKINS, M.D., Consultant

VALLUVAN JEEVANANDAM, M.D., Consultant

MARC KATZ, M.D., Consultant

JAMES NEATON, Ph.D., Consultant

PRESENT (CONTINUED):

KENNETH ZAHKA, M.D., Consultant

MARCIA S. YAROSS, Ph.D., Industry

Representative

LINDA MOTTLE, M.S.M., R.N., C.C.R.P., Consumer  
Representative

FDA PARTICIPANTS:

GERRY GRAY, Ph.D. Associate Director, Division  
of Biostatistics

MATTHEW HILLEBRENNER, M.S.E.

SONNA PATEL, Ph.D., Division of Cardiovascular  
Devices

WOLF SAPIRSTEIN, M.D., Division of  
Cardiovascular Devices

JAMES P. SWINK, Panel Executive Secretary

GERETTA WOOD, Director, Advisory Panel Program

YUNLING XU, Ph.D., Division of Biostatistics

MINGDONG ZHANG, M.D., M.P.H., Ph.D., Division  
of Epidemiology

BRAM ZUCKERMAN, M.D., Director, Division of  
Cardiovascular Devices

SPONSOR PRESENTERS:

JAMES M. ANDERSON, M.D., Ph.D., Case Western  
Reserve University

CARL LEWIS BACKER, M.D., Children's Memorial  
Hospital and Northwestern University Medical  
School

SPONSOR PRESENTERS (CONTINUED):

DANIEL COHN, Ph.D., The Hebrew University of  
Jerusalem

GERE dizEREGA, M.D., USC School of Medicine

PHILIP T. LAVIN, Ph.D., Averion International  
Corporation

JAMES E. O'BRIEN, JR. ,M.D., University of  
Missouri School of Medicine and Children's

Mercy Hospital

ELI PINES, Ph.D., Vice President and Chief  
Scientific Officer, SyntheMed, Inc.

SAMUEL WEINSTEIN, M.D., Albert Einstein  
College of Medicine

PUBLIC SPEAKERS:

PETER LURIE, M.D., M.P.H., Health Research  
Group, Public Citizen

C O N T E N T S

PAGE

Call to Order..... 5

Conflict of Interest and Deputization to  
Voting Member Status Statements..... 8

Panel Introductions..... 13

First Open Public Hearing..... 13

Sponsor Presentation..... 18

Sponsor Q & A..... 80

FDA Presentation.....136

FDA Q & A.....169

Panel Deliberations.....239

FDA Questions.....369

Second Open Public Hearing.....379

FDA and Sponsor Summations.....385

Panel Vote.....443

Wrap Up and Adjourn.....358

1 P-R-O-C-E-E-D-I-N-G-S

2 (8:03 a.m.)

3 CHAIR YANCY: Good morning. My  
4 name is Clyde Yancy. I am the Medical  
5 Director of the Baylor Heart and Vascular  
6 Institute at Baylor University Medical Center  
7 in Dallas, Texas. And I am chairing this  
8 morning the Circulatory System Devices Panel  
9 and I am calling the meeting to order.

10 If you haven't already done so,  
11 please sign the attendance sheets that are on  
12 the tables by the doors. If you wish to  
13 address this panel during one of the open  
14 sessions, please be certain that you have  
15 given your name to Ms. Anne Marie Williams at  
16 the registration table. This is very  
17 important. Again, if you plan to address this  
18 panel, please be certain to give you name to  
19 Ms. Williams. If you are presenting in any of  
20 the open public sessions today, we need an  
21 electronic copy of your presentation and that,  
22 likewise, must be given to Ms. Williams.

1           I note for the record that the  
2           voting members present constitute a quorum, as  
3           required by 21 C.F.R. Part 14. I would also  
4           like to add that the panel participating in  
5           the meeting today has received training in FDA  
6           device law and regulations.

7           If you have an electric device,  
8           please put it on vibrate or silence, so as not  
9           to disturb the meeting.

10           Mr. Swink, our Executive Secretary  
11           for the Circulatory System Device Panel will  
12           make some introductory remarks. Thank you.

13           MR. SWINK: I'll read the conflict  
14           of interest statement.

15           "The Food and Drug Administration  
16           is convening today's meeting of the  
17           Circulatory System Devices Panel of the  
18           Medical Devices Advisory Committee of the  
19           Center for Devices and Radiological Health  
20           under the Authority of the Federal Advisory  
21           Committee Act of 1972. With the exception of  
22           the industry representative, all members and

1 consultants of the panel are special  
2 government employees or regular federal  
3 employees from other agencies and are subject  
4 to federal conflict of interest laws and  
5 regulations.

6 The following information on the  
7 status of this panel's compliance with federal  
8 ethics and conflict of interest laws covered  
9 by, but not limited to those found at 18  
10 U.S.C. Section 208 are being provided to  
11 participants in today's meeting and to the  
12 public.

13 FDA has determined that members  
14 and consultants of this panel are in  
15 compliance with federal ethics and conflicts  
16 of interest laws. Under 18 U.S.C. Section  
17 208, Congress has authorized the FDA to grant  
18 waivers to special government employees who  
19 have financial conflicts when it is determined  
20 that the Agency's need for a particular  
21 individual's services outweighs his or her  
22 potential financial conflicts of interest.

1                   Related to discussions of today's  
2                   meeting, members and consultants of this panel  
3                   who are SGEs have been screened for potential  
4                   financial conflicts of interests of their own,  
5                   as well as those imputed to them, including  
6                   those of their employer, spouse, or minor  
7                   child. These interests may include  
8                   investments, consulting, expert witness  
9                   testimony, contracts, grants, CREDAs,  
10                  teaching, speaking, writing, patents royalties  
11                  and primary employments.

12                  Today's agenda involves the review  
13                  and discussion of a pre-market approval  
14                  application sponsored by SyntheMed, formerly  
15                  known as Life Medical Sciences, for the REPEL-  
16                  CV, which is a surgical adjuvant indicated for  
17                  reducing the incidence, severity, and extent  
18                  of post-operative adhesion formation in  
19                  patients undergoing cardiac surgery.

20                  Based on the agenda of today's  
21                  meeting and all financial interest reported by  
22                  the panel members and consultants, no

1 conflicts of interest waivers have been issued  
2 in connection with this meeting.

3 A copy of this statement will be  
4 available for review at the registration table  
5 during this meeting and will be included as  
6 part of the official transcript.

7 Marcia S. Yaross, Ph.D. is serving  
8 as the industry representative, active on  
9 behalf of all related industry and is employed  
10 by Biosense Webster, a Johnson and Johnson  
11 company.

12 We would like to remind members  
13 and consultants that if the discussions  
14 involve any other products or firms not  
15 already on the agenda for which the FDA  
16 participant has a personal or imputed  
17 financial interest, that participants need to  
18 exclude themselves from such involvement and  
19 their exclusion will be noted for the record.

20 FDA encourages all other  
21 participants to advise the panel of any  
22 financial relationships that they may have

1 with any firms at issue."

2 I'll read the temporary members  
3 voting statement.

4 "Pursuant to the authority granted  
5 under the medical device advisory committee  
6 charter of the Center for Devices and  
7 Radiological Health dated October 27, 1990 and  
8 as amended August 18, 2006, I appoint James D.  
9 Neaton, Ph.D. as a voting member of the  
10 Circulatory System Devices Panel for the  
11 duration of this meeting on September 19,  
12 2007.

13 For the record, Dr. Neaton serves  
14 as a consultant to the Cardiovascular and  
15 Renal Drugs Advisory Committee of the Center  
16 for Drug Evaluation and Research. He is a  
17 special government employee who has undergone  
18 the customary conflict of interest review and  
19 has reviewed the material to be considered at  
20 this meeting."

21 This is signed by Randall W.  
22 Lutter, Deputy Commissioner for Policy and

1           dated August 22, 2007.

2                       Pursuant to the authority granted  
3           under the Medical Devices Advisory Committee  
4           Charter of the Center for Devices and  
5           Radiological Health dated October 27, 1990 and  
6           as amended August 18, 2206, I appoint the  
7           following individuals as voting members of the  
8           Circulatory System Devices Panel for the  
9           duration of this meeting on September 19,  
10          2007. Michael J. Domanski, John W. Hirshfeld,  
11          Judah Z. Weinberger, Valluvan Jeevanandam,  
12          Eugene Blackstone, Kenneth Zahka, Richard  
13          Hopkins, and Marc Katz.

14                      For the record, these individuals  
15          are special government employees and are  
16          consultants to this panel under the Medical  
17          Devices Advisory Committee. They have  
18          undergone the customary conflict of interest  
19          review and have reviewed the material to be  
20          considered at this meeting.

21                      In addition, I appoint Clyde W.  
22          Yancy, M.D. to act as a temporary chairperson

1 for the duration of this meeting."

2 This was signed by Daniel G.  
3 Shultz, M.D., Director, Center for Devices and  
4 Radiological Health and dated on August 22,  
5 2007.

6 Before I turn the meeting back  
7 over to Dr. Yancy, here are a few general  
8 announcements.

9 The transcripts of today's meeting  
10 will be available from Neal Gross and  
11 Company. Information on purchasing videos of  
12 today's meeting can be found on the table  
13 outside of the meeting room. And presenters  
14 of the panel who have not already done so,  
15 shall provide FDA with hard copies of their  
16 remarks, including overheads.

17 Thank you very much.

18 CHAIR YANCY: Good morning again.  
19 At this meeting, the panel will be making a  
20 recommendation to the Food and Drug  
21 Administration on the pre-market approval  
22 application, PMA P070005 for the REPEL-CV

1 Bioresorbable Adhesion Barrier Film. The  
2 REPEL-CV is a surgical adjuvant indicated for  
3 reducing the incidence, severity, and extent  
4 of post-operative adhesion formation in  
5 patients undergoing cardiac surgery via  
6 sternotomy.

7 Before we begin, I would like to  
8 ask our panel members, who are generously  
9 giving their time today and other FDA staff  
10 seated at this table to introduce themselves.  
11 Please state your name, your area of  
12 expertise, your position and affiliation. And  
13 we'll start with Dr. Zuckerman.

14 DR. ZUCKERMAN: Good morning.  
15 Bram Zuckerman, Director, FDA Division of  
16 Cardiovascular Devices.

17 DR. HIRSHFELD: John Hirshfeld.  
18 I'm an interventional cardiologist. And I'm  
19 at the University of Pennsylvania, which is  
20 different than what it says on the panel  
21 roster. I do not live in St. Louis. So,  
22 we're Philllies' fans, rather than the

1 Cardinals' fans.

2 CHAIR YANCY: My daughter just  
3 went to Wash U., so I'm a Cardinals' fan now.

4 DR. DOMANSKI: I'm Mike Domanski.  
5 I am an interventional cardiologist as well.  
6 I'm at the National Heart, Lung, and Blood  
7 Institute and I'm Chief of the  
8 Atherothrombosis and Coronary Artery Disease  
9 Branch.

10 DR. WEINBERGER: I'm Judah  
11 Weinberger. I'm at Columbia University and  
12 I'm an interventional cardiologist as well.

13 DR. SOMBERG: I'm John Somberg,  
14 Professor of Medicine and Pharmacology, Rush  
15 University, Chicago, Illinois.

16 DR. PAGE: Richard Page. I'm a  
17 cardiologist electrophysiologist. I am Head  
18 of Cardiology at the University of Washington  
19 in Seattle.

20 MR. SWINK: James Swink, Executive  
21 Secretary for this meeting.

22 DR. NEATON: I'm Jim Neaton,

1 Professor of Biostatistics for the University  
2 of Minnesota.

3 DR. BLACKSTONE: Eugene  
4 Blackstone, Head, Clinical Research,  
5 Department of Thoracic Cardiovascular Surgery,  
6 Cleveland Clinic.

7 DR. JEEVANANDAM: Vall  
8 Jeevanandam. I'm a cardiac surgeon. I'm the  
9 Chief of CT Surgery at the University of  
10 Chicago.

11 DR. ZAHKA: Ken Zahka, Director of  
12 Pediatric Cardiology, Case Western Reserve  
13 University.

14 DR. KATZ: Marc Katz, I'm a  
15 cardiac surgeon and Medical Director of the  
16 Bon Secours Heart and Vascular Institute in  
17 Richmond, Virginia.

18 DR. HOPKINS: Richard Hopkins, it  
19 says I'm at Brown University, which I was for  
20 11 years, but I have just recently left and am  
21 Director of Cardiovascular Research and Chief  
22 of the Adolescent Adult Cardiac Reconstructive

1 Cardiac Surgery Program at Children's Mercy  
2 Hospital in Kansas City.

3 DR. YAROSS: Marcia Yaross, Vice  
4 President, Clinical Quality Regulatory and  
5 Health Policy at Biosense Webster in Diamond  
6 Bar, California, and industry representative  
7 to the panel.

8 MS. MOTTLE: Linda Mottle,  
9 Director for the Center for Healthcare  
10 Innovation and Clinical Trials at ASU,  
11 Consumer Rep.

12 CHAIR YANCY: Thank you very much.  
13 We obviously have a very distinguished panel  
14 and I appreciate your presence.

15 We will now proceed with the open  
16 public hearing portion of the meeting.

17 Both the Food and Drug  
18 Administration and the public believe in a  
19 transparent process for information gathering  
20 and decision making. To ensure such  
21 transparency at the open public hearing  
22 session of the Advisory Committee meeting

1           today, FDA believes that it is important to  
2           understand the context of any individual's  
3           presentation. For this reason, FDA encourages  
4           you, the open public hearing speaker or  
5           industry speaker at the beginning of your  
6           written or oral statement, to advise the  
7           committee of any financial relationship that  
8           you may have with the sponsor, its product  
9           and, if known, its direct competitors. For  
10          example, this financial information may  
11          include the sponsor's payment of your travel,  
12          lodging, or other expenses in connection with  
13          your attendance at the meeting.

14                       Likewise, FDA encourages you, at  
15          the beginning of your statement, to advise the  
16          committee if you do not have such financial  
17          relationships. If you choose not to address  
18          the issue of financial relationships at the  
19          beginning of your statement, it will not  
20          preclude you from speaking.

21                       We have been notified that one  
22          individual has requested to speak either at

1           this morning's session or at the afternoon  
2           session. Is Peter Lurie available to speak  
3           with us?

4                           (No response.)

5                   CHAIR YANCY: Having no response,  
6           are there any other individuals in the  
7           audience who would like to address the panel  
8           at this moment?

9                           (No response.)

10                   CHAIR YANCY: Given that no one  
11           else has come forward, we will proceed with  
12           today's agenda.

13                   Please note that there will be a  
14           second opportunity for an open public forum  
15           this afternoon. We ask you to speak clearly  
16           into this microphone to allow the  
17           transcriptionist to provide accurate recording  
18           of this meeting. Please state your name and  
19           the nature of any financial interest you may  
20           have in this or another medical device  
21           companies.

22                   We will now yield to the sponsor

1 so that they may proceed with their  
2 presentation.

3 I would like to remind public  
4 observers at this meeting that while this  
5 meeting is open for public observation, public  
6 attendees may not participate, except at the  
7 specific request of the panel.

8 You may begin.

9 DR. PINES: Good morning. I'm Eli  
10 Pines. I'm Vice President and Chief  
11 Scientific Officer of SyntheMed, Inc. I am an  
12 employee of SyntheMed and I have a financial  
13 interest in the company.

14 What I would like to do at the  
15 outset is thank the FDA for organizing the  
16 meeting and the FDA panel. On behalf of the  
17 sponsor and the participants, I want to thank  
18 the FDA for organizing the meeting and the  
19 panelists for taking time away from their busy  
20 schedule to review our data and provide  
21 insight and input.

22 The participants present at

1           today's meeting include, who will be  
2           presenting include Dr. Carl Lewis Backer,  
3           cardiac surgeon and investigator, Dr. Philip  
4           Lavin, a statistician, Dr. James O'Brien,  
5           cardiac surgeon and investigator in the study,  
6           myself, Dr. Eric Rose, who is a cardiac  
7           surgeon. Unfortunately, Dr. Rose had a death  
8           in the family. He is unable to attend today's  
9           meeting. So, Dr. Carl Backer will present in  
10          his behalf. And Dr. Samuel Weinstein, who is  
11          an associate professor at the Albert Einstein  
12          College of Medicine.

13                         In addition, James Anderson, a  
14          pathologist, Dr. Daniel Cohn, a polymer  
15          scientist, Michael Diamond, a post-operative  
16          adhesion consultant, and Dr. Gere diZerega, a  
17          tissue repair consultant, as well as Jules  
18          Mitchel, a regulatory consultant, and Kathleen  
19          Rodgers, a toxicologist consultant are in  
20          attendance.

21                         What we'd like to do today is  
22          present the data of our four clinical studies,

1 if you will. The journey began in roughly the  
2 1999 time vintage when we initiated the first  
3 pilot study, which was conducted at Columbia  
4 University in New York. Subsequent to that,  
5 in 2002, we initiated what we call the  
6 feasibility study in pediatric patients at  
7 Children's Hospital Los Angeles. In 2004, we  
8 initiated the pivotal study, which is the  
9 subject matter of today's meeting. And that  
10 study was completed in 2006.

11 Roughly half-way into the pivotal  
12 study, we initiated what we call the European  
13 study. All studies were completed in the 2006  
14 time frame and a database was locked roughly  
15 in October of 2006.

16 Today's agenda includes Dr.  
17 Backer, who will give you an overview of  
18 REPEL-CV and present the complications and  
19 etiology associated with post-operative  
20 cardiac adhesions. He will discuss the  
21 clinical, the needs and the requirements of a  
22 clinical study trial designed to assess post-

1           operative cardiac adhesions. And finally, he  
2           will discuss the justification of the clinical  
3           program and the indication for use. I will  
4           follow by brief overview of the pre-clinical  
5           safety and effectiveness data.

6                         And then we'll have the clinical  
7           development program presented. Dr. Samuel  
8           Weintstein will present the pre-pivotal  
9           studies to including the pilot, the  
10          feasibility, and the European study that I  
11          mentioned previously.

12                        Dr. James O'Brien will present the  
13          pivotal study design. Dr. Backer will present  
14          the pivotal study results and conclusions.  
15          Dr. Philip Lavin will present some statistical  
16          considerations. Dr. Carl Backer will conclude  
17          with the overall conclusions of the clinical  
18          studies. And finally, Dr. Phil Lavin will  
19          discuss the post-approval study.

20                        Oh, I neglected to mention one  
21          thing. In front of you, you have a packet  
22          that looks like this. If you could open it,

1           inside you'll see the sample of the REPEL-CV,  
2           which we are going to be describing today.

3                     DR. BACKER: Good morning. My  
4           name is Carl Backer. I'm a cardiac surgeon at  
5           Children's Memorial Hospital in Chicago, also  
6           at Northwestern University Medical School. I  
7           am a paid consultant to SyntheMed. I do not  
8           have any financial interest in the company.

9                     It's my pleasure to be here this  
10          morning. I'm actually giving Dr. Rose's talk.  
11          We're sorry that Dr. Rose could not be with us  
12          due to, again, a death in his family.

13                    The proposed indication for use of  
14          REPEL-CV is as a surgical adjuvant indicated  
15          for reducing the incidence, severity and  
16          extent of post-operative adhesion formation in  
17          patients undergoing cardiac surgery via  
18          sternotomy incision. And I think Eli has just  
19          asked you all to look at your little sample.  
20          This proposed would be used in both children  
21          and adults.

22                    The device that you have in front

1 of you, REPEL-CV, is a sterile, single use,  
2 synthetic, bioresorbable polymeric film  
3 composed of poly-lactic acid and polyethylene  
4 glycol. PLA and PEG are used extensively in  
5 implantable resorbable medical devices. PLA,  
6 in particular, is used in resorbable sutures,  
7 surgical meshes, drug delivery systems and PEG  
8 is used in surgical sealants in drug delivery  
9 systems.

10 This slide I would like to use to  
11 illustrate the problem for the cardiac surgeon  
12 with adhesions. The panel here to your left  
13 shows a heart being opened through a median  
14 sternotomy incision. This is a primary  
15 operation and you can clearly see all of the  
16 vital structures that are of importance to the  
17 surgeon. This is the patient's ascending  
18 aorta, the right ventricle, the coronary  
19 arteries, you can see the right atrial  
20 appendage poking out, the edges of the  
21 pericardium. This heart is easily approached  
22 by the cardiac surgeon and the operation is

1 not going to be complicated by adhesions.

2 In contrast, the panel over here  
3 to the right is a patient that is having their  
4 fourth median sternotomy operation. This is  
5 a 12-year-old boy and you can see immediately  
6 that the surgical planes are obliterated.

7 You cannot see the precise, pristine anatomy  
8 that you see in a primary operation. You can  
9 see the towels are saturated with blood. This  
10 child has already had a lot of bleeding on the  
11 way in. In point of fact, this is the  
12 surgeon's finger on a small hole that was  
13 created in the aorta during the dissection.  
14 This necessitated this child being placed on  
15 cardiopulmonary bypass using the femoral  
16 vessels and the child went on to develop,  
17 because of the complications of this re-  
18 operation and the femoral bypass, renal  
19 failure and was in the hospital for  
20 approximately four weeks. So the problem is  
21 pretty clearly illustrated by this slide.

22 The cardiac grading system that

1 was used in our study created adhesions from  
2 none to severe. And none, obviously was no  
3 adhesions. Mild adhesions were defined as  
4 filmy, non-cohesive adhesions requiring blunt  
5 dissection. Moderate adhesions were defined  
6 as filmy, non-cohesive, requiring a  
7 combination of blunt and selective sharp  
8 dissection. And then finally, the severe  
9 adhesions were the dense, cohesive adhesions  
10 that require extensive sharp dissection. And  
11 these severe adhesions are the ones that we  
12 really want to focus on. These are the ones  
13 that are clinically significant and that  
14 really create a problem for the cardiac  
15 surgeon.

16 This illustration I want to use to  
17 set up a video that I am going to display  
18 which illustrates the problem with adhesions.  
19 But this is a patient's sternum and the  
20 patient's head would be over here. The  
21 patient's feet would be here. And you can  
22 see, the sternum has been opened, this is a

1 re-operation, and there are dense adhesions of  
2 the heart to the back of the sternum. And in  
3 fact, in this particular area, this is the  
4 patient's ascending aorta was stuck directly  
5 to the posterior aspect of the sternum. And  
6 again, it is these dense adhesions that are of  
7 particular difficulty for the cardiac surgeon.

8 This video is of adhesions and re-  
9 operative cardiac surgery and this is a  
10 patient I operated on. This is a six-month-  
11 old child that shows the hemoclips beginning  
12 to elevate the sternum. This is a six-month-  
13 old child undergoing a re-operation after a  
14 Norwood operation for hypoplastic left heart  
15 syndrome. And this shows the, that was  
16 dissecting under the sternum.

17 This is the sternal saw coming in.  
18 We slowly elevate the sternum away from the  
19 heart. Now the sternum has been completely  
20 opened. The sternal retractor is being  
21 placed. This is the lung here. Heart up top.  
22 Again, you can see that the surgical planes

1 are obliterated.

2 Now this is an example of severe  
3 adhesions. This is a tedious sharp  
4 dissection. Another example of sharp  
5 dissection, severe adhesions. This is the  
6 patient's right atrium. This is the edge of  
7 the pericardium. You can see this is very  
8 tedious.

9 At this point, a small bleeding  
10 point is going to be created here. You can  
11 see the suction coming in. Then I'm going to  
12 cauterize it. And then the atrium  
13 fibrillates. You can see the atrium down here  
14 fibrillating. The atrium or the ventricle can  
15 fibrillate during cautery and re-entry, which  
16 can create a very dangerous situation.

17 Now here is an example of the type  
18 of adhesion we prefer to see. This is what we  
19 would call moderate adhesions. These are  
20 relatively easily sharply dissected. And then  
21 as we continue along the inferior aspect of  
22 the heart, these are very mild adhesions,

1           which probably could be just swept away.

2                       And finally, if you'll notice,  
3           there's a little pocket right down here where,  
4           for whatever reason, in this patient, there  
5           were no adhesions whatsoever. And that would  
6           be our goal.

7                       So, in this video, we have seen  
8           the extent of severe, moderate, mild, and no  
9           adhesions.

10                      Well the problem with these  
11           adhesions at the time of re-operation is that  
12           they obscure cardiac landmarks. They can be  
13           potentially life-threatening to the patient.  
14           For example, that boy where there was a hole  
15           created in the ascending aorta. And the  
16           operation is much more challenging to the  
17           surgeon.

18                      The analogy that Dr. Rose likes to  
19           give, it's a pilot flying a plane from airport  
20           to the other. It's much easier to do that  
21           when there's clear blue, sunny skies, than  
22           when you're flying through a thunderstorm. In

1           nearly all instances, the plane will  
2           eventually arrive at the other airport, but it  
3           becomes much more challenging and much more  
4           difficult to fly through a thunderstorm than  
5           through clear, blue, sunny skies.

6                         It has been show that re-operative  
7           cardiac surgery has a higher mortality and  
8           morbidity rate. The complications include  
9           inadvertent vascular or cardiac entry, which  
10          can result in fatal hemorrhage, prolonged  
11          surgical time, increased blood loss and  
12          prolonged cardiopulmonary bypass, which can  
13          lead to the type of complications that I  
14          showed you in that boy with renal failure and  
15          prolonged hospital stay.

16                        Currently, there is no FDA  
17          approved product indicated for the reduction  
18          of post-operative cardiac adhesions. Most  
19          patients, in fact, receive no specific therapy  
20          to reduce post-operative cardiac adhesions.

21                        REPEL-CV is a temporary barrier  
22          that mechanically separates the opposing

1 surfaces of the heart from interconnecting  
2 with each other via fibrin bridges. REPEL-CV  
3 biodegrades and is resorbed over time like  
4 other resorbable medical devices such as  
5 resorbable sutures.

6 This flow chart shows the effect  
7 of REPEL-CV on adhesion formation. We begin  
8 with the median sternotomy, which causes a  
9 surgical trauma. There is blood and  
10 inflammation formed in the mediastinum. This  
11 leads to fibrinogenesis. The fibrin bridges  
12 connecting opposing surface lead to the  
13 fibrous adhesions, which become the problem,  
14 as I showed you in that video.

15 The effect of the REPEL-CV on this  
16 cascade is to act as a temporary barrier  
17 separating the epicardial surfaces of the  
18 heart from the sternum and the pericardium and  
19 decreasing the extent and severity of fibrous  
20 adhesions that are formed during the healing  
21 process.

22 The purpose of our clinical

1 program was two-fold. The first was to  
2 demonstrate safety of REPEL-CV. The second  
3 was to demonstrate effectiveness, as measured  
4 by a reduction in the extent of severe post-  
5 operative cardiac adhesions.

6           Unfortunately there are no, when  
7 we look at considerations of a clinical trial  
8 designed to assess post-operative cardiac  
9 adhesions, unfortunately, there are no good  
10 non-invasive methods to assess the severity of  
11 these post-operative adhesions. The  
12 assessment of safety and effectiveness  
13 requires a patient population that undergoes  
14 sequential sternotomies that occur in a  
15 predictable and practical time window. The  
16 first sternotomy would be the time period  
17 where the patients would be randomized to  
18 treatment. The second sternotomy would be  
19 where we would assess the safety and  
20 effectiveness of the therapy.

21           The only two patient populations  
22 that undergo sequential sternotomies are

1 patients having a bridge to transplant with a  
2 left ventricular assist device and a selected  
3 group of pediatric patients.

4 First to discuss the left  
5 ventricular assist device, we did not feel  
6 these patients were appropriate for this  
7 therapy. The mechanical stresses generated by  
8 the left ventricular assist devices large  
9 pulsating outflow graft prematurely fragments  
10 REPEL-CV and can compromise its barrier  
11 properties.

12 On the other hand, this selected  
13 group of pediatric patients with a specific  
14 anatomic diagnosis require planned sequential  
15 sternotomies that occur within a practical  
16 time window. It should be noted that the  
17 etiology and complications of post-operative  
18 cardiac adhesions are common to patients of  
19 all ages and all cardiac procedures. However,  
20 the rationale for our clinical program that  
21 was used in this study was that these  
22 pediatric patients require sequential

1 sternotomies for surgical correction of  
2 congenital heart disease and are the only  
3 appropriate, predictable and practical patient  
4 population for assessing a device designed to  
5 reduce post-operative cardiac adhesions.

6           These patients have first initial  
7 sternotomy usually within the first several  
8 weeks of life and then the second sternotomy  
9 is planned at approximately six months of  
10 life.

11           Dr. Pines will now discuss the  
12 preclinical safety and effectiveness.

13           DR. PINES: Thank you, Dr. Backer.  
14 Again, I am Eli Pines. I am employee of  
15 SyntheMed and I have no financial interest.

16           The journey really began in the  
17 preclinical setting. We used several  
18 preclinical models to assess the efficacy of  
19 REPEL-CV. The model essentially consisted of  
20 traumatizing the surface of the heart and  
21 retrosternal space. The animals were  
22 randomized to either treatment or control and

1           appropriately treated. The chest was closed  
2           and necropsy was performed three to four weeks  
3           subsequent to implantation.

4                       In the preclinical effectiveness  
5           models, we used two species, canine and  
6           rabbits. In the canine, we had two models, if  
7           you will. One model comprised of traumatizing  
8           the surface of the heart and the sternum, the  
9           other model comprised of traumatizing the  
10          surface of the heart and the pericardium.

11                      On the right side of the slide,  
12          you'll see the results. In the case of the  
13          first model, the surface of the heart through  
14          the sternum, there were four animals, all of  
15          whom had zero area involved with adhesions.  
16          In contrast, 78 percent of the dogs had, I'm  
17          sorry. There were four dogs. Seventy-eight  
18          percent of the area was involved with  
19          adhesions.

20                      On the model where we looked at  
21          the surface of the heart and the pericardium,  
22          there were ten animals. The average area of

1           involvement was 12 percent in the REPEL-CV  
2           group and 78 percent in the control group.  
3           There were 11 animals in the control group.

4                       In the rabbit, the model was  
5           similar to the, if you will, to the first  
6           model in the dog, where we traumatized the  
7           surface of the heart and the sternum. There  
8           were eight rabbits per group. And as you see,  
9           in the REPEL-CV group, all of the animals were  
10          free of adhesion, whereas in the control  
11          group, 78 percent of the area was involved  
12          with adhesions.

13                      Subsequent to the efficacy data,  
14          we initiated the preclinical safety and  
15          biocompatibility studies, which consisted of  
16          the standards test that one would perform to  
17          demonstrate the safety of an absorbable  
18          implantable medical device. The various  
19          studies are listed on the slide. The  
20          conclusions were that the above studies showed  
21          the device to be safe and biocompatible.

22                      Dr. Weinstein will proceed.

1 DR. WEINSTEIN: Good morning. My  
2 name is Sam Weinstein and I am Associate  
3 Professor of Surgery at the Albert Einstein  
4 College of Medicine in New York, where I am  
5 the Director of Pediatric Cardiothoracic  
6 Surgery and the Director of the Adult  
7 Congenital Cardiac Surgery program. I am here  
8 as a paid consultant to the company and also  
9 own a nominal amount of stock. And I  
10 apologize if I sound a little bit congested.  
11 I seem to have come down with something.

12 I would like to discuss the  
13 development of the clinical program from the  
14 pilot study which began in 1999 through the  
15 feasibility study in 2002, to the European  
16 study in 2005, which actually started after  
17 the pivotal study had begun.

18 The application of REPEL is common  
19 in all of the studies performed. Prior to  
20 sternal closure, it is placed on the surface  
21 of the heart, below the sternotomy. It is  
22 positioned between the epicardium and the

1 sternum extending laterally beyond the  
2 pericardial edges, tacked in place with four  
3 Vicryl sutures.

4 Here in cross-section, the REPEL  
5 lies over the surface of the heart underneath  
6 the sternum, extending laterally beyond the  
7 pericardial edges. And these are the Vicryl  
8 sutures. Here's how it looks in vivo. The  
9 head of the patient is here. The feet are up  
10 here. This is the patient's right. This is  
11 the patient's left. This is a chest tube  
12 coming out the bottom. This is the REPEL  
13 lying over the surface. It is a clear porous  
14 structure and this is a pacing wire from  
15 underneath it, exiting the patient.

16 The investigational site, which is  
17 assessed at the time of the second sternotomy,  
18 is defined as the area directly below the  
19 sternotomy site, between the epicardium and  
20 the sternum, extending to the lateral edges  
21 of the pericardium, the area here outlined in  
22 blue.

1                   The pilot study, which was the  
2                   first time that REPEL was used in human  
3                   patients, was performed in adults receiving  
4                   sternotomies for open heart surgery. It was  
5                   a controlled, randomized safety study  
6                   performed at two centers, Columbia  
7                   Presbyterian in New York and Baylor-Texas  
8                   Medical Center. Safety variables looked at  
9                   were adverse events, clinical laboratory  
10                  tests, and medications.

11                  A total of 27 patients were  
12                  randomized and the patients received either  
13                  coronary artery bypass graft, valvular  
14                  surgery, or left ventricular assist device  
15                  placement. A total of five patients were  
16                  withdrawn from the study. Two patients, one  
17                  after re-exploration for bleeding 12 hours  
18                  surgery, another for a malignant arrhythmia  
19                  leading in death. Unfortunately, these events  
20                  are not uncommon in this patient population.  
21                  Two patients elected not to return to the  
22                  study in the REPEL group and one patient in

1 the control group elected not to return to the  
2 study.

3 The number of adverse events in  
4 both groups was similar. And the number of  
5 serious adverse events between the two groups  
6 was also similar. There were no safety  
7 concerns observed when comparing REPEL-CV  
8 versus control.

9 And another conclusion or perhaps  
10 key observation from the pilot study was that  
11 the LVAD patient population would not be an  
12 appropriate model for assessing an adhesion  
13 barrier. The mechanical stress generated by  
14 the LVAD's pulsating outflow graft prematurely  
15 fragmented REPEL-CV, compromising its barrier  
16 properties. The LVAD outflow graft is a  
17 unique prosthesis, in that it not only runs  
18 outside the heart, but through the entire  
19 mediastinum from the abdomen to the ascending  
20 aorta, generating a unique mechanical stress.

21 The feasibility study and all  
22 subsequent studies were performed in the

1 pediatric population because of ability to  
2 have staged sequential median sternotomy  
3 procedures within a six month time interval.

4 It was an evaluator masked, controlled,  
5 randomized safety and effectiveness study  
6 performed at the Children's Hospital of Los  
7 Angeles. Winfield Wells was the principal  
8 investigator.

9 Safety variables were adverse  
10 events, clinical laboratory tests and  
11 medications. The effectiveness endpoint was  
12 the percentage of the investigational site  
13 with severe adhesions are those most  
14 clinically relevant to both patient and  
15 surgeon.

16 A total of 13 patients were  
17 randomized. Two were withdrawn from each  
18 group due to death. One patient was withdrawn  
19 from the REPEL group for a protocol violation  
20 and another patient was withdrawn by the  
21 surgeon prior to chest closure, leaving seven  
22 patients completing the study.

1                   None of the patients in the REPEL  
2                   group presented at the second sternotomy with  
3                   severe adhesions. Three of the four patients  
4                   in the control group presented with a majority  
5                   of investigational site with severe adhesions.

6                   In the executive summary provided  
7                   to you by the FDA, there is mention of four  
8                   moderate infections and two mediastinal events  
9                   not further described. I hope that this slide  
10                  will help clarify those events.

11                  The four moderate infections, one  
12                  was a peripheral intravenous tip that grew a  
13                  positive culture, and one was a central line  
14                  tip sent on surveillance, which grew positive  
15                  for organisms. Both patients were treated  
16                  with antibiotics and their infections  
17                  resolved.

18                  A third patient was treated for a  
19                  presumed superficial infection, which was  
20                  culture negative. And a fourth had a positive  
21                  culture obtained when a surveillance culture  
22                  was sent from the mediastinum prior to

1 closure. Those two patients, as well, were  
2 felt to have resolved their infection with  
3 antibiotics.

4 Of the two mediastinal events, one  
5 was a mediastinal hematoma that developed  
6 prior to closure. This hematoma was evacuated  
7 and the sternum was closed uneventfully. The  
8 second was a prolonged open sternum, which  
9 defined by MedDRA is a Mediastinal disorder.  
10 This patient is well after mediastinal  
11 exploration and washout, was closed  
12 uneventfully. Neither of the mediastinal  
13 events were due to a mediastinal infection.

14 There were no safety concerns  
15 observed when comparing REPEL-CV versus  
16 control. The treatment benefit approached  
17 significance and this information helped  
18 support the U.S. pivotal trial and the  
19 European study.

20 The European study design would be  
21 the same as the U.S. pivotal study, except  
22 that there were no controls. The population,

1           again, was pediatric patients with complex  
2           critical congenital heart disease requiring  
3           sequential median sternotomies for palliation.  
4           The study design was an open label, multi-  
5           center safety and effectiveness study and the  
6           objective was to support European regulatory  
7           requirements. It was performed in three  
8           centers in Europe, two in Germany and one in  
9           France.

10                       The only safety variables looked  
11           at were serious adverse events with the  
12           effectiveness endpoint, the mean percentage of  
13           the investigational site with severe  
14           adhesions.

15                       A total of 19 patients were  
16           enrolled. Four patients were withdrawn, three  
17           following death and one after an emergent  
18           chest opening. The three mortalities in 19  
19           patients is not inconsistent with this  
20           critical patient population and, actually,  
21           somewhat slightly better than expected  
22           published results.

1                   This left 15 patients completing  
2                   the study. Of the 15 patients, only two  
3                   presented with severe adhesions.

4                   The serious adverse events from  
5                   the feasibility study were consistent with the  
6                   clinical experience for this study population,  
7                   those of critical neonates undergoing staged  
8                   median sternotomies.

9                   The incidence and extent of severe  
10                  adhesions were low and consistent with the  
11                  feasibility study.

12                  Thank you.

13                  DR. O'BRIEN: Good morning. My  
14                  name is Jim O'Brien. I am an assistant  
15                  professor of Surgery at the University of  
16                  Missouri School of Medicine and I'm also a  
17                  cardiac surgeon at the Children's Mercy  
18                  Hospital in Kansas City, where I specialize in  
19                  the treatment of patients with congenital  
20                  heart disease, both in the pediatric and the  
21                  adult population.

22                  I'm here this morning as an

1 investigator for the pivotal study. I also am  
2 a paid consultant for SyntheMed; however, I  
3 have no financial interest in the company.

4 I'd like to outline for you this  
5 morning the design of the pivotal study. Our  
6 study was a multi-center, comparative,  
7 randomized, evaluator-masked study. The two  
8 primary objectives, first to demonstrate  
9 safety, and second, demonstrate the  
10 effectiveness as measured by a reduction in  
11 the extent of the severe post-operative  
12 cardiac adhesions.

13 The population consisted of  
14 patients who underwent planned sequential  
15 sternotomies at a standard surgical strategy  
16 for the defined group of the pediatric  
17 patients. These patients all have severe  
18 congenital heart disease and required an  
19 initial sternotomy within one month of life,  
20 followed by a planned second sternotomy at  
21 approximately six months of life.

22 The population if expected to have

1 a high incidence of post-operative  
2 complications. This is because the majority  
3 had a single ventricle and were cyanotic both  
4 before and following their palliative surgery.  
5 Many of these patients have hypoplastic left  
6 heart syndrome. And this is an extremely  
7 high-risk population with mortality, even in  
8 the most experienced of centers, approaching  
9 30 percent.

10 Following the first sternotomy,  
11 clinical management included a delayed sternal  
12 closure until the patients, once the patients  
13 were hemodynamically stable. The majority of  
14 other patients had their sternum open for a  
15 few days, mostly in the two to three day  
16 range.

17 Fifteen sites participated in the  
18 trial. The patients were randomized into two  
19 groups. One group was treated with the REPEL-  
20 CV bioresorbable film and the other group was  
21 a control. Allocation was performed to each  
22 treatment by the center computer generated

1 block randomization code. The patients were  
2 randomized into the study just prior to their  
3 chest closure.

4 Our major inclusion criteria were  
5 that the patients had no previous sternotomy  
6 and that they had a cardiac lesion which  
7 required the sequential sternotomies, the  
8 second one anticipated within two to eight  
9 months.

10 Exclusion criteria were the use of  
11 approved or unapproved treatment to prevent  
12 the adhesions or the closure of the  
13 pericardium at the time of their surgery.

14 The study stages are as outlined  
15 here. Visit zero is the enrollment. Visit  
16 one was at the time of the first sternotomy.  
17 The patients were then randomized at the time  
18 of chest closure, whether that was a primary  
19 chest closure or a delayed sternal closure.  
20 Visit two was a safety evaluation done at  
21 three to eight weeks post-randomization. And  
22 visit three was the planned second sternotomy,

1 at which time they had their safety and  
2 effectiveness assessed.

3 These are the illustrations you  
4 have seen before. Just prior to chest  
5 closure, the REPEL-CV film is placed between  
6 the sternum and the surface of the heart. You  
7 can see the cross-sectional area and this is  
8 looking down from above.

9 The film was placed between the  
10 posterior table of the sternum of the  
11 epicardial surface of the heart. This is the  
12 region where the presence of severe adhesions  
13 can lead to life-threatening complications in  
14 the re-operation. The film then extended  
15 beyond the lateral edges of the pericardium,  
16 as you see here. At that level, it was  
17 between the pericardial edge and the  
18 epicardial surface of the heart. The film is  
19 placed loosely in this position and it is  
20 tacked place using absorbable sutures, roughly  
21 at the four corners.

22 The investigational site, which

1 was assessed at the time of the second  
2 sternotomy, was defined as the area between  
3 the sternotomy site, or below the sternotomy  
4 site between the lateral edges of the  
5 pericardium, thus corresponding to the area  
6 where the film was placed.

7 As Dr. Backer already described,  
8 we used a cardiac adhesion grading system  
9 which ranged from none to severe. The severe  
10 being these dense cohesive adhesions where the  
11 mediastinum structures are essentially welded  
12 together. And these are the clinically  
13 significant adhesions.

14 Our prospective measurements of  
15 safety. The assessments included death,  
16 adverse effects as coded by MedDRA, and events  
17 common to this population.

18 The common events was a category  
19 of events that were prospectively defined in  
20 the protocol as adverse events commonly  
21 associated with this high-risk patient  
22 population. They were captured as such,

1 unless their frequency, duration, or severity  
2 was different than typically seen for this  
3 patient population. If they were different,  
4 they were captured as an Adverse Event and you  
5 see them listed below.

6 Our primary endpoint was the mean  
7 percent of the study-defined investigational  
8 site with severe or Grade 3 adhesions. Our  
9 main secondary endpoints were the percent of  
10 patients with severe adhesions, the percent of  
11 patients by worst degree of adhesions, and the  
12 mean percent of the investigational site by  
13 adhesion severity.

14 Our safety population consisted of  
15 all randomized and treated patients. There  
16 were 73 in the REPEL-CV group and 69 in the  
17 control group.

18 Our intent-to-treat population  
19 consisted of all randomized and treated  
20 patients who underwent the adhesion  
21 evaluations at the time of the planned second  
22 sternotomy. There were 56 in the REPEL group

1 and 54 in the control. Our intent-to-treat  
2 population will be used to evaluate the  
3 effectiveness.

4 At this time, I would like to turn  
5 the podium over to Dr. Backer, who will go  
6 through the results and conclusions.

7 DR. BACKER: Thanks, Jim. It's my  
8 pleasure to now present to you the results and  
9 conclusions of the pivotal study. I would  
10 just mention for myself, I do pediatric  
11 cardiac surgery. I also operate on adults  
12 with congenital heart disease. And I'm the  
13 Director of the heart transplant program at  
14 the Children's Memorial Hospital.

15 I'd like to begin by thanking the  
16 participating centers. It was really actually  
17 a pleasure for me to work with the other  
18 investigators. I think we had a really  
19 premiere group of Children's Hospitals that  
20 took part in this study. And again, I wanted  
21 to acknowledge the work that all of the other  
22 investigators and centers helped with this

1 study.

2 Well, let's get into the results.  
3 In the demographics of the two patient  
4 populations, REPEL-CV, the mean age of the  
5 patients at the time of the primary sternotomy  
6 was 12 days. In the control group, the mean  
7 age was 13 days. This was not significantly  
8 different.

9 The mean weight of the REPEL  
10 patients was 3.02 kilos versus 3.3 kilos in  
11 the control group. This was statistically  
12 significant, but probably not clinically  
13 significant, 3.1 versus 3.3 kilos.

14 The majority of the patients had  
15 the operation which we refer to as a Norwood  
16 procedure, which is a complex neonatal  
17 operation involving an aortal pulmonary shunt  
18 of some type, an atrial septectomy, and then  
19 a reconstruction of the ascending aorta,  
20 pulmonary artery and repair of coarctation.  
21 This really one of the most complex procedures  
22 that congenital heart surgeons perform. And

1           this was approximately 70 percent in each  
2           group.

3                         The majority of the operations  
4           were performed on cardiopulmonary bypass, 80  
5           percent in the REPEL group, 90 percent in the  
6           control group. And as Dr. O'Brien mentioned,  
7           most of these patients, and again, about 70  
8           percent in each group had delayed closure of  
9           the chest. This meant that they underwent  
10          their initial operation, they were transferred  
11          to the intensive care unit with a silastic  
12          skin patch sealing the skin and then two to  
13          three days later, sometimes four or five days,  
14          when they were hemodynamically stable, they  
15          had their chest closed, usually in the  
16          intensive care unit at the bedside.

17                        To go through the patient  
18          disposition, beginning with our initial  
19          population that was randomized, 73 in the  
20          REPEL group, 71 in the control group, there  
21          were two patients that were randomized but not  
22          treated. They were protocol violations and

1           they were removed from the control group.  
2           This gives us our safety population of 73  
3           patients in the REPEL group, 69 in the control  
4           group. There were 17 patients in each of the  
5           two groups that were withdrawn prior to the  
6           planned second sternotomy, leaving us with an  
7           intent to treat population of 56 in the REPEL  
8           group and the 54 in the control group.

9                        To look at those 17 patients  
10          withdrawn prior to the second sternotomy,  
11          there were eight in each group withdrawn  
12          because of an emergent chest exploration,  
13          which I would say is not unexpected, given the  
14          nature of this patient population. I  
15          mentioned earlier the two protocol violations  
16          in the control group both were considered  
17          protocol violations because the surgeon placed  
18          a pericardial patch at the time of the chest  
19          closure not within the protocol.

20                       Finally, there were nine deaths in  
21          the REPEL group, seven deaths in the control  
22          group, not unexpected in this high-risk

1 patient population. Again, that leaves us 17  
2 patients withdrawn prior to the second  
3 sternotomy in each group.

4 The median time to the second  
5 sternotomy was similar between the two groups;  
6 156 days for the REPEL patients, 148 days for  
7 the control patients.

8 I'd like to first touch on the  
9 safety results and after that I will go to the  
10 effectiveness of the REPEL.

11 Again, first I want to talk about  
12 the mortality which, at first glance, seems  
13 rather high for both groups. The overall  
14 mortality in the REPEL group was 16.4 percent  
15 to 12 patients. The overall mortality in the  
16 control group was 9 patients, at 13 percent,  
17 these were not statistically different.

18 Again, prior to the second sternotomy, that  
19 was nine versus seven. Again, not  
20 significantly different.

21 If one looks at just three recent  
22 publications, 2006, 2005, 2002, regarding the

1 mortality of the Norwood procedure, you can  
2 see that the mortality of 24 percent, 22  
3 percent, and 19 percent is actually somewhat  
4 higher than the reported mortality in our  
5 either control group or the REPEL-CV group.

6 Dr. O'Brien mentioned that we  
7 categorized a group of events which we called  
8 common events. And you can see they were very  
9 common in this high-risk patient group. The  
10 results however, were that the treatment  
11 groups were really comparable. And if you go  
12 through these, for example, hemodynamic  
13 instability requiring inotropic support was 75  
14 percent in the REPEL group, 74 percent in the  
15 control group. Again, electrolyte  
16 disturbances, 73 percent REPEL, 73 percent  
17 control. Essentially, the two treatment  
18 groups were comparable for these common  
19 events, which again, we expected in this high-  
20 risk neonatal cardiac surgery population.

21 A summary of the adverse events  
22 and the serious adverse events is shown here.

1           In the REPEL group, there were 51 patients  
2           that had at least one adverse event. They had  
3           a total of 135 events. In the control group,  
4           there were 49 patients that had an adverse  
5           event, 123 total events.

6                         In the REPEL group there were 37  
7           patients that had a serious adverse event,  
8           with 63 events in those patients. In the  
9           control group, there were 32 patients that had  
10          a serious adverse event, a total of 53 events.  
11          Again, these were not -- these were similar in  
12          incidence.

13                        The adverse events by descending  
14          frequency, more than four percent, or of  
15          particular clinical interest are shown here.  
16          Again, these were clinically very similar. I  
17          draw your attention to cardiac arrest; seven  
18          in the REPEL group, six in the control group.  
19          Pleural effusion, four in the REPEL group,  
20          three in the control group. Superficial wound  
21          infection, four in the REPEL group, three in  
22          the control group. Wound dehiscence,

1 superficial wound dehiscence, four in the  
2 REPEL group, three in the control group.

3 And the second part of this, now  
4 we are looking at frequency. Again, greater  
5 than four percent are of particular clinical  
6 interest, so these are very infrequent.

7 Regarding mediastinitis, there were a  
8 total four patients in the REPEL group, there was  
9 one in the control group. But breaking that down,  
10 and we'll look at this in detail in a minute, two  
11 of these patients occurred prior to the second  
12 sternotomy and we felt were possibly related to the  
13 device, one in the control group. Two of the  
14 patients that had mediastinitis occurred after the  
15 second sternotomy, remote from the placement of the  
16 device.

17 And then you can see the rest of the  
18 adverse events again, were very similar in  
19 occurrence.

20 All of the serious adverse events are  
21 listed in this slide. And again, if you look on  
22 balance, these two were very similar between the

1 two groups.

2 I want to focus briefly on  
3 mediastinitis, because this was a potential  
4 concern. Mediastinitis, obviously, is a potential  
5 safety concern because we are placing a foreign  
6 material in the mediastinum. Mediastinitis is  
7 defined as a deep infection involving the  
8 mediastinum or sternum that requires all of the  
9 following: re-exploration of the sternum,  
10 debridement of the sternum, and prolonged  
11 antibiotic therapy.

12 Looking again at recent articles  
13 regarding the incidence of mediastinitis, the  
14 overall incidence of mediastinitis following median  
15 sternotomy in diverse pediatric populations has  
16 been reported between 1.4 and 6.7 percent.

17 The largest contemporary review of  
18 mediastinitis from the Children's Hospital of  
19 Philadelphia looked at 3,071 pediatric patients  
20 that had a median sternotomy. There were a total  
21 of 43 cases of mediastinitis for an incidence of  
22 1.4 percent. I would note that 18 of the 43

1 patients that had mediastinitis were patients with  
2 hypoplastic left heart syndrome. Again, 70 percent  
3 of the patients in both the REPEL and the control  
4 group in our series were hypoplastic left heart  
5 syndrome patients that had a Norwood-type  
6 operation.

7 In that series, delayed sternal closure  
8 was an independent risk factor for mediastinitis.  
9 The odds ratio for this 9.3. Again, our patient  
10 series, both the REPEL and the control group, 70  
11 percent of the patients had a delayed sternal  
12 closure.

13 In this review, the median time of onset  
14 of mediastinitis was 11 days. And this ranged  
15 between 4 and 34 days. And I think you'll see how  
16 this becomes important when we look at our results.  
17 And in this series, the mediastinitis was described  
18 as being related to the most recent sternotomy  
19 surgery.

20 Now, looking at our series of patients,  
21 again comparing REPEL-CV with control, first  
22 focusing on after the first sternotomy, there were

1 two patients in the REPEL group, one in the control  
2 group. After the second sternotomy, there were  
3 again, two in the REPEL group, none in the control  
4 group. So this was 2.7 percent, 1.4 percent and  
5 3.6 percent. Again, the overall incidence of  
6 mediastinitis following median sternotomy in those  
7 several reviews has been reported between 1.4  
8 percent and 6.7 percent.

9 Now, looking a little more closely at  
10 those patients, these are the three patients that  
11 developed mediastinitis after the first sternotomy.  
12 In the control group, a patient developed  
13 mediastinitis at 12 days after the sternotomy.  
14 This resolved with sternal debridement, antibiotic  
15 therapy. In the REPEL-CV group, this patient was  
16 at increased risk of mediastinitis because they had  
17 a delayed sternal closure. This mediastinitis  
18 onset was 14 days after the first sternotomy.  
19 Again, within that normal time window. And in this  
20 patient, the mediastinitis resolved with  
21 appropriate therapy.

22 The third patient was actually my

1 patient. And this was quite unusual. This patient  
2 presented with a red elevated area at the lower  
3 portion of the sternum 120 days after the initial  
4 sternotomy. This actually occurred four days  
5 following a cardiac catheterization and we found a  
6 staphylococcus aureus and a small amount of pus  
7 beneath a sternal suture at the very lower portion  
8 of the sternum. This resolved with debridement of  
9 this limited area and antibiotic therapy.

10 There were two patients that developed  
11 mediastinitis after the second sternotomy. The  
12 first patient was a REPEL patient who went 165 days  
13 until the time of their second sternotomy. This  
14 patient had onset of mediastinitis four days after  
15 the second sternotomy. Again, this resolved with  
16 antibiotic therapy and with a sternal debridement.

17 The second patient had an urgent  
18 operation. There were only 50 days to the second  
19 sternotomy. This patient had developed cyanosis  
20 and was hypoxic and had a relatively urgent  
21 operation to upsize a shunt. This patient  
22 developed the mediastinitis 30 days after the

1 second sternotomy. The other interesting clinical  
2 information is that the child had a gastrostomy  
3 tube placed 22 days after the second sternotomy,  
4 which was eight days, so the infection at 30 days  
5 after the second sternotomy was eight days  
6 following placement of the gastrostomy tube. This  
7 patient again, the infection resolved with  
8 appropriate therapy.

9 So our conclusion regarding  
10 mediastinitis is that the incidence of  
11 mediastinitis in this study is at the lower rate  
12 reported in the literature and there was no  
13 different between the REPEL-CV patients and the  
14 control patients.

15 I'd like to spend a minute on the  
16 adverse events that were rated by the investigator  
17 as possibly device related. And this was a total  
18 of six in the REPEL-CV group and one in the control  
19 group.

20 First regarding the mediastinitis,  
21 again, I think I've discussed this in detail just  
22 prior to this. There was one superficial wound

1 infection in each group reported as possibly device  
2 related. There was one patient in the REPEL-CV  
3 group reported as having a post-operative thoracic  
4 procedure complication, none in the control group.  
5 This was a sternal nonunion that was repaired at  
6 the time of the second operation. There was one  
7 patient with low cardiac output reported in the  
8 REPEL-CV group and none in the control group.

9 The rating scale for the investigators  
10 to use regarding whether or not the adverse event  
11 was related to the device was that the event was  
12 definitely not related, probably not related,  
13 possibly related, probably or definitely. Of note,  
14 there were no events that were definitely device  
15 related. No events were probably device related.  
16 All of the seven events listed above were "coded as  
17 possibly device related." Also of note, all of  
18 these events resolved as reported by the  
19 investigator.

20 So, in conclusion, regarding the safety  
21 of the REPEL device in the pivotal study, there  
22 were no statistical or clinical differences in

1 adverse events, serious adverse events, and  
2 mortality when comparing REPEL-CV versus controls.  
3 The observed adverse events, serious adverse and  
4 mortality rates were completely consistent with the  
5 clinical experience for this high risk study  
6 population. There was no pattern for events  
7 indicating a safety concern when comparing REPEL-CV  
8 versus control.

9 Now I would like to move on to the  
10 effectiveness of REPEL-CV.

11 The primary effectiveness endpoint,  
12 again, described by Dr. O'Brien, was the mean  
13 percent of the investigational site with severe  
14 adhesions. And these are the adhesions that,  
15 clinically, are the most significant to the cardiac  
16 surgeon. In the control group, 47 percent of the  
17 investigational site was involved with severe  
18 adhesions. This was decreased by over 50 percent  
19 to 21.3 percent in the REPEL group, the "p" value  
20 as shown here. This was our primary effectiveness  
21 endpoint.

22 We had four secondary effectiveness

1 endpoints. The first is the percent of patients  
2 with severe adhesions. In the control group, this  
3 was 72.2 percent. In the REPEL group, this was  
4 30.4 percent. Again, a greater than 50 percent  
5 reduction in the percent of patients with severe  
6 adhesions.

7 A second secondary effectiveness  
8 endpoint was the mean percent area as involved by  
9 mild, moderate, and severe adhesions. What we  
10 found here was a distribution shift in adhesion  
11 severity favoring REPEL-CV. The mean percent area  
12 involved dropped from this large amount of severe  
13 adhesions to much fewer severe adhesions and more  
14 in the mild and moderate category. This is the  
15 mean percent area involved with adhesions.

16 If we look at this by percent of  
17 patients by worst degree of adhesions, again, there  
18 was a shift in this distribution curve; 72.2  
19 percent of the control patients had severe  
20 adhesions as their worst degree of adhesions versus  
21 30.4 percent of the REPEL group. Again, this curve  
22 was shifted.

1                   Our fourth secondary effectiveness  
2                   endpoint was the time to dissect the adhesions at  
3                   the investigational site. And this was somewhat  
4                   disappointing, mostly based on the standard  
5                   deviation. The dissection time in the REPEL-CV  
6                   group was 25.9 plus or minus 21.1 minutes. The  
7                   dissection time in the control group was 25.0  
8                   minutes, plus or minus 21.8 minutes. These were  
9                   not statistically different.

10                   But I would draw your attention again to  
11                   this very large standard deviation and our  
12                   retrospective analysis of this was that the  
13                   dissection time at the different centers was  
14                   affected by multiple variables. The first was that  
15                   we had no standard technique specified in the  
16                   protocol for sternal re-entry. The surgeons were  
17                   encouraged to continue using whatever technique  
18                   they had been using for their sternal re-entry  
19                   prior to the pivotal study.

20                   Second was there was a variable  
21                   experience of the surgeons at the time of the  
22                   second re-operation varying from surgical fellows

1 to experienced clinical surgeons.

2 Third in the congenital population,  
3 there is extremely heterogeneous anatomy. These  
4 patients can have and did have anatomic variations,  
5 such as dextrocardia, transposition of the great  
6 arteries, heterotaxy syndrome, shunts crossing the  
7 midline and other different difficult anatomies  
8 that made the dissection times quite variable. And  
9 again, I remind you that we had 15 different  
10 centers participating in this study.

11 So our final conclusions are that we  
12 felt that we met our primary effectiveness  
13 endpoint. The objective, as defined in the  
14 original hypothesis, was that we wanted to achieve  
15 a 20 percent reduction in the mean percent of  
16 investigational site with severe adhesions. We  
17 obtained a 26 percent reduction in the percent of  
18 severe adhesions at the investigational site.

19 Regarding the secondary effectiveness  
20 endpoints, multiple prospectively defines  
21 statistical analyses confirmed the effectiveness of  
22 REPEL-CV. The percent of patients with severe

1           adhesions was decreased by 42 percent. There was  
2           a significant shift in the percentage of patients  
3           by worst degree of adhesions.

4                        The final conclusion slide is that the  
5           safety and effectiveness data demonstrate that  
6           REPEL-CV does not present additional risk to  
7           patients undergoing cardiac surgery and REPEL-CV  
8           does significantly reduce the extent and severity  
9           of post-operative cardiac adhesions.

10                      Thank you for your attention.

11                      DR. LAVIN: Okay, my name is Philip  
12           Lavin. I'm a biostatistician and our CRO performed  
13           the efficacy analyses that have been presented here  
14           today. And we also performed independent  
15           assessments of the biases in the study. And I want  
16           to just take us through some of the overviews and  
17           also in response to some of the things which you  
18           might be hearing from the FDA later on.

19                      Here we have a summary of the safety  
20           results. I draw your attention to the four major  
21           adverse event categories that we looked at, the  
22           overall AEs, overall SAEs, deaths, and the

1 incidence of mediastinitis. We compute here and we  
2 show here the 90 percent confidence intervals for  
3 the idea of being able to see, you know, is the  
4 confidence interval inclusive of zero indicative of  
5 no difference, and also how broad are the  
6 confidence intervals. And with 90 percent, it's  
7 easier to see a signal than it is if I drew a 95  
8 percent confidence interval.

9 So, for example, just to summarize for  
10 the overall AE rate, we actually, REPEL-CV, had a  
11 1.1 percent lower incidence of overall AEs,  
12 slightly higher, though for SAEs, slightly higher  
13 for death, and slightly higher for mediastinitis.

14 The Fisher Exact test, which you've seen  
15 already and you'll also see from the FDA are also  
16 shown here for comparison. The last column  
17 demonstrates the non-inferiority calculation. And  
18 these are provided, again, at the request of the  
19 FDA. We had not prospectively defined in the  
20 protocol a non-inferiority threshold, so I wanted  
21 to share with you what type of a non-inferiority  
22 test would be possible.

1           So, to be able to rule out a ten percent  
2           disadvantage, ten percent higher overall for REPEL-  
3           CV, the "p" value for that would be around 0.08, so  
4           we would miss being able to rule it out, but we  
5           would be quite close. And similarly, for SAEs,  
6           similarly for deaths. And for mediastinitis,  
7           because the rates are so low, the ability to rule  
8           out a five percent excess was certainly was  
9           examined here. So we overall do not see any  
10          significant trend for safety, even adjusting for  
11          things as multiple comparisons for doing all of  
12          these possible tests.

13                 So our conclusions are that the safety  
14          that we have in the study is robust.

15                 The next slide addresses the efficacy.  
16          In my professional career and I have stood before  
17          panels like this on thirty other occasions, I've  
18          never really had the opportunity to stand before a  
19          panel and say that we exceeded the alternative  
20          hypothesis. We did so here. So, there is a first  
21          even in my statistical career.

22                 So just to summarize here, 26 percent

1       versus 20 for the mean percent, a Grade 3. That 20  
2       percent advantage was consistently seen in every  
3       pre-planned subgroup, whether it be the blinded or  
4       the un-blinded or the Norwood, or the un-bypass,  
5       off-bypass. So that 20 percent advantage was  
6       certainly quite durable.

7               We also saw, in addition to the efficacy  
8       advantage, we saw that advantage carry over to the  
9       other endpoints. We looked at the patient level  
10      and we also examined from the shift perspective.  
11      So we conclude here that the efficacy and the  
12      safety results are indeed robust and durable.

13             DR. BACKER: Thanks, Phil. Now I'd like  
14      to give the final overall conclusions.

15             The pivotal study. In our pivotal study  
16      the safety and effectiveness of REPEL-CV have been  
17      demonstrated. The adverse event profile of REPEL-  
18      CV was similar to surgery-only control patients and  
19      to the population at large. Statistical analyses  
20      of secondary effectiveness endpoints and subgroup  
21      analyses confirmed statistical significance. The  
22      primary effectiveness endpoint exceeded the

1 clinical objective in the pivotal study.

2 The rationale for the indication of use  
3 for REPEL-CV is shown here. Complications of  
4 adhesions contribute to the mortality and morbidity  
5 of re-operative cardiac surgery. I showed you that  
6 video and those pictures of the dense, severe  
7 adhesions which are a real problem for the cardiac  
8 surgeon.

9 The etiology and complications of post-  
10 operative cardiac adhesions are common to patients  
11 of all ages and all procedures. The incidence of  
12 re-operation following coronary artery bypass graft  
13 procedures is estimated to be between 15 and 25  
14 percent, typically 8 to 20 years following the  
15 first procedure. For valvular procedures, re-  
16 operation rate, depending on the type of valve  
17 inserted of course, is higher and the time to re-  
18 operation more variable. It is not possible to  
19 predict which of these patients, coronary bypass  
20 graft, valve insertion, will require re-operation  
21 the future.

22 REPEL-CV is a surgical adjuvant

1 indicated for reducing the incidence, severity, and  
2 extent of post-operative adhesion formation in  
3 patients undergoing cardiac surgery via sternotomy.

4 Thank you.

5 DR. LAVIN: Okay. I wanted to also  
6 share with you some of our thoughts regarding the  
7 post approval study. In preparation for this  
8 meeting, our group was asked to pull together a  
9 protocol and to suggest to the FDA, make a  
10 recommendation, what type of design might we  
11 consider to demonstrate long-term safety of REPEL-  
12 CV. And here, by way of background, I indicate  
13 some of the preambles and thinking going into our  
14 design of the trial.

15 First, the FDA agreed with SyntheMed  
16 that the final design of the PAS, including these  
17 inclusion and exclusion criteria in the endpoints  
18 would occur after the panel meeting. We will  
19 accept your input and deliberations and, if there  
20 is a decision to move forward, then we'll obviously  
21 work together closely with the Agency to come up  
22 with the proposed indication of use to be reflected

1           again, in patients all undergoing a sternotomy.

2                       By way of other background, we do not  
3           see any safety signals across the four clinical  
4           studies that have been presented here. In addition  
5           to that, we think that we would like to go forth  
6           and suggest, since it was of concern to the FDA,  
7           that we actually think about powering the PAS study  
8           from the perspective of the mediastinitis incidence  
9           as a means of being able to plan and power the  
10          trial.

11                      Now, if a post approval trial is  
12          warranted, we would propose the following paradigm.  
13          Namely, that the trial represent real life  
14          experience, that an adult population be used as the  
15          basis for assessment in this trial and that we  
16          would work closely with the FDA in coming up with  
17          the safety endpoints and the duration of follow-up.

18                      In terms of a traditional PAS trial, we  
19          have an opportunity to do either a randomized  
20          design or a single arm study. And in this case,  
21          we're using a single arm trial, namely because many  
22          of us have experiences with the STS database, have

1 a lot of respect for that database and have worked  
2 with it before. And I would respectfully submit  
3 that this would represent a very strong control  
4 group, especially since many of the sites that we  
5 plan to use for the PAS are already members and are  
6 experienced with this database.

7 So other considerations that go into it  
8 from a statistical perspective. First off, the  
9 concept of long term follow-up. How long should we  
10 follow these patients for? Should it be for 10 to  
11 12 years or should it be something more finite?  
12 Well, we have the experience that we gained from  
13 our clinical studies, namely, the vast majority of  
14 the AEs are reported in the interval while they are  
15 in the hospital and for an eight week follow-up  
16 thereafter. So this is very similar, in many  
17 respects, to what is being collected from STS.

18 One of the other discussion points that  
19 the FDA wanted us to give some attention to is the  
20 choice of an offset. Why four percent for  
21 mediastinitis? Why is that reasonable? And the  
22 thinking goes something like this.

1                   We saw a rate of mediastinitis in a  
2                   pediatric population of around two percent. When  
3                   we looked at the literature, we saw rates in the  
4                   one to seven percent range. In thinking that the  
5                   four percent represented the cushion that we had,  
6                   that we could go up from two percent up to six  
7                   percent, trying to not push to the extreme of  
8                   seven. So the concept of a four percent comes from  
9                   that remaining edge that we had between the two  
10                  percent that we observed and the six or seven  
11                  percent upper bound that we saw in the literature.  
12                  That's where the four percent offset comes from.

13                  And we also suggest that no interim  
14                  analysis be done simply because, you know, the  
15                  surgeons hopefully will know what they are doing  
16                  and they are experts and that we'll be able to not  
17                  get into alpha spending by looking at the data. So  
18                  our feeling is that no interim analysis would be  
19                  necessary because we would like to be able to  
20                  complete the trial in a rapid manner.

21                  The statistical methodology that we  
22                  would use for this would be to calculate one-sided

1 upper bound exact confidence interval for the event  
2 rates, namely, with using a binomial test.

3 Now the protocol specifics would be to  
4 come up with the adult population that we come up  
5 and agree here on CP bypass. The endpoints would  
6 be the adverse events that are captured in the STS  
7 database. And this also includes mediastinitis.  
8 It would be a non-inferiority design, as I've  
9 already alluded to, and the objective here would be  
10 to rule out that the REPEL-CV incidence rate is  
11 higher than the STS database by a predetermined  
12 offset.

13 The statistics will all be predicated on  
14 an 80 percent power to be able to rule out this  
15 offset excess that I've just described. And again,  
16 calculating 95 percent upper one-sided confidence  
17 bounds on safety using the STS database as that  
18 frame of reference.

19 The protocol specifics, as I mentioned  
20 earlier, to use multi-centers, all STS experienced,  
21 a sample size of 170 subjects for the two percent  
22 to rule out the six, and also following patients

1 for the same amount of time that they would have  
2 been followed had they been in the STS database.  
3 And also the final analysis being done when all 170  
4 patients have completed the study.

5 DR. PINES: With this we conclude the  
6 sponsor's presentation. I want to thank you for  
7 your time.

8 CHAIR YANCY: I'd like to thank the  
9 sponsor for your presentation. It was very  
10 thorough, very professional, and we appreciate the  
11 information that you delivered.

12 At this time, we have several minutes.  
13 We are considerably ahead of time, so we can  
14 proceed with questions to the sponsor. The  
15 questions should be for points of clarification.  
16 If there are additional data points that you would  
17 request from the sponsor, this gives them  
18 sufficient time to get that information and make it  
19 available during the afternoon. Or, if there are  
20 other concerns that have been raised based on the  
21 presentation, we can pursue those now.

22 Let me begin the questions with just two

1           questions specifically about the pediatric  
2           population. The first has to do with any unique  
3           issues related to IRB approval since the study was  
4           being done and on neonates, essentially. And the  
5           second question is the incidence of adhesions seen  
6           in the pivotal trial was approximately 74 percent  
7           in the control population. Is that consistent with  
8           the pediatric surgical experience in these  
9           patients?

10                         DR. PINES: I'm going to let Dr. Backer  
11           address the latter and I will address the first  
12           one.

13                         In terms of the IRB approvals, we  
14           approached 17 institutions. We got approval at 17  
15           institutions. As was stated in the presentation,  
16           we proceeded with 15 centers. There were two  
17           centers that, in one case, that didn't have --  
18           subsequent to IRB approval, they did not have the  
19           infrastructure to properly document and monitor the  
20           study. So we withdrew that center. In another  
21           center, the investigators prematurely left before  
22           we initiated the study. So they did not enroll any

1 patients.

2 In terms of IRB difficulties, we had  
3 none. We had only supporting documents based on  
4 the preclinical data. Moreover, in this case, we  
5 had the luxury of two completed studies that showed  
6 no safety signals whatsoever. So, I think it's  
7 fair to say that within two to three months, we got  
8 the IRB approval from all 17 institutions.

9 CHAIR YANCY: Thank you. The clinical  
10 question, please?

11 DR. BACKER: Yes, the question was about  
12 adhesions in neonates and what do we typically see?

13 CHAIR YANCY: Your control group in the  
14 pivotal trial had about 74 percent. Is that  
15 consistent with your overall clinical experience?

16 DR. BACKER: I would say the answer to  
17 that question is yes, and I would refer you to the  
18 video that I showed, which was an untreated child.  
19 That video was taken after the study had been  
20 completed, but showed you the dense adhesions,  
21 showed you the variation of adhesions in that child  
22 with a combination of severe, moderate, mild, and

1           then that little tiny pocket of no adhesions. But  
2           that videotape, I think is very representative of  
3           what we see after these operations. And I would  
4           say that 70 percent is exactly what I would have  
5           expected.

6                         CHAIR YANCY: Okay, thank you.

7                         DR. PINES: Just one point of  
8           clarification. It was 70 percent of the severe  
9           adhesions. It's roughly 100 percent of the  
10          patients have adhesions, be it mild, moderate, or  
11          severe.

12                        CHAIR YANCY: Thank you again. Let's  
13          being with our first panel question, please. Dr.  
14          Somberg?

15                        DR. SOMBERG: Thank you. My first  
16          question is to Dr. Pines. Maybe you can tell me  
17          the duration and the range of the survival of this  
18          prosthetic material that is placed?

19                        DR. PINES: Sure. The material is  
20          designed to be resorbed, histologically gone within  
21          28 days.

22                        DR. SOMBERG: Twenty-eight days.

1 DR. PINES: So the biocompatibility  
2 studies that I was alluding to in rabbits and rats,  
3 essentially at 28 days, there were no gross  
4 material observable and histologically, the  
5 material was gone as well.

6 DR. SOMBERG: What about in the human  
7 studies?

8 DR. PINES: In the human study --

9 DR. SOMBERG: I know you can't have  
10 serial ones, but --

11 DR. PINES: Sure.

12 DR. SOMBERG: -- was there any material  
13 found in the re-operation point?

14 DR. PINES: Sure. Part of the protocol  
15 called for at the time of the second sternotomy, if  
16 there was any signals of remnants or any material  
17 that looks like a foreign body material, the  
18 requirement was that the biopsy would be taken and  
19 would be sent to pathology and pathology would  
20 report.

21 And included in the PMA submission is  
22 the detailed histology reports that were conducted

1 at the respective institutions as well as a  
2 detailed histology report that was conducted by one  
3 of our consultants who is here today, Dr. James  
4 Anderson. And if you would like any additional  
5 information, he would be happy to provide that.

6 I think it's fair to say that there were  
7 some -- I think it would be more appropriate for  
8 Dr. Anderson to address that.

9 DR. SOMBERG: The question really is, is  
10 the barrier for the most part gone, I guess, after  
11 28 days, is what you have asserted?

12 DR. PINES: Yes, sir.

13 DR. SOMBERG: Okay. That's what I  
14 really want to know, not that there may be some  
15 microscopic remnants there.

16 Another follow-up question, if I may?  
17 And the other question would be to the clinical  
18 surgeons, specifically Dr. Backer. Could you give  
19 me an idea on the surgical literature, which I am  
20 not that familiar with, but I do remember my  
21 rotations through cardiothoracic surgery that the  
22 adhesions may develop in the adult population on a

1 variable rate and experience? And I remember  
2 anecdotally being told by some noted surgeons that  
3 the duration of the time from operation to re-  
4 operation, they have an impact on the adhesions.  
5 In other words, very very old or people who have  
6 had maybe one or two early operations and then in  
7 a ten year period would have more. Is there any  
8 literature or data supporting that the adhesion is  
9 really due to the early phase? Because  
10 essentially, you have used a surrogate model, the  
11 pediatric population where you could re-operate  
12 from two to eight months. In your slide you  
13 mentioned eight to twenty years as the re-operation  
14 for the adult was going to be the main use of this  
15 product.

16 So therefore, is the insult something in  
17 the 28 day period that you're going to deal with,  
18 or do we have to worry about a continuum of  
19 potential adhesion formation which is not really  
20 looked at in the adult?

21 DR. BACKER: My answer to that would be  
22 based mostly on my experience operating on adults

1           that have congenital heart disease. And I would  
2           say that the incidence of adhesions is quite  
3           variable, not predictable. And in some patients,  
4           the adhesions seem to mature over time. And if you  
5           operate on a patient 20 years after an initial  
6           procedure, the adhesions are relatively mature and  
7           somewhat easier to go through.

8                         But on the other hand, I have had  
9           patients that have had a single operation. Some  
10          patients we do a re-operation after the Fontan  
11          procedure, some of these patients had a single  
12          operation at the age of six or seven, the Fontan  
13          operation, and then I've re-operated on them when  
14          they were 35 years old and they have severe dense  
15          adhesions throughout the mediastinum that we did  
16          not predict and we were actually hoping that this  
17          would be an easy operation because of the duration  
18          between the initial operation and our procedure.  
19          And that did not prove to be the case. There were  
20          dense severe adhesions, very clinically  
21          significant.

22                         So I think that the main point is that

1           it is not predictable and that there is no real  
2           tendency that as time goes by that these become  
3           less of an issue.

4                         Does that answer your question?

5                         DR. SOMBERG:  It's helpful.  Is there  
6           anyone, any other clinicians from the sponsor's  
7           point of view who would like to address the issue?  
8           Because I'm wrestling with the idea of something  
9           that is an acute intervention that was looked at  
10          for a short window time, two to eight months, is  
11          now going to be extrapolated for eight to twenty  
12          years?

13                        DR. diZEREGA:  Thank you for your  
14          question, Dr. Somberg.  My name is Gere diZerega.  
15          I am a professor at the Keck School of Medicine at  
16          the University of Southern California.  I have been  
17          a consultant on this project, actually, since it's  
18          preconception.  We began working with the animal  
19          models.  I think I helped provide some perspective.  
20          And I do have a financial interest in the company.

21                        We've been looking at responsive tissue  
22          from an adhesion perspective in a variety of

1 mesothelial surfaces for a number of years. The  
2 pericardium does have a mesothelial surface and its  
3 response to surgical injury has been well studied.  
4 And it's very clear from the standpoint of view of  
5 adhesion formation following surgery, that's a  
6 relatively acute event.

7           So whether or not an adhesion is going  
8 to form, yes, no, occurs as Dr. Backer was  
9 indicating, in the early postoperative interval.  
10 As time goes on, as months become years, and as  
11 years become decades, if the adhesion formed during  
12 the acute postoperative interval, it does change.  
13 It does undergo, as Dr. Backer indicated,  
14 maturation. It can have more collagen as a result  
15 of fibroblast. It can have vascularization and in  
16 even in some instances calcification. But whether  
17 or not it's there and its consistency, the overall  
18 surface area involved and the type of adhesion it  
19 is going to become, that's actually an acute event,  
20 and that's why the duration of the retention of  
21 this biomaterial in the pericardial space was  
22 designed to last as long as it did.

1                   So in other words, we did animal models  
2                   to determine how long the biomaterial should be  
3                   there, so that it was there no longer than  
4                   necessary. And it is exactly this time period that  
5                   was able to achieve these types of events at  
6                   reducing the severe adhesions. It's an acute  
7                   event, not a chronic event.

8                   CHAIR YANCY: Thank you. Let's go to  
9                   our next question from Dr. Hirshfeld.

10                  DR. HIRSHFELD: Thank you. I'd like to  
11                  ask you to discuss the clinical relevance of your  
12                  primary efficacy endpoint. I think you quite  
13                  convincingly demonstrated that the endpoint  
14                  variable, as you measured it, was favorably  
15                  affected by the device. And I think the  
16                  photographs that were shown and the video that were  
17                  shown were quite convincing that these adhesions  
18                  are not things that help surgeons do re-operations.

19                  Nonetheless, in terms of clinical  
20                  outcomes, I don't see any evidence in your data  
21                  that the patients had better clinical outcomes,  
22                  beginning with the dissection times, which were the

1 same, and continuing with all the various types of  
2 post-operative complications which could, in some  
3 way, have been loosely connected to the technical  
4 aspects of doing the operation.

5 I would have hoped there would at least  
6 be a signal in your data that suggested that the  
7 patients who received the device had better  
8 outcomes in terms of other adverse events. And I  
9 wonder if you could clarify this issue for us, as  
10 to whether what we're looking at is truly a  
11 clinically relevant endpoint.

12 DR. PINES: Sure. I'm going to let Dr.  
13 Weinstein and then Dr. O'Brien respond to the  
14 question. Thank you.

15 DR. WEINSTEIN: Thank you for your  
16 question. There is, as you can imagine, very  
17 little literature from centers on catastrophic  
18 complications from re-operations. Very few centers  
19 like to write reports about the injuries traded  
20 upon re-operative median sternotomy.

21 What literature we do know from, and a  
22 great degree of it comes from the Cleveland Clinic,

1 is that in re-operative adult surgery, the  
2 mortality rate is increased from three to five  
3 times that of non-re-operations. Complications  
4 seen stem from the five percent incidence of injury  
5 to the LAD vessel, to the increased prolonged time  
6 in surgery, increased transfusion requirements,  
7 femoral-femoral bypass, which means intervention  
8 into the femoral vessels which have their own  
9 morbidity associated with it, renal failure, and  
10 neurologic injury.

11 In this study, there was not an increase  
12 in mortality and many of those other endpoints were  
13 not evaluated specifically. I would like to refer  
14 again to the analogy that Dr. Rose has liked to use  
15 in that if you had a choice of being the airplane  
16 that's flying at night in the bad weather with bad  
17 winds, or having a plane that flies in the middle  
18 of the day, landing on the ground, it's the ease  
19 and the ability to maneuver that aircraft. Whether  
20 the morbidities are decreased or not versus the  
21 mortality, the data is not able to address.

22 CHAIR YANCY: Dr. Domanski.

1 DR. DOMANSKI: Yes. I'd like to follow  
2 up on that because the obvious question to ask was  
3 gee, you don't see any real difference in the  
4 clinical results.

5 On the other hand, I'd like to ask you,  
6 you know, I don't do cardiac surgery, but it's  
7 fairly impressive to look at those adhesions. I  
8 wonder to what degree, and this is a pretty skilled  
9 group of people that did this, it looks like a  
10 fairly carefully picked group, and I guess if I  
11 were trying to get through a difficult operation,  
12 I'll use your analogy, your analogy is actually,  
13 usually I don't like argument by analogy, but that  
14 one is a pretty good one. You know, there are a  
15 lot of people who fly around in these little  
16 private airplanes and get themselves into the kind  
17 of weather you're talking about and end up dead.  
18 But the commercial pilots, the guys who have a lot  
19 of experience who are really good at it, get you  
20 through the weather and you know you end up on the  
21 ground with them giving you the time of the local  
22 destination.

1 I wonder if there is any way of helping  
2 us understand how the skill level varies for people  
3 doing this and how this helps people who are  
4 perhaps not eminent folks get through it.

5 DR. WEINSTEIN: Thank you for that  
6 question. Every researcher will have a different  
7 degree of experience with re-operative surgery.  
8 Pediatric surgeons I think on the whole, and the  
9 adult surgeons and pediatric surgeons on the panel  
10 can speak to it as well, probably have as much re-  
11 operative experience as surgeons that are out  
12 there. A fair degree of our patients come for re-  
13 operations. As we see in the study, there is a  
14 percentage of our population who require three  
15 operations to survive to adulthood.

16 Depending on the adult-type practice you  
17 would have, for adult surgeons, the increasing of  
18 re-operation, the incidence of re-operation is  
19 increasing over time. It used to be closer to ten  
20 percent. It's thought to be closer to 20 percent  
21 by the end of this decade. So I think there is a  
22 variable degree of experience, depending on your

1 practice, and I think the incidence of re-operation  
2 is increasing.

3 DR. DOMANSKI: Do we have an  
4 understanding of how the numbers, you know, or how  
5 the experience impacts on mortality? Because I'm  
6 wondering whether this device, which frankly may  
7 make your life easier but not really make much  
8 difference to your patients at the end of the day,  
9 because you fly through the weather, I'm wondering  
10 whether it would help other people fly through  
11 weather they wouldn't get through.

12 I mean, that's what I really want to try  
13 to get at because otherwise, the question of  
14 clinical effectiveness starts to be more worrisome  
15 and I'm trying to give you way out.

16 DR. WEINSTEIN: I'm trying to be  
17 respectful of all of the centers out there that  
18 perform cardiac surgery. We were very selective in  
19 picking the sites. We went to only the finest  
20 centers in the country, with some of the finest  
21 surgeons. I think that with an inadequate amount  
22 of experience or just a lack of experience in

1           general, the device becomes more helpful.

2                       CHAIR YANCY:  Dr. Page, please?

3                       DR. PAGE:  I want to thank the sponsors  
4           for a very well organized presentation.  A couple  
5           technical issues I think Dr. Backer will best be  
6           able to address for me.

7                       In terms of the adhesions, I understand  
8           the importance of the anterior surface of the heart  
9           being protected from the sternum.  That's clear.  
10          But there's still an inflammatory fibrotic process  
11          that, essentially you're putting a barrier down, so  
12          that that, if I understand it correctly, still is  
13          unabated on the surface of the heart.

14                      And one of the issues that you showed  
15          there was the adhesions between the heart and the  
16          sternum, but also just the fact that this fibrotic  
17          inflammatory process actually obscures anatomic  
18          landmarks on the surface of the heart and the other  
19          great vessels in the mediastinum.  And in that way,  
20          help me understand how this barrier would have an  
21          affect.

22                      And then, if I may, Dr. Yancy, I will

1 have one other follow up question.

2 DR. BACKER: Thank you for the question.  
3 I think that the, you know, one of the reasons that  
4 we selected that investigational surgical site was  
5 to have a defined area to look at. Clearly, if we  
6 could reduce adhesions further out along the edge  
7 of the ventricle and the atrium, that's going to be  
8 helpful. And personally, if this product is  
9 approved, I would like to do that in my patients,  
10 is bring it further out to reduce the adhesions  
11 adjacent to the atrium and adjacent to the  
12 ventricle.

13 But again, one of the key problems with  
14 the sternal re-entry is when you're actually going  
15 through the sternum, that if you get into the  
16 ventricle or the atrium, that can be a catastrophic  
17 problem where you have to convert to femoral bypass  
18 like in that 12-year-old boy that I showed, which  
19 leads to a cascade of complications. You know,  
20 poor perfusion during the bypass run, lots of  
21 bleeding, renal failure, etcetera, etcetera,  
22 etcetera.

1           So for this particular study, placing  
2           the REPEL device immediately below the sternum and  
3           trying to reduce the adhesions in that critical  
4           area underneath the sternum, helps the surgeon at  
5           the time of sternal re-entry to make the sternal  
6           re-entry that much safer. But decreasing adhesions  
7           anywhere around the heart would be a real benefit.

8           DR. PAGE: But if I understand  
9           correctly, of those photographs that you showed,  
10          one is the pristine virgin heart, if you will, and  
11          the other was after the sternum had been retracted,  
12          but you are looking down at a heart covered with --

13          DR. BACKER: Right.

14          DR. PAGE: -- fibrotic material. Was  
15          there any difference, is it better, worse, or the  
16          same, in the part of the heart that was adjacent to  
17          this device?

18          DR. BACKER: Well I actually don't know  
19          that we have the, we don't really have the answer  
20          to that because we were all blinded, you know, at  
21          the time of the reevaluations. We didn't know  
22          whether the patient had received the REPEL device

1 or not at the time of the re-operation, the  
2 investigation. We were just limited to evaluating  
3 that investigational site beneath the sternum.

4 DR. PAGE: I see. And you were not  
5 specifically looking at that as one of the  
6 variables?

7 DR. BACKER: We didn't look at that as  
8 a variable. And again, we were blinded.

9 DR. PAGE: And my follow-up was, in  
10 terms of the masking, I saw that there were  
11 problems in identifying an appropriate person to be  
12 masked --

13 DR. BACKER: Yes.

14 DR. PAGE: -- during this assessment.  
15 But even for those who were truly masked, help me  
16 understand how that happened, how well that could  
17 happen in the OR itself. And finally, while this  
18 device does resorb, just as with a suture that's  
19 resorbed, you can tell if there was a suture beyond  
20 the duration of its actual having any ability to  
21 hold tissues together. Is there material that  
22 while you went in, once you had a little bit of

1           experience, you would recognize that there was this  
2           device there in the first place?

3                       DR. BACKER: All right. I'll take first  
4           question first with regard to the masking. The way  
5           that that worked was if the patient was enrolled in  
6           the study, the implanting surgeon at the time of  
7           the chest closure could not be the surgeon for the  
8           sternal re-entry. So we didn't know whether the  
9           patient had to receive the device or not, we just  
10          knew that the patient was in the study.

11                      And then typically at most pediatric  
12          cardiac surgical institutions, there is only two or  
13          three surgeons. So that meant it was one of two  
14          people. And the problem with that was that  
15          frequently, even if the other surgeon was out of  
16          town at a meeting, or on vacation, or sick, or  
17          doing a transplant, and the problem with these  
18          patients again was that there is a limited time  
19          window for the second operation. So we didn't have  
20          the luxury to say okay, bring them back in a month  
21          or two months. And that's when the evaluators were  
22          not masked, although we attempted to do that in