SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Bioresorbable Adhesion Barrier

Device Trade Name: REPEL-CV® Bioresorbable Adhesion Barrier

Applicants Name and Address: SyntheMed, Inc.
200 Middlesex Essex Turnpike
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Iselin, NJ 08830

Date of Panel Recommendation: September 19, 2007

Premarket Approval Application (PMA) Number: P070005

Date of Approval to Applicant: March 6, 2009

II. INDICATIONS FOR USE

REPEL-CV Bioresorbable Adhesion Barrier (hereinafter called REPEL-CV) is indicated for reducing the severity of post-operative cardiac adhesions in pediatric patients who are likely to require reoperation via sternotomy.

III. CONTRAINDICATIONS

None

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the REPEL-CV labeling.

V. DEVICE DESCRIPTION

REPEL-CV Bioresorbable Adhesion Barrier is a single use, synthetic, bioresorbable polymeric film composed of poly-lactic acid (PLA) and polyethylene glycol (PEG). This film is designed to provide a temporary barrier within the chest cavity to reduce the area of severe adhesion formation between the chest wall and the cardiac surface unprotected by pericardium. The REPEL-CV is designed to interrupt the process of adhesion formation and reduces the severity of the adhesions.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Conventional procedures used to reduce severity of postoperative adhesions of the heart to mediastinal structures after cardiovascular surgery include bovine/heterologous pericardium, hydrophilic solutions, resorbable polymeric matrices, polytetrafluoroethylene (PTFE) membranes, and procedures to re-establish coverage with parietal pericardium.[1-9]

VII. MARKETING HISTORY

REPEL-CV has been marketed in Europe (including the UK, Germany, Italy, Turkey, Greece, France, Spain and Sweden) since September 2006. There have been no reported adverse events to date.

The REPEL-CV has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The pivotal study for the REPEL-CV was a multi-center, randomized, evaluator-masked, parallel, comparative study to evaluate the safety and effectiveness of REPEL-CV in its ability to reduce the severity and extent of post-operative adhesions following pediatric cardiovascular surgery. The study enrolled 144 pediatric patients from 15 United States study sites, fulfilling the inclusion criteria and having none of the exclusion criteria, were enrolled into the study after their legal representative (guardian) had signed the informed consent form. The following sections detail the occurrence of adverse events during the course of the study.

Adverse Effects of the Device on Health

In the REPEL-CV treatment group, 51 patients experienced 135 AEs and in the control treatment group, 49 patients experienced 123 AEs. Thirty-seven (37) patients experienced 63 SAEs in the REPEL-CV treated group and thirty-two (32) patients experienced 53 SAEs in the control group. The death rate following the first sternotomy and prior to the second sternotomy, was 12.3% (9/73) for REPEL-CV vs. 10.1% (7/69) for Control. The overall death rate was 16.4% (12/73) for REPEL-CV vs. 13.0% (9/69) for Control.

The majority of the patients participating in the pivotal trial required cardiac surgery when less than 14 days old. All patients were cyanotic both before and following surgery, and more than 90% had a single ventricle. In addition, in approximately 75% of the patients closure of the initial sternotomy required delay of several days, as a routine procedure, Table 1 tabulates all adverse events occurring at a frequency $\geq$ 2% in either the treatment or control arms, and for which frequency of REPEL-CV's AEs was not 0%.

Table 1. Adverse Events ≥ 2% by Descending Frequency

	REPEL-CV (N=73)	Control (N=69)
MedDRA Preferred Term	N (%)	N (%)
Cardio-Respiratory Arrest	4 (5.5%)	2 (2.9%)
Pleural Effusion	4 (5.5%)	3 (4.3%)
Wound Dehiscence (superficial)	4 (5.5%)	3 (4.3%)
Wound Infection (superficial)	4 (5.5%)	3 (4.3%)
Ascites	3 (4.1%)	0
Cardiac Arrest	3 (4.1%)	4 (5.8%)
Bronchiolitis	3 (4.1%)	0
Cardiac Output Decreased	3 (4.1%)	1 (1.4%)
Hypoxia	3 (4.1%)	2 (2.9%)
Pulmonary Artery Stenosis	3 (4.1%)	1 (1.4%)
Mediastinitis(prior to 2nd sternotomy)	2 (2.7%)	1 (1.4%)
Mediastinitis (after 2nd sternotomy)	2 (3.6%)	0
Cyanosis	2 (2.7%)	1 (1.4%)
Coarctation of the Aorta	2 (2.7%)	3 (4.3%)
Necrotising Colitis	2 (2.7%)	3 (4.3%)
Bacteraemia	2 (2.7%)	2 (2.9%)
Respiratory Syncytial Virus Infection	2 (2.7%)	0
Convulsion	2 (2.7%)	7 (10.1%)
Atelectasis	2 (2.7%)	0
Diaphragmatic Paralysis	2 (2.7%)	1 (1.4%)
Respiratory Distress	2 (2.7%)	3 (4.3%)
Haemodynamic Instability	2 (2.7%)	0
Hypotension	2 (2.7%)	0
Pyrexia	1 (1.4%)	2 (2.9%)
Gastroenteritis	1 (1.4%)	2 (2.9%)
Oxygen Saturation Decreased	1 (1.4%)	7 (10.1%)
Chylothorax	1 (1.4%)	2 (2.9%)

Potential Adverse Effects of the Device on Health

Potential adverse events related to cardiac procedures can include the following:

- Adhesions
- Aortic insufficiency
- Arrhythmia
- Cardiac arrest
- Cardiac tamponade
- Cerebral emboli
- Death or irreversible morbidity

- Diaphragm paralysis to placation
- GI/Digestive tract complication
- Hemorrhage
- Injury to vessels or tissue
- Ischemia
- Low cardiac output
- Wound infection
- Mediastinitis
- Myocardial infarction
- Neurological deficits
- Organ system dysfunction/failure
- Pericardial effusion
- Pleural effusion
- Positive culture for infection /sepsis
- Psuedo aneurysm
- Pulmonary emboli
- Pulmonary hypertension
- Re-exploration
- Renal dysfunction/failure
- Respiratory distress
- Shunt revision
- Sternal wound edge dehiscence
- Stroke or cerebral infarction
- Vessel thrombosis

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

Objectives. The objectives of the laboratory studies were to test the safety and biocompatibility, hydrated tensile strength, and sterilization of the REPEL-CV.

The following GLP studies were conducted to support the safety and biocompatibility of REPEL-CV. These studies, with the exception of the infectivity study, were conducted under USP and ISO 10993 Guidelines.

Cytotoxicity Test USP Elution Method - The cytotoxicity study indicated that extracts of the test article did not cause cell lysis or toxicity.

Genotoxicity Ames Test - The genotoxicity studies indicated that the product is not mutagenic based on the *Salmonella typhimurium* reverse mutation study using both saline and ethanol extraction procedures.

Chromosomal Aberration Test and Sister Chromatid Exchange Test - It was demonstrated that the extract from the test article was not considered genotoxic to

Chinese Hamster Ovary cells in the presence or absence of S9 metabolic activation.

Rabbit Pyrogen Study - The material was shown to be non-pyrogenic using a protocol to determine material mediated pyrogenicity in a rabbit model.

Hemolysis - The results of the hemolysis study indicated that the test article extract was slightly hemolytic. The mean hemolytic index was 3% (slightly hemolytic grade = 3-10%).

USP Intracutaneous Toxicity Test in Rabbits of Extracts (saline/oil) - There was no evidence of significant irritation or toxicity from sodium chloride or cottonseed oil extracts of the test article when injected intracutaneously in rabbits.

Surgical Subcutaneous Implantation Study in the Rat with Histopathology - In the surgical subcutaneous implantation study in the rat, at days 3, 7, and 14, the test article and control sites had capsule formation up to 0.5 mm, and there were portions of implants visible in all animals. By day 29, the test article was no longer visible. At days, 7, 14 and 29, the test article was considered a non-irritant.

Delayed Contact Sensitization Study in the Guinea Pig (saline/oil) -The guinea pig maximization test was conducted to evaluate the potential for delayed dermal contact sensitization. Under the conditions of the study, the sodium chloride and cottonseed oil extracts of the test article showed no evidence of causing delayed dermal sensitization.

Infectivity - Under the conditions of the study, the test article did not appear to potentiate mortality or abscess formation.

Peritoneal Implantation in the Rabbit (Surgical Method, 1 Week and 4 Weeks) - The study in the rabbit was performed to evaluate the microscopic and macroscopic reactions following peritoneal implantation. Under the conditions of the study, the test article did not appear to elicit treatment-induced effects in comparison with the surgical controls.

Intraperitoneal Toxicity Study in the Rat - In this study, the test article was evaluated for its potential to cause systemic toxicity following intraperitoneal implantation. Under the conditions of the study, there was no significant evidence of systemic toxicity. Microscopic examination of tissues did not indicate any evidence of a toxicologically significant response. Hematology and clinical chemistry data indicated no device-related effects.

USP Systemic Study in the Mouse - The study was performed to evaluate whether saline and cottonseed oil extracts of the test article had the potential for systemic toxicity in the mouse. Under the conditions of the study, there was no mortality or evidence of significant systemic toxicity from the extracts.

Embryo/Fetal Development in Rats - The study was performed to determine the potential of the test article to induce maternal and developmental toxicity after maternal exposure during the critical period of organogenesis. Results indicated no developmental toxicity.

Muscle Implantation Study in the Rabbit with Histopathology - The study was performed to determine the potential that the test article is a muscle irritant. Under conditions of the study, the test article was designated a non-irritant.

Twenty-Eight Day Cardiac Biocompatibility Study in the Rabbit - The study of the test article indicated no untoward or gross histological reactions.

Systemic Toxicity Study in Weanling Rats (1 and 4 weeks) -There was no significant evidence of systemic toxicity and no evidence of nephrotoxocity from the test article implanted in the intraperitoneal cavity of rats.

In summary, the above studies showed the test article to be nontoxic and biocompatible.

The testing described below (hydrated tensile strength study and USP 23 antimicrobial preservative effectiveness study) was performed on REPEL, a product similar to REPEL-CV. The differences between the products are shown in Table 2:

Table 2. Differences between REPEL and REPEL-CV

	REPEL	REPEL-CV
PEG:PLA (by weight)	64:35	47:52
Thickness (microns, μ)	200 μ	150 μ

The constituents and their respective concentrations are very similar for REPEL and REPEL-CV. Therefore, although the testing described was performed on REPEL, the conclusion is applicable to REPEL-CV as well.

The objective of the hydrated tensile strength study is to correlate the REPEL hydrated tensile strength with its qualitative suture pull-out strength. Devices were hydrated for the cited intervals and for each time period the device's hydrated tensile strength and suture pull-out strength were determined. With increasing hydration time the hydrated tensile strength and the suture pull-out strength decreased. The minimum acceptable hydrated tensile strength for the device was 400 psi.

The objective of the USP 23 antimicrobial preservative effectiveness study is to determine if REPEL could be stored without causing an increase in the bioburden for the material. The inoculated samples were incubated in sealed vessels and

recovery of viable organisms was performed at the cited intervals by standard plate count. For the tested organisms (with the exception of *Escherichia coli*) the device met the requirements of USP 23 APE test. For Escherichia coli, the device exhibited ~ 2 log reduction in growth after 21 days. The device did not support bacterial growth.

Animal Studies

Objectives. The objectives of the animal studies were to determine the safety and preliminary effectiveness of the REPEL-CV. FDA reviewed summary reports of nine separate animal studies in two species (dog, rabbit).

Table 3. Summary of REPEL-CV® Short Term Placement and Nonclinical Efficacy Studies

Study Title	Study Objective	Conclusions
Observation of REPEL and REPEL-CV® after short term placement in animals (Rabbit)	Method development of materials and procedures to be used in later studies. Also, determine the ability of the material to remain intact at the site of placement at various times post-operatively.	The material with higher levels of polylactic acid (REPEL-CV) was able to hold sutures for longer periods and maintained integrity when placed over an uninjured sidewall for at least 4 hours post-operatively.
Observation of REPEL and EO/LA 1.5 (REPEL-CV) after short term placement in animals (Rabbit).	Method development of materials and procedures to be used in later studies. To also determine the ability of the material to remain intact at the site of placement at various times post-operatively.	The material with higher levels of polylactic acid (EO/LA=1.5 =REPEL-CV) was able to hold sutures for longer periods and maintained integrity when placed over an uninjured sidewall for at least 16 hours post-operatively.
Design evaluation of cardiovascular EO/LA films (1.5, 2.5, 3.0) in the prevention of epicardial-pericardial adhesions in the canine cardiac model.	To evaluate the efficacy of films of EO/LA ratios 1.5, 2.5 and 3.0 in their ability to reduce adhesion formation between the epicardium and pericardium in a canine model.	All films were efficacious in reducing adhesion formation. The film with EO/LA ratio 1.5 (REPEL-CV) was the most efficacious.
Observation of Repel, EO/LA 1.5 (60 μm thick) after short term placement in animals (Rabbit)	Method development of materials and procedures to be used in later studies. To also determine the ability of the material to remain intact at the site of placement at various times post-operatively.	This material can be held in closely packed spaces in the abdominal cavity for long periods of time (72hrs) without sutures. However, at sites of organ movement (e.g., bowel), the material should be anchored to maintain placement.
Design evaluation of bioresorbable polymer films (EO/LA ratios of 1.5; 2.5; 3.0) in the canine model for the reduction of retrosternal adhesions.	To evaluate the efficacy of bioresorbable polymer films (EO/LA ratios of 1.5; 2.5; 3.0) in the reduction of retrosternal adhesions in the canine model.	Films with EO/LA ratios of 2.5 and 3.0 were highly efficacious in reducing adhesion formation. The film with an EO/LA ratio of 1.5 (REPEL-CV) was most efficacious and the dogs treated with this material were free of adhesions.

Study Title	Study Objective	Conclusions
Design evaluation of cardiovascular EO/LA film (1.5), Lot 082097, in the prevention of retrosternal adhesions in the rabbit cardiac model.	To evaluate the efficacy of a film with an EO/LA ratio of 1.5, REPEL-CV® Lot 082097, in its ability to reduce adhesion formation between the sternum and epicardium in the rabbit model.	REPEL-CV® (EO/LA ratio 1.5) was highly efficacious and the rabbits treated with this material were free of adhesions.
Design evaluation of REPEL-CV® cardiovascular (CV), EO/LA film 1.5, in the prevention of epicardial-pericardial adhesions in the canine cardiac model.	To evaluate the efficacy of a film with an EO/LA ratio of 1.5, REPEL-CV® Lot 082097, in its ability to reduce adhesion formation between the epicardium and pericardium in the canine model.	REPEL-CV® (EO/LA ratio 1.5) was highly efficacious in reducing adhesion formation in this canine model.
Design evaluation of REPEL-CV®cardiovascular (CV), EO/LA film 1.5, in the prevention of retrosternal adhesions in the rabbit cardiac model.	To evaluate the efficacy of a film with an EO/LA ratio of 1.5, REPEL-CV®, Lot F00298, in the reduction of adhesion formation between the sternum and epicardium in a rabbit model.	REPEL-CV® (EO/LA ratio 1.5) was highly efficacious in reducing adhesion formation in this rabbit model.
Design evaluation of cardiovascular EO/LA film (1.5), Lot No. I01498, in the prevention of retrosternal adhesions in the rabbit cardiac model	To evaluate the efficacy of a film with an EO/LA ratio of 1.5, REPEL-CV®, Lot I01498, in the reduction of adhesion formation between the sternum and epicardium in a rabbit model.	REPEL-CV® (EO/LA ratio 1.5) was highly efficacious in reducing adhesion formation in this rabbit model.

These studies indicated a high degree of effectiveness in reducing the severity of adhesion formation when used in a simulated human thoracic surgical intervention. No safety concerns were identified across these nine studies.

X. SUMMARY OF CLINICAL STUDIES

SyntheMed sponsored three feasibility/pilot clinical studies and one pivotal clinical study to evaluate the safety and effectiveness of REPEL-CV. Three studies were conducted in the United States under IDE G980030 and one study was performed in Europe to support the CE Mark. Table 4 includes a list of the clinical studies..

Table 4. Summary of Clinical Trials

Name	N	Description
Study 1. A Comparative, Evaluator-Blinded, Randomized, Parallel Study to Determine the Safety of REPEL-CV® for Reducing Post-Operative Adhesions Following Adult Cardiothoracic Surgery (Protocol # LMS9802RCV)	15 REPEL-CV 12 Control	Safety study in adult patients undergoing CABG, Valvular and LVAD procedures
Study 2. A Comparative, Evaluator-Blinded, Randomized, Parallel Study to Determine the Safety and Effectiveness of REPEL-CV® for Reducing Post-Operative Adhesions Following Pediatric Cardiothoracic Surgery (Protocol # LMS0001RCVP)	7 REPEL-CV 6 Control	Safety and effectiveness study in pediatric patients undergoing staged cardiac surgical procedures to correct congenital cardiac malformations
Study 3. Open Label, Multicenter Study to Determine the Effectiveness of REPEL-CV® for Reducing Post-Operative Adhesions Following Pediatric Cardiothoracic Surgery (Protocol # LMS0104RCV)	19 REPEL-CV	Open safety and effectiveness study in pediatric patients undergoing staged cardiac surgical procedures to correct congenital cardiac malformations
Study 4. A Comparative, Evaluator-Masked, Randomized, Parallel, Multicenter Study to Determine the Safety and Effectiveness of REPEL-CV® for Reducing Post-Operative Adhesions Following Pediatric Cardiothoracic Surgery (Protocol # LMS0103RCV)	73 REPEL-CV 71 Control	Safety and effectiveness pivotal study in pediatric patients undergoing staged cardiac surgical procedures to correct congenital cardiac malformations

Feasibility Studies

Study 1

This study was conducted in 1998 as a randomized trial at a two-hospital, single center and included adult patients. Although designed as a feasibility study for safety, assessment of adhesion extent at the time of re-explorative cardiac surgery was also conducted by a masked evaluator. Twenty-seven (27) patients were randomized who underwent a coronary artery bypass graft (CABG) operation (9 REPEL-CV, 11 Control), valve operations (4 REPEL-CV, 1 Control), and 2 cases (REPEL-CV) of left ventricular assist devices (LVADs) implanted for bridging to transplant. One of the patients with an LVAD suffered from coagulopathy, noted as possibly related to the device. The extent of adhesions at re-exploration of the 2 LVAD patients was not dissimilar to that usually associated with temporary LVAD implants.

Study 2

This study focused on the determination of safety and effectiveness of REPEL-CV for reducing post-operative adhesions in pediatric patients with an age range of 3-7 days. There were a total of 13 pediatric patients randomized in a single center study (n=7 received REPEL-CV and n=6 were the Control group). Masked evaluators assessed the extent and severity of adhesions at re-operation. These pediatric patients generally underwent delayed primary chest closure and in those cases, patients randomized to REPEL-CV had a temporary dressing with the device which was replaced at the time of delayed primary closure. At secondary exploration, adhesions were rated by severity using a Grade 0 to 2 scale (shown in Table 5) and extent as the percent of surgical site (bare cardiac surface) affected by each grade of adhesion.

Table 5. Adhesion Severity Scale for Study 2

Adhesion Severity	Description
0	**No** adhesions
1	**Filmy** adhesions (non-cohesive, requires a combination of blunt and selective sharp dissection to separate the tissues between the epicardium and the sternum)
2	**Dense** adhesions (cohesive, requires extensive sharp dissection to separate the tissues between the epicardium and the sternum)

There were a total of 7 patients who completed the study. Of the 7, three received the REPEL-CV. While the differences between the adhesion results for the patients were not significant for the sample size, there was a suggestion of effectiveness that prompted the initiation of a pivotal and European study.

Serious adverse events (SAEs) occurred in 3 patients in each cohort. These were listed as cardiac in all cases except for a single infection in a Control patient. There were 4 additional infections in REPEL-CV patients listed as moderate in severity (IV line catheter tip, pulled line tip, (-) growth from superficial sternal wound and (+) growth from mediastinal swab at closure). All infections were resolved with antibiotic treatment. Mediastinal events consisting of mediastinal hematoma (prior to closure) and prolonged open sternum, were listed for REPEL-CV patients. Two were noted as severe and none for the Controls.

Study 3

This study was an Open Label, outside United States (OUS), single arm study that enrolled 19 REPEL-CV patients undergoing staged congenital cardiac procedures in a multi-center trial. The objective of this study was to gain European clinical experience with the REPEL-CV. The performance (effectiveness) endpoints were

the percent of patients with any Grade 3 (severe) adhesions and the patient-specific percentage of the study-defined surface area of the investigational surgical site with Grade 3 adhesions at the time of the 2nd sternotomy.

The grading scale used for this study is shown in Table 6.

Table 6. Adhesion severity scale for Study 3

Grade 0 = **No** adhesions
Grade 1 = **Mild** Adhesions (filmy, non-cohesive adhesions requiring blunt dissection to separate the space between the epicardium and sternum)
Grade 2 = **Moderate** adhesions (filmy, non-cohesive adhesions requiring a combination of blunt and selective sharp dissection to separate the space between the epicardium and the sternum)
Grade 3 = **Severe** adhesions (dense, cohesive adhesions requiring extensive sharp dissection to separate the space between the epicardium and the sternum)

Of the 19 patients enrolled, 15 completed the study. In the absence of Control patients, the data describes the average rates of % adhesion in the 15 REPEL-CV treated patients.

The mean age for these patients was 12.9 days, with a range of 4-54 days. All patients had Norwood procedures, excepting 2 shunt cases and 1 pulmonary artery banding. Four patients were discontinued from the study for SAEs, three resulting in death. The three deaths were cardiac-related, and the other patient who did not complete study had their shunt revised and device removed prematurely. Another SAE was described as "cerebral cramp" with patient recovery.

A mean of 10% of the investigational surgical sites in 15 patients had Grade 0 adhesions, 60% had grade 1, 20% had grade 2, and 11% had grade 3 adhesions at re-exploration. An upper confidence limit of 75.6% having grade 2 or 3 adhesions was calculated for this small sample size.

Pivotal Study – Study 4

Objectives. The objectives of this pivotal study were to evaluate the safety and effectiveness of REPEL-CV in its ability to reduce the severity and extent of post-operative adhesions following pediatric cardiovascular surgery.

Study Design

This was a multi-center, randomized, evaluator-masked, parallel, comparative study to evaluate the safety and effectiveness of REPEL-CV in its ability to reduce the severity and extent of post-operative adhesions following pediatric cardiovascular surgery. Pediatric patients from 15 United States study sites, fulfilling the inclusion criteria and having none of the exclusion criteria, were enrolled into the study after their legal representative (guardian) had signed the informed consent form. Upon enrollment, but prior to surgery, patients underwent the required screening evaluations including clinical laboratory tests (hematology and chemistry).

Inclusion Criteria

1. Patients requiring staged cardiovascular sternotomy procedures
2. No previous sternotomy
3. Weight greater than 2.5 kilograms
4. It is anticipated that the second sternotomy procedure will be performed two to eight months subsequent to the initial sternotomy procedure
5. Patient is not a participant in another invasive device or drug study during the course of this study
6. Patient's legal representative willing and able to provide written informed consent

Exclusion Criteria

1. Use of approved or unapproved treatments to prevent adhesions during the course of the study
2. Use of Extracorporeal Membrane Oxygenation (ECMO) preoperatively, intraoperatively, or before chest closure (Patient does not qualify unless it is routinely used for this procedure at the respective Medical Center)
3. Absorbable hemostats remaining at the investigational surgical site at time of randomization and chest closure
4. Positive microbiology culture of the surgical site prior to randomization
5. More than 120 hours (5 days) between the time of the sternotomy to time of chest closure
6. Evidence of thick, discolored or malodorous discharge in the wound, or other gross evidence of mediastinitis
7. The pericardium closed prior to chest closure

Primary Safety Endpoint

Safety was assessed by comparing the type, severity, relationship, and timing of adverse experiences (including death) for each REPEL-CV group in the safety population.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the percent of the study-defined investigational surgical site (ISS) with severe (Grade 3) adhesions at the second sternotomy procedure. The same scale used in Study 3 was used for the pivotal study:

> Grade 0 = **No** adhesions
>
> Grade 1 = **Mild** Adhesions (filmy, non-cohesive adhesions requiring blunt dissection to separate the space between the epicardium and sternum)
>
> Grade 2 = **Moderate** adhesions (filmy, non-cohesive adhesions requiring a combination of blunt and selective sharp dissection to separate the space between the epicardium and the sternum)
>
> Grade 3 = **Severe** adhesions (dense, cohesive adhesions requiring extensive sharp dissection to separate the space between the epicardium and the sternum)

The null and alternative hypotheses for the primary endpoint are:

$$H_0: \mu_t \geq \mu_c$$
$$H_a: \mu_t < \mu_c,$$

where μ_t and μ_c are the percent of the study-defined investigational surgical site with severe adhesions (Grade 3) at the second sternotomy procedure for REPEL-CV (μ_t) and Control (μ_c) groups.

Secondary Endpoints

The secondary effectiveness endpoints evaluated at the second sternotomy procedure included:

1. The percentage of patients with Grade 0, 1, or 2 as worst degree. [Note: This endpoint is the complement of the percentage of patients with Grade 3 (severe) adhesions and will be referred to as such for simplicity.]
2. Patient-specific percentage of the study-defined surface area (the investigational surgical site) with Grade 0, 1, and 2 adhesions. This endpoint is meant to compare the patient-specific percentage of the study-defined surface area within each adhesion grade.
3. Time to placement of the sternal retractor at the second surgery. [Note: This endpoint represents dissection time of adhesions at the investigational surgical site.]
4. The percentage of patients by worst degree of adhesions within the investigational surgical site.

Three patient populations were used for these evaluations:

1. The Evaluable population consisted of all randomized patients who underwent the adhesion evaluations at the time of the planned second sternotomy. The evaluable population was used to evaluate effectiveness and investigational surgical site observations at the second sternotomy.

2. The Per-Protocol (PP) population consisted of all randomized patients who had the planned second sternotomy at least two months after randomization, underwent the adhesion evaluations, and had no major protocol violations. The PP population was used for confirmatory analysis of effectiveness.

3. Safety population consisted of all patients who were randomized and treated.

For purposes of this summary, the results and discussion of the effectiveness measurements will focus on the evaluable group, as the results for the PP population were similar.

Patient Assessments

Patients were assessed during three scheduled visits after the screening visit. These included the initial sternotomy procedure and time of chest closure (Visit 1), Weeks 3-8 post-chest closure (Visit 2), and time of second sternotomy procedure (Visit 3). The anticipated duration of patient participation, from the time of initial sternotomy to the second sternotomy procedure, ranged from 2 to 8 months. An assessment schedule is provided in Table 7.

Table 7. Frequency of assessments

Activity	Screening V0	Initial Surgery & Time of Chest Closure V1	Weeks 3 – 8 Post Chest Closure V2	Time of 2nd Surgery V3
Inclusion/Exclusion Criteria	X	X		
Medical History	X			
Physical Examination	X			
Primary Diagnosis	X			
Informed Consent	X			
Safety Assessments		X	X	
Investigational Surgical Site Assessments				X
Adverse Events		X	X	X
Laboratory Tests	X	X[1]	X[2]	
Medication	X	X	X	
Wound Healing Assessment *at a Minimum of One Month* After Second Sternotomy				X

Demographic Data

Patients were randomized at 15 study sites. Table 8 summarizes the patient disposition by treatment group and includes the reasons for withdrawal.

Standardized reasons for withdrawal were used to impose consistency across investigator sites. The control treatment group had two protocol violations and these subjects were discontinued from the study. These two patients were randomized but not treated as per the protocol.

Table 8. Patient Disposition

	REPEL-CV	Non-Treatment Control
Randomized	73	71
Safety Population***	73 (100%)	69 (97.2%)
Evaluable Population*	56 (76.7%)	54 (76.1%)
Did not undergo the planned second sternotomy	17 (23.3%)	17 (23.9%)
PP Population**	54 (74.0%)	49 (69.0%)
Second sternotomy within 2 months of randomization	2 (2.7%)	5 (7.0%)
Discontinued (withdrawn) Reclassified[a]	20	18
Adverse events	19	16
Protocol Violation	0	2
Withdrew Consent	1	1
Other	0	0

* Evaluable population includes patients who underwent the adhesion evaluations at the time of the planned second sternotomy.

** PP population includes patients who had the 2nd sternotomy at least 2 months after randomization, underwent the adhesion evaluations, and had no major protocol violations.

*** Safety population includes all randomized and treated patients

[a] Investigator reasons for early study withdrawal were reclassified to establish consistency across responses. The study investigator indicated that patient who received study control, completed the study because the second sternotomy was performed and efficacy evaluations were completed. The investigator also indicated a reason for early withdrawal (adverse event) due to the patient's death following the procedure.

The demographic variables for the evaluable population are summarized in Table 9. The evaluable patients are the population used to conduct the data analysis of the primary and secondary endpoints. The safety population is used for the safety endpoint. The majority of the patients were Caucasian or African American. Patients in the REPEL-CV treatment group were slightly smaller than those in the control group, although the difference was not clinically relevant. In addition, fewer patients in the REPEL-CV group experienced use of Heart-Lung Bypass.

Table 9. Demographics – Study 4

	REPEL-CV	Non-Treatment Control
	N=56	N=54
Age (days)		
Mean ± SD	13.6 ± 15.8	11.4 ± 9.0
Median	9.0	9.0
Range	2.0 - 93.0	2.0 -63.0
Gender		
Male	31 (55.4%)	38 (70.4%)
Female	25 (44.6%)	16 (29.6%)
Race		
Caucasian	34 (60.7%)	33 (61.0%)
African American	15 (26.8%)	9 (16.7%)
Hispanic	6 (10.7%)	6 (11.1%)
Asian	0 (0.0%)	3 (5.6%)
Other	1(1.8%)	3 (5.6%)
Height (cm)		
Mean ± SD	46.6 ± 7.7	49.9 ± 2.5
Median	48.0	50.0
Range	18.0 – 55.0	44.0 – 57.0
Weight (kg)		
Mean ± SD	3.0 ± 0.5	3.3 ± 0.5
Median	3.0	3.4
Range	2.1 – 4.5	2.5 – 4.6
Procedure Type		
Norwood	38 (67.9%)	43 (79.6%)
Non-Norwood	18 (32.1%)	11 (20.4%)
Use of Heart-Lung Bypass Machine		
Yes	45 (80.4%)	51 (94.4%)
No	11 (19.6%)	3 (5.6%)
Chest Closure Delay		
Delay	40 (71.4%)	43 (79.6%)
No Delay	16 (28.6%)	11 (20.4%)

*These data represent the evaluable patients.

Data Analysis and Results for Safety

Table 10 summarizes the adverse events and death. No differences in adverse events occurring post-randomization between the REPEL-CV and the non-treatment control group were detected.

Table 10. Summary of Adverse Events and Death – Safety Population

	REPEL-CV (n=73)		Control (n=69)	
	Patients	Events	Patients	Events
Number of Patients (percent) With at Least One Adverse Event	51 (69.9%)	135	49 (71.0%)	123
Possibly, Probably or Definitely Treatment Related Adverse Events	6 (8.2%)	6	1 (1.4%)	1
Number of Patients (percent) With at Least One Serious Adverse Events	37 (50.7%)	63	32 (46.4%)	53
Number of Possibly, Probably or Definitely Treatment Related Serious Adverse Events	4 (5.5%)	4	0	0
Number (percent) of Deaths (following the 1st and 2nd sternotomies)	12 (16.4%)	-	9 (13.0%)	-

In the REPEL-CV group, the most frequently observed post-randomization adverse events were: Infections and Infestations (26.0%), Cardiac Disorders (24.7%), Respiratory, Thoracic and Mediastinal Disorders (23.3%), and Vascular Disorders (9.6%). In the non-treatment control group, the most frequently observed post-randomization adverse events were: Infections and Infestations (24.6%), Respiratory, Thoracic and Mediastinal Disorders (18.8%), and Cardiac Disorders (18.8%). These results do not suggest that REPEL-CV is associated with an increased risk of adverse events among these more frequent events. It should be noted that: 1) the above adverse event profiles include adverse events associated with the patient's surgical procedure and the patient's medical condition, and 2) the adverse event profiles in both treatment groups were expected and consistent with the clinical experience for this study population as well as being identified as anticipated adverse events in the Protocol.

Deaths and Other Serious Adverse Events

Table 11 summarizes the overall death rate. The death rate following the first sternotomy was 12.3% (9/73) for REPEL-CV vs. 10.1% (7/69) for Control. The overall death rate was 16.4% (12/73) for REPEL-CV vs. 13.0% (9/69) for Control with the inclusion of three REPEL-CV deaths and two Control deaths following the second sternotomy.

Table 11. Death Rates for Each Treatment Group*

	REPEL-CV	Control
Overall	16.4% (12/73)	13.0% (9/69)
95% CI (REPEL-CV - Control)	(-8.7%, 15.4%)	

*These data represent the evaluable patient population.

The distribution of adverse events and death between the REPEL-CV and control groups was similar. The adverse event profiles and death in both treatment groups were expected and consistent with the surgical procedures and clinical condition of this study population. The 95% confidence interval of the difference between the REPEL-CV and the Control was (-8.7%, 15.4%) for overall death rate.

Adverse Events of Special Interest

Mediastinitis was defined as infection involving the mediastinum or sternum that required re-exploration and debridement.

Four patients in the REPEL-CV treatment arm of the study and one in the control group developed mediastinitis. Of the four patients in the REPEL-CV group, two patients required open debridement and antibiotic following the first operation (2/73, 2.7%), and two patients following the second surgery (2/56, 3.5%). In the control group one patient required open debridement and antibiotic following the first sternotomy (1/69, 1.4%). The control patient was identified during a *post hoc* data review.

Table 12 shows the incidence of mediastinitis after the first and second sternotomies for REPEL-CV (2.7%) and the Control (1.4%).

Table 12. Incidence of Mediastinitis

Treatment at First Sternotomy	Onset of Mediastinitis (Days After 1st Sternotomy)	Incidence of Mediastinitis
REPEL-CV	~ 120	2.7% (2/73)
	14	
CONTROL	12	1.4% (1/69)
	Onset of Mediastinitis (Days After 2nd Sternotomy)	
REPEL-CV	30	3.6% (2/56)
REPEL-CV	4	

Although mediastinitis was noted as occurring in the treatment and control patients, the frequency of this event is not enough to draw any conclusions.

Data Analysis and Results for Primary Effectiveness Endpoint

The results presented are for the primary clinical endpoint: mean percent of the investigational surgical site (area) with Grade 3 (severe) adhesions. These data are shown in Table 13 for the evaluable population.

Table 13. Investigational Surgical Site Adhesion Assessments at Visit 3*

Extent of Severity (% Area)		REPEL-CV (N=56)	Control (N=54)	p-value**
% Area with Grade 3 (Severe) Adhesion	**Mean ± SD**	**21.3 ± 36.5**	**47.3 ± 42.7**	**0.0008**
	Median	**0.0**	**35.0**	**0.0001**
% Area with Grade 2 (Moderate) Adhesion	Mean ± SD	44.8 ± 36.3	35.5 ± 35.4	
	Median	45.0	25.0	
% Area with Grade 1(Mild) Adhesion	Mean ± SD	31.0 ± 35.8	16.2 ± 26.8	
	Median	20.0	0.0	
% Area with Grade 0 (No) Adhesion	Mean ± SD	2.9 ± 13.8	0.9	
	Median	0.0	0.0	

*These data represent the evaluable patient population.
**A t-test was used to compare treatment means and the Wilcoxon rank sum test for the medians

The mean percent of the study-defined surface area with severe (Grade 3) adhesions at the time of the second surgery was 21.3% for REPEL-CV (n= 56) and 47.3% for Control (n= 54; p=0.0008 for the mean and p=0.0001 for the median).

Effect of Un-masked Evaluation

For this study, in some instances, the surgeon who randomized the patient also assessed the adhesions at the second sternotomy. These observations were classified as unmasked evaluations and could have biased the surgeon's assessment. The primary effectiveness endpoint was separately evaluated for patients undergoing masked and unmasked assessments.

The results for the masked and unmasked evaluations are presented in Table 14.

Table 14. Percent Area with Severe (Grade 3) Adhesions for the Masked and Unmasked Evaluations

Group	REPEL-CV	Control
Overall (Evaluable; N=110)	56	54
Mean ± SD (%)	**21.3 ± 36.5**	**47.3 ± 42.7**
Masked Evaluation (N=84)	43	41
Mean ± SD (%)	24.0 ± 38.6	50.4 ± 44.0
Unmasked Evaluation (N=26)	13	13
Mean ± SD (%)	12.5 ± 27.9	37.7 ± 38.1

Data Analysis and Results for Secondary Effectiveness Endpoints

In terms of secondary effectiveness endpoints:

1. The percentage of patients with Grade 3 adhesions as worst degree of adhesions was 30.4% (17/56) in the REPEL-CV group and, in comparison, 72.2% (39/54) of the Control group had Grade 3 adhesions. This data is shown in Table 15. There was a one-grade shift downwards favoring REPEL-CV.

Table 15. Patients by Worst Degree of Adhesions Within the Investigational Surgical Site (ISS)

	REPEL-CV (N=56)	Control (N=54)
Patients (Percentage) with Grade 3: Severe Adhesions*	**17 (30.4%)**	**39 (72.2%)**
Patients by Worst Degree of Adhesions**		
Grade 0: No Adhesions	1 (1.8%)	0 (0.0%)
Grade 1: Mild Adhesions	6 (10.7%)	2 (3.7%)
Grade 2: Moderate Adhesions	32 (57.1%)	13 (24.1%)
Grade 3: Severe Adhesions	17 (30.4%)	39 (72.2%)
* Fisher's exact test p-value ** Wilcoxon rank sum test p-value		

2. The mean percent of the study-defined surface area with mild (Grade 1) adhesions was higher in the REPEL-CV group than in the Control group, where the mean was 31.0% for REPEL-CV (N= 56) and 16.2% for Control (N= 54).

3. No difference in adhesion dissection time was detected between the REPEL-CV and the control. The mean dissection time was 25.9 minutes (n=55) for the REPEL-CV group, and it was 25.0 minutes (n=53) for the control group.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

SAFETY

No obvious differences were observed between the REPEL-CV and control groups in the number of adverse events, number of patients with at least one adverse event, number of serious adverse events, number of patients with at least one SAE, or mortality.

There was no evidence of adverse effects on vital signs or physical examination associated with treatment with REPEL-CV, nor any impact on the types or number of concomitant medications.

The mortality rate, though higher for the treatment group than the control group, was nevertheless comparable to literature reports for conventional treatment of similar cases.

EFFECTIVENESS

Effectiveness was evaluated in three studies at the time of re-sternotomy. In all three studies, it was concluded that REPEL-CV reduced the severity of adhesions as compared to those patients (control) who did not receive the product. By extension, the benefit accruing to the patient could include decreased operating time, decreased hemorrhage, and decreased morbidity and mortality.

The study results for the evaluable population demonstrated a statistically significant reduction (26.0%) in the mean percentage of the investigational surgical site with severe (Grade 3) adhesions favoring the REPEL-CV (21.3% vs. 47.3%, p=0.0008). In addition, the percentage of patients with severe adhesions at the investigational site as the worst degree was 30.4% (17/56) for the REPEL-CV and 72.2% (39/54) for the control treatment group. The percentage of patients by worst degree of adhesions also favored REPEL-CV. The distribution of the worst degree of adhesions showed a one-grade shift downwards that also favored REPEL-CV.

RISK-BENEFIT ANALYSIS

Cardiac surgery is associated with the development of adhesions to surrounding mediastinal structures which can be both extensive and densely fibrotic and can seriously complicate re-exploration. The severity of these adhesions at re-exploration within 2-8 months can be reduced with use of the REPEL-CV thereby facilitating a second procedure.

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATIONS

At an advisory panel meeting held on September 19, 2007, the Circulatory System Devices Panel recommended that SyntheMed's PMA for the REPEL-CV Bioresorbable Adhesion Barrier be approved subject to the submission to and FDA approval of the following:

(1) Removal of the contraindication that prevents use of the device in patients with left ventricular assist devices;
(2) Modification of the indications statement to remove "incidence and extent," ; limit use of the device to a pediatric population as defined by FDA; and specify that patients receiving the device would have a high likelihood of a reoperation; and
(3) Development of a post-approval study to evaluate long-term safety and effectiveness.

XIII. CDRH DECISION

CDRH concurred with the Circulatory System Devices Panel recommendation of September 19, 2007. FDA issued an approval order on March 6, 2009. The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

The post-approval study consists of a multi-center, comparative, randomized study of pediatric patients (<21 years) undergoing cardiac procedures via sternotomy and to include the data obtained from the study in a separate postapproval study report. This study is to evaluate the rate of rare safety events observed during the premarket study in a more generalized population. This evaluation is accomplished using a non-inferiority design. The goal of the study is to evaluate whether REPEL-CV is inferior to the controls in the incidence of a composite safety end point that includes mediastinitis, exploratory surgery for re-bleeding, and cardiac tamponade. The study will include 320 patients in the REPEL-CV group and 320 patients in the control group. An interim analysis will be conducted when 200 patients in the REPEL-CV group and 200 patients in the control group complete the safety evaluation. The final analysis will be completed once all patients complete six months of follow-up. Patients in the study will be followed while hospitalized (Stage 1), 3-4 weeks post-operation (Stage 2), 8-10 weeks post operation (Stage 3), and 6 months post operation (Stage 4) to monitor the development of adverse events.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

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