

**Adult Clinical Experience with REPEL-CV™**  
*SyntheMed, Inc., Little Silver, New Jersey, USA.*

## **A Comparative, Evaluator-Blinded, Randomized, Parallel Study to Determine the Safety of REPEL-CV™ for Reducing Post-Operative Adhesions Following Adult Cardiothoracic Surgery**

*Eli Pines, Ph.D., SyntheMed, Inc., Little Silver, New Jersey, USA.*

### **SUMMARY**

The study was designed as a comparative, evaluator-blinded, randomized, parallel clinical trial to determine the safety of REPEL-CV for reducing post-operative cardiovascular adhesions following adult cardiothoracic surgery. Safety was evaluated by analysis of adverse events, clinical laboratory results, and concomitant medication. The REPEL-CV treated patients showed similar profiles for these safety parameters as the non-treatment control group. Based on the safety measures monitored in this study, it was concluded that REPEL-CV does not present an additional safety risk to the adult patient population studied.

Based on the above, the FDA approved the initiation of a feasibility study to assess the safety and efficacy of REPEL-CV in pediatric patients scheduled to undergo staged sternotomy procedures. This study will be communicated in the accompanying paper.

### **INTRODUCTION**

Surgical trauma to the surface of the heart, surrounding structures and vessels during cardiac procedures often leads to the unwanted consequence of the formation of dense, vascular, cohesive post-operative cardiac adhesions. The dissection of these adhesions, which obscure cardiac architecture and landmarks, make a repeat sternotomy time consuming and dangerous. At the time of cardiac re-operative procedures, the risks associated with these adhesions can include prolonged surgical time and excessive bleeding. The probability of inadvertent entry into a critical structure or vessel (e.g., the right ventricle, aorta, right atrium and any aortocoronary bypass graft, etc.) is also increased. These injuries can result in severe hemorrhage with significant morbidity and mortality [1-8].

Several attempts have been made to ameliorate the formation of post-operative cardiac adhesions by the use of either synthetic or biological pericardial substitutes or bioresorbable adhesion barriers [9-18]. The results to date have not been satisfactory and these materials are not commonly used clinically.

SyntheMed, Inc. has developed REPEL-CV to reduce the formation of post-operative adhesions following cardiac surgery. REPEL-CV is an easy to use, non-adherent, compliant, transparent, bioresorbable and biocompatible polymeric film comprising poly-lactic acid (PLA) and polyethylene glycol (PEG). These components have been used extensively in implantable, absorbable medical devices and have an established safety profile. REPEL-CV provides a temporary barrier to mechanically separate potentially opposing surfaces from interconnecting with each other. It thus serves to reduce post-operative adhesion formation during the healing process. REPEL-CV is absorbed from the site of implantation within 28 days.

Previously, in preclinical post-operative cardiac adhesion studies in canine and rabbit, REPEL-CV was shown to significantly reduced adhesion formation; additionally the capsule formation induced by permanent or slowly resorbed barriers was avoided [19-20].

Based on preclinical safety and effectiveness data for REPEL-CV, the United States Food and Drug Administration (FDA) granted SyntheMed, Inc. an Investigational Device Exemption (IDE) to conduct the initial clinical safety study in an adult patient population.

## STUDY DESIGN

This was a randomized, evaluator-blinded, comparative, parallel group study to determine the safety of REPEL-CV for the purpose of reducing post-operative adhesions following adult cardiothoracic surgery. The primary inclusion criteria were patients requiring open-heart sternotomy procedures. Other inclusion criteria included:

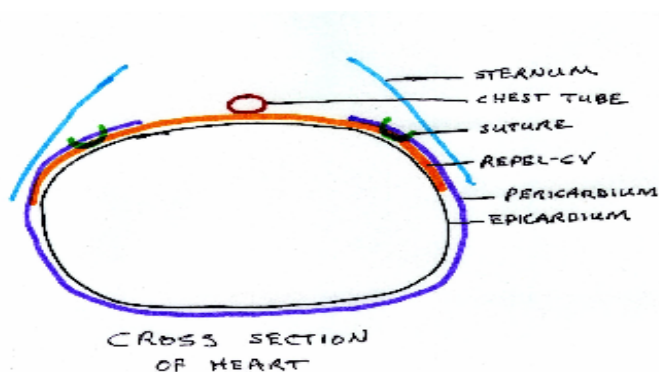
- Male or female between the ages of 18 and 65 years;
- First sternotomy procedure for patient undergoing CABG or valvular procedures;
- Prothrombin Time  $\leq$  16

Patients were excluded from the use of approved or unapproved devices to prevent adhesions and were only enrolled into the study after they (or their legal representative) had signed the informed consent form. Upon enrollment, but prior to surgery, the patient underwent the required screening evaluations including clinical laboratory tests (hematology, chemistry, urinalysis). Just prior to chest closure, the patient was reviewed and confirmed to have met all exclusion criteria. The patient was then randomized either to treatment with REPEL-CV or to a control group that was to receive no treatment.

For patients randomized to the REPEL-CV group, REPEL-CV was soaked for approximately two (2) minutes in Ringer's lactate or saline solution; all irrigation fluids and instillates were removed from the pericardial cavity; REPEL-CV was then cut and trimmed to the appropriate size and applied to the surface of the heart, to the area directly below the sternotomy site and extending laterally sufficiently beyond the pericardial edges so that the tack sutures can be properly placed; it was then tucked between the epicardium and the pericardium and sutured to the pericardium using 2 or 3 tack sutures per edge.

The diagram below illustrates the placement of REPEL-CV.

### Diagram: Cross-Section of the Heart and Placement of REPEL-CV



All patients were monitored for adverse events on an ongoing basis. Extensive clinical laboratory tests were performed at baseline, on day five post-surgery or at the time of discharge, whichever occurred sooner; and at the follow-up safety visit scheduled between 2 - 6 weeks post-surgery. All baseline and concomitant medications were recorded in the Case Report Forms. The study was completed when 22 patients had completed the safety follow-up visit.

## RESULTS

The table below summarizes patient disposition by treatment group. Twenty-seven patients were enrolled into the study. Enrollment was discontinued after 22 patients completed the follow-up safety visit. Fifteen patients were randomized to the REPEL-CV group and 12 to the control group. Eleven of the 15 REPEL-CV patients and 11 of the 12 control patients completed the study. Of the four patients in the REPEL-CV group who were discontinued from the study, two refused to come back and two were discontinued due to adverse events. One patient experienced severe bleeding that required re-exploration and one patient with history of arrhythmia and automated internal cardiac defibrillator developed severe

**Adult Clinical Experience with REPEL-CV™**  
*SyntheMed, Inc., Little Silver, New Jersey, USA.*

malignant arrhythmias and died shortly thereafter. These adverse events were considered “not related” to the study device. In the control group, one patient refused to come back.

**Table I: Patient Disposition**

	<i>REPEL-CV</i>	<i>CONTROL</i>
Total Randomized	15	12
CABG	9	11
Valve	4	1
LVAD	2	0
Completed	11	11
Discontinued for:		
Adverse events	2	0
Refusal to come back	2	1

**Adult Clinical Experience with REPEL-CV™**  
 SyntheMed, Inc., Little Silver, New Jersey, USA.

**Adverse events:** The table below summarizes of the adverse events by treatment group, surgical procedure, body system, preferred term and severity.

**Incidence of Adverse Events By Treatment Group, Surgical Procedure, Body System, Preferred Term and Severity**

	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
<b>CABG</b>								
	<b>REPEL-CV (N=9)</b>				<b>Control (N = 11)</b>			
Cardiovascular								
Arrhythmia	0	0	1	1	0	0	0	0
Atrial Fibrillation	1	1	0	2	1	0	0	1
Supraventricular Tachycardia	0	0	0	0	0	1	0	1
Hemorrhage	0	1	0	1	0	0	0	0
Phlebitis	1	0	0	1	0	0	0	0
Respiratory								
Lung Edema	0	0	0	0	0	0	1	1
Pleural Effusion	0	1	0	1	0	1	0	1
Pneumonia	0	0	0	0	1	0	0	1
<b>VALVE</b>								
	<b>REPEL-CV (N = 4)</b>				<b>Control (N = 1)</b>			
Cardiovascular								
Atrial Fibrillation	1	1	0	2	0	0	0	0
Atrial Flutter	0	1	0	1	0	0	0	0
Supraventricular Tachycardia	1	0	0	1	0	0	0	0
Ventricular Tachycardia	0	0	1	1	0	0	0	0
Hypotension	0	0	0	0	0	0	1	1
Pericardial Effusion	0	0	0	0	0	1	0	1
Respiratory								
Pleural Effusion	0	1	0	1	0	0	0	0
<b>LVAD</b>								
	<b>REPEL-CV (N = 2)</b>				<b>Control (N = 0)</b>			
Cardiovascular								
Ventricular Tachycardia	0	0	1	1	-	-	-	-
Hemic/Lymphatic								
Coagulation Disorders	0	0	1	1	-	-	-	-
Leukopenia	1	0	0	1	-	-	-	-
Respiratory								
Pleural Effusion	1	0	0	1	-	-	-	-
Pulmonary Hypertension	1	0	0	1	-	-	-	-

**Clinical Laboratory Test:** The Clinical laboratory tests results over time (screening, five days post-chest closure (or day of discharge) and at the safety follow-up visit were not statistically different between the two treatment groups.

**Concomitant Medications:** Analysis of concomitant medications demonstrated similar profiles of use for treated and control patients.

## CONCLUSION

The study described was a comparative, evaluator-blinded, randomized, parallel clinical trial to determine the safety of REPEL-CV for reducing post-operative cardiovascular adhesions following adult cardiothoracic surgery. Results showed that:

- The REPEL-CV treated patients did not develop adverse events unexpected for their respective surgical procedure and the adverse events profiles were similar between the treated and control groups.
- The Clinical laboratory tests results over time (screening, five days post-chest closure (or day of discharge) and at the safety follow-up visit were not statistically different between the two treatment groups.
- Concomitant medication uses was similar in both treatment groups, and expected and consistent with the clinical experience for these study populations.

## **Adult Clinical Experience with REPEL-CV™**

*SyntheMed, Inc., Little Silver, New Jersey, USA.*

Based on the clinical and laboratory safety measures monitored in this study, it was concluded that REPEL-CV did not present an additional safety risk to the adult patient population evaluated in this study and undergoing the aforementioned cardiothoracic procedures.

## **ONGOING CLINICAL TRIAL**

Based on the safety and effectiveness data presented in this and the accompanying communication the FDA approved the initiation of the U.S. study entitled “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.” Several Competent Authorities in Europe, like wise, approved the initiation of the European study entitled “Open Label, Multicenter Study to Determine the Effectiveness of REPEL-CV™ for Reducing Post-Operative Adhesions Following Pediatric Cardiothoracic Surgery.” These studies are ongoing and it is anticipated that they will be completed in 2006.

## **References**

1. Brown AH, Braimbridge MV, Saber EF. The complications of median sternotomy. *J Thorac Cardiovasc Surg* 1969;58:189–97.
2. Londe S, Sugg WL. The challenge of reoperation in cardiac surgery. *Ann Thorac Surg* 1974;17:157– 62.
3. Macmanus Q, Starr S. Surgical considerations in patients undergoing repeat median sternotomy. *J Thorac Cardiovasc Surg* 1975;69:138– 43.
4. Parr GVS, Kirklin JW. The early risk of re-replacement of aortic valves. *Ann Thorac Surg* 1997;23:319–22.
5. Merav AD, Brodman R. A simple technique for tension-free pericardial closure. *Ann Thorac Surg* 1979;28:399–400.
6. English TAH, Milstein BB. Repeat open intracardiac operation, analysis of fifty operations. *J Thorac Cardiovasc Surg* 1978;76:56–60.
7. Culliford AT, Spencer FC. Guidelines for safely opening a previous sternotomy incision. *J Thorac Cardiovasc Surg* 1979;78:633– 8.
8. Schaff HV, Orszulak TA. The morbidity and mortality of reoperation for coronary artery disease and analysis of late results with use of actuarial estimate of event-free interval. *J Thorac Cardiovasc Surg* 1983;85:508–15.
9. Duncan DA, Yaacobi Y, Goldberg EP et al. Prevention of postoperative pericardial adhesions with hydrophilic polymer solutions. *J Surg Res* 1988;45:44–9.
10. Dobell AR, Jain AK. Catastrophic hemorrhage during redo sternotomy. *Ann Thorac Surg* 1984;37:273– 8.
11. Laks H, Hammond G. Use of silicone rubber as a pericardial substitute to facilitate reoperation in cardiac surgery. *J Thorac Cardiovasc Surg* 1981;82:88–92.
12. Meus PJ, Wernly JA. Long-term evaluation of pericardial substitutes. *J Thorac Cardiovasc Surg* 1983;85:54– 8.
13. Revuelta JM, Rinaldi RG. Expanded polytetrafluoroethylene surgical membrane for pericardial closure. *J Thorac Cardiovasc Surg* 1985;89:451–5.
14. Bunton RW, Xabregas AA. Pericardial closure after cardiac operations. *J Thorac Cardiovasc Surg* 1990;100:99 – 107.
15. Gallo JJ, Pomar JL. Heterologous pericardium for the closure of pericardial defects. *Ann Thorac Surg* 1978;26:149–54.
16. Mathisen SR, Sauvage LR. Prevention of retrosternal adhesions after pericardiotomy. *J Thorac Cardiovasc Surg* 1986; 92:92– 8.
17. Heydorn WH, Daniel JS. A new look at pericardial substitutes. *J Thorac Cardiovasc Surg* 1987;94:291– 6.
18. Gabbay S, Guindy AM. New outlook on pericardial substitution after open heart operations. *Ann Thorac Surg* 1989;48: 803–12.
19. Okuyama N, Wang C, et al. Reduction of Retrosternal and Pericardial Adhesions With Rapidly Resorbable Polymer Films. *Ann. Thorac. Surg.*, 1999; 68:913-820.
20. Okuyama N, Rodgers K, et al. Prevention of Retrosternal Adhesion Formation in a Rabbit Model Using Bioresorbable Films of Polyethylene Glycol and Polylactic Acid. *J. Surg. Research*, 1998; 78:118-122