# 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

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

## SUMMARY

The study presented is a comparative, evaluator-blinded, randomized, parallel, single center clinical trial to determine the safety and effectiveness of REPEL-CV for reducing post-operative adhesions following pediatric cardiothoracic surgery. This feasibility study, which enrolled 13 patients, was conducted to compare REPEL-CV treatment to a non-treatment control. The **effectiveness data** available from this feasibility study suggest that REPEL-CV reduces the extent and severity of post-operative adhesions following pediatric cardiothoracic surgery. The **safety data** show 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. Based on the safety measures monitored in this study, it was also concluded that REPEL-CV did not present an additional safety risk to the pediatric patient population studied.

Based on the above, the FDA and several European Regulatory Authorities approved the initiation of ongoing multi-center studies. These ongoing studies reflect the design and patient population of the above neonate study.

## 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, and the accompanying communication in an adult patient population the United States Food and Drug Administration (FDA) granted SyntheMed, Inc. an Investigational Device Exemption (IDE) to conduct this study.

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The clinical safety and effectiveness of REPEL-CV was evaluated in neonate patients who required a staged series of surgical corrections of congenital heart malformations through median sternotomy. This neonate patient population is the ideal and only practical cardiac surgery patient population in whom the efficacy of a product designed to reduce the formation of post–operative cardiac adhesions can be assessed in a timely manner.

The population studied in this clinical trial included newborns diagnosed with Hypoplastic Left Heart Syndrome (HLHS) undergoing staged reconstructive procedures. These patients have a high risk of death, infections and multiple complications and typically chest closure is delayed 2-4 days. HLHS patients typically spend weeks in Pediatric ICU and require close cardiac monitoring. Patients with HLHS are subject to sudden cardiac arrest, poor perfusion through their shunt, infections and lethal arrhythmias**.** At the time of their cardiac re-operative procedures, these patients experience the unwanted consequences associated with the presence of clinically significant post-operative adhesions.

## STUDY DESIGN

This was a randomized, evaluator-masked, comparative, parallel group study to evaluate the safety and effectiveness of REPEL-CV for the purpose of reducing post-operative cardiovascular adhesions in pediatric patients undergoing staged cardiothoracic sternotomy procedures. Pediatric patients fulfilled the inclusion criteria, which included:

- Male or female newborns up to one year of age;
- No previous sternotomy;
- Patients requiring staged cardiovascular sternotomy procedures;
- Patients expected to be on the heart-lung bypass machine during the first procedure;
- It is anticipated that the chest will be closed at least 24 hours after the initial surgery [delayed chest closure];
- Patient could not be a participant in another invasive device or drug study during the course of the study

Additionally all exclusion criteria had to be met; these included:

- Use of approved or unapproved treatment to prevent adhesions;
- If it was anticipated that the second sternotomy procedure was to be performed before two months or after eight months subsequent to the initial sternotomy procedure

Patients were enrolled into the study after their legal representative had signed the informed consent form. Upon enrollment, but prior to the first sternotomy, patients underwent the required screening evaluations including clinical laboratory tests (hematology and chemistry). Four visits were scheduled after the screening visit:

- First sternotomy procedure (Visit 1),
- Chest closure (Visit 2) (~ 3days after the sternotomy),
- Safety follow-up evaluation (Visit 3), and
- Second sternotomy procedure (Visit 4).

No additional patients were enrolled into the study after thirteen (13) patients were randomized into the study.

At the time of the first sternotomy (Visit 1), just prior to temporarily dressing the sternotomy site (delayed chest closure patients), the patient was reviewed to confirm there were no exclusion criteria associated with the time of the first sternotomy procedure. The patient was then randomized to either treatment with REPEL-CV or to the control group, which received no treatment. For patients randomized to receive REPEL-CV, just prior to temporary and delayed chest closures 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 (Fig. 1), 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 (Fig. 2 ).

The diagram below (Fig. *2)* illustrates the placement of REPEL-CV.

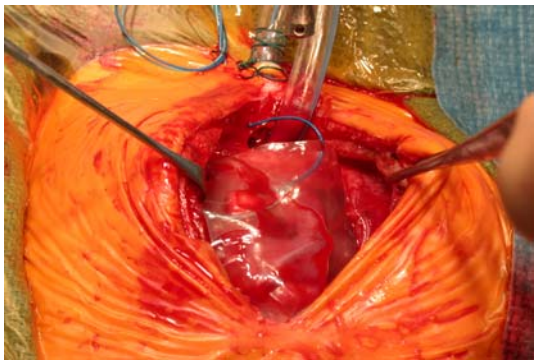

*Fig. 1 REPEL-CV is placed over the epicardial surface prior to chest closure.*

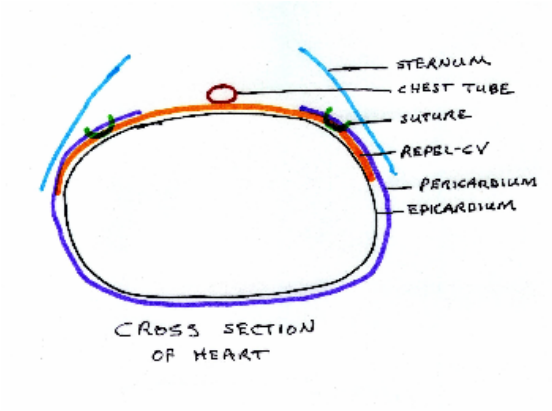


*Fig. 2 Diagram illustrating the placement of REPEL.CV.*

At Visit 2, REPEL-CV was removed. For each patient treated with REPEL-CV, if in the opinion of the investigator there was nothing indicating an adverse event or response associated with the initial placement of REPEL-CV (e.g., evidence of thick, discolored or malodorous discharge in the wound; any friable tissue underlying the sternum; "more than usually encountered" fibrinous adhesions). Then just prior to delayed chest closure, a new piece of REPEL-CV was placed at the investigative surgical site as described above.

A safety follow-up visit (Visit 3) was scheduled 3 - 8 weeks after randomization. At this visit clinical laboratory tests were performed.

The second sternotomy procedure (Visit 4) was performed between 2 and 8 months after the first sternotomy. At that time, a cardiac surgeon who was masked to the randomization code assessed the extent and severity of the adhesions at the investigational surgical site.

All patients were monitored for adverse events on an ongoing basis. Hematology and blood chemistry clinical laboratory tests were performed at screening (Visit 0), on day five after chest closure or at the time of discharge, whichever occurred sooner, and at the follow-up visit (Visit 3). All baseline and concomitant medications through Visit 3 (safety follow-up visit) were recorded in the Case Report Forms.

**Adhesion assessment at Time of Second Sternotomy:** At the time of the second sternotomy procedure, the extent and severity of the adhesions were assessed at the investigative surgical site. The investigative surgical site was defined as: the area on the surface of the heart located directly below the sternotomy site and extending laterally to the pericardial edges. **Severity** was graded according to:

**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).

**Extent** was defined as the percent of the investigational surgical site area involvement with each adhesion severity grade.

The primary effectiveness endpoint was the percentage of the study-defined surface area that was covered with dense adhesions (Grade 2) at the second surgery (Visit 4), i.e., the area involved with clinically significant and challenging adhesions.

## RESULTS

All randomized patients were one week old or younger at the time of the initial surgery. The table below summarizes patient disposition by treatment group. Thirteen patients were randomized into the study. Seven patients were randomized to the REPEL-CV group and six to the non-treatment control group.

## Table: Patient Disposition

| | REPEL-CV | Non-Treatment Control |
|---|---|---|
| Randomized | 7 | 6 |
| Completed | 3 | 4 |
| Discontinued for: | | |
| Investigator's decision/exclusion criteria | 1 | 0 |
| Serious Adverse events | 2 | 2 |
| Protocol Violation | 1 | 0 |

Three of the seven patients in the REPEL-CV treatment group completed the study. Four patients did not undergo the second sternotomy procedure. The reasons for discontinuations included: two deaths; one patient placed on ECMO and device not applied at chest closure; one patient inadvertently was not randomized. All of the discontinuations were determined to be "not related" to the study device. Four of the six patients in the non-treatment control group completed the study. Death was the reason for the two control patients who did not undergo the second sternotomy procedure.

The initial procedures for the seven (7) patients who subsequently underwent the second sternotomy included:

- Five Norwoods;
- One central shunt, PA ligation and atrial septectomy, and;
- One Damus-Stansel- Kaye, atrial septectomy and patch augmentation of the aortic arch

The mean time between the first surgery and the time to delayed chest closure (approximately 92 hours) was comparable between the REPEL-CV treatment and the non-treatment control groups. The mean time between the first and the second surgeries (approximately five months) was comparable between the REPEL-CV treatment and the non-treatment control groups

**Effectiveness analysis:**

The primary effectiveness endpoint was the patient specific percentage of the study-defined surface area, the investigational surgical site, with dense adhesions (Grade 2) at the second surgery (Visit 4), i.e., the area involved with clinically significant and challenging adhesions. Of the 13 randomized patients, seven patients completed the study and were eligible for endpoint effectiveness analysis at the time of the second sternotomy. The table below summarizes the findings for the seven patients who underwent the second sternotomy procedure.

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## Table: Effectiveness Data

| Extent of Severity | Area with Grade 0 % | Area with Grade 1 % | Area with Grade 2 % |
|---|---|---|---|
| Pt's ID# | **REPEL-CV** | | |
| 1 | 35 | 65 | 0 |
| 5 | 50 | 50 | 0 |
| 7 | 0 | 100 | 0 |
| **Average** | **28.3 ± 25.7** | **71.7 ± 25.7** | **0** |
| | **Non-Treatment Control** | | |
| 4 | 0 | 33.3 | 66.7 |
| 6 | 0 | 100 | 0 |
| 8 | 0 | 0 | 100 |
| 9 | 0 | 0 | 100 |
| **Average** | **0** | **33.3 ± 47.1** | **66.6 ± 47.1** |
| **p-value** | **0.071** | **0.264** | **0.062** |
| Grade "0" - **No** Adhesions<br>Grade "1" - **Filmy** Adhesions<br>Grade "2" - **Dense** | | | |

None of the three REPEL–CV treated patients had "dense" adhesions (Grade 2) at the investigative surgical site. In contrast, three of the four non-treatment control patients had extensive "dense" adhesions at the investigative surgical site. The average percentage of the study-defined surface area with "dense" adhesions (Grade 2) at the second sternotomy is zero (0%) for the REPEL-CV treatment group and 66.6% for the non-treatment control group (p = 0.062; p value based on one-way ANOVA).

**Safety Analysis:**

**Adverse Events:** Six of the seven patients in the REPEL-CV treatment group experienced 30 adverse events, 12 of which were severe in intensity. One of the patients experienced 12 of these 30 adverse events. Three of the six patients in the non-treatment control group experienced 11 adverse events, 10 of which were severe in intensity. All of the adverse events were considered "not device-related." Three patients in the REPEL-CV treatment group had three serious adverse events and two patients in the non-treatment control group had three serious adverse events. All serious adverse events were considered "not device-related."

## Table: Incidence of Adverse Events by Treatment Group, System Organ Class, Preferred Term and Severity

| **Med DRA** | **Mild** | **Moderate** | **Severe** | | **Mild** | **Moderate** | **Severe** | |
|---|---|---|---|---|---|---|---|---|
| System Organ Class/ Preferred Term | **REPEL–CV (N=7)** | | | | **Non-Treatment Control (N = 6)** | | | |
| **Cardiac Disorders** | | | | | | | | |
| Cardiac arrest neonatal | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 2 |
| Cardiac function disturbance post operative | - | - | - | - | 0 | 0 | 1 | 1 |
| Cardiogenic shock | 0 | 0 | 1 | 1 | - | - | - | - |
| Myocardial rupture | 0 | 0 | 1 | 1 | - | - | - | - |
| Pericardial effusion | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 |
| **Infection and Infestations** | | | | | | | | |
| Anaerobic bacterial Infection NOS | 1 | 0 | 0 | 1 | - | - | - | - |
| Enterococcal sepsis | 0 | 0 | 1 | 1 | - | - | - | - |
| Fungal sepsis | - | - | - | - | 0 | 0 | 1 | 1 |
| Staphylococcal infection | 0 | 4 | 0 | 4 | 0 | 1 | 0 | 1 |
| Staphylococcal sepsis | 0 | 0 | 1 | 1 | - | - | - | - |
| | | | | | | | | |

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| Med DRA | Mild | Moderate | Severe | | Mild | Moderate | Severe | |
|---|---|---|---|---|---|---|---|---|
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | | | | | |
| Bronchial obstruction | - | - | - | - | 0 | 0 | 1 | 1 |
| Mediastinal disorder NOS | 0 | 0 | 1 | 1 | - | - | - | - |
| Mediastinal haematoma | 0 | 0 | 1 | 1 | - | - | - | - |
| Mediastinal hemorrhage | 1 | 1 | 0 | 2 | | | | |
| Pleural effusions | 0 | 2 | 0 | 2 | 0 | 0 | 1 | 1 |
| Pneumothorax NOS | 1 | 0 | 0 | 1 | - | - | - | - |
| Pulmonary hypertension | - | - | - | - | 0 | 0 | 1 | 1 |
| Respiratory distress | 0 | 2 | 1 | 3 | - | - | - | - |
| **Surgical and Medical Procedures** | | | | | - | - | - | - |
| Cardiac operation NOS | 0 | 0 | 1 | 1 | - | - | - | - |
| **Vascular Disorders** | | | | | | | | |
| Hemodynamic instability | 0 | 0 | 1 | 1 | - | - | - | - |
| Vena cava thrombosis | - | - | - | - | 0 | 0 | 1 | 1 |

**Clinical Laboratory Test Results:** Hematology and blood chemistry test results for screening, 5 days post-chest closure (or day of discharge) and at the safety follow-up visit were not statistically different between the two treatment groups. The "out of range" laboratory results for all patients were considered "not related" to the study device.

**Concomitant Medications:** The class of medications, average number of medications and the frequency and duration of usage were similar for the two groups.

## CONCLUSIONS

**Effectiveness Conclusions:** This was a comparative, evaluator-blinded, randomized, parallel, single center study to determine the safety and effectiveness of REPEL-CV for reducing post-operative adhesions following pediatric cardiothoracic surgery. This feasibility study, which included 13 randomized patients, was conducted to compare REPEL-CV treatment to a non-treatment control. It was anticipated that the data obtained from this study would provide information to assist in the design of the pivotal trial.

The effectiveness data available from this feasibility study suggest that REPEL-CV reduces the extent and severity of post-operative adhesions following pediatric cardiothoracic surgery. In spite of the small sample size of seven completed patients (3 REPEL-CV and 4 non-treatment controls), trends for effectiveness for the reduction in the extent of dense adhesions approached statistical significance ($p = 0.062$).

**Safety Conclusions:** 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 observed mortality rate was expected for this high-risk patient population. The concomitant medication profiles and the clinical laboratory tests were similar for the two treatment groups.

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 pediatric patient population evaluated in this study and undergoing the aforementioned cardiothoracic procedures.

## Ongoing Clinical trials

Based on the safety and effectiveness data presented in this 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.

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