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1. SUMMARY OF SAFETY AND EFFECTIVENESS

1.1. General Information

1.1.1. Device Generic Name

Resorbable Adhesion Barrier

1.1.2. Device Trade Name

REPEL-CV

1.1.3. Applicants Name and Address

SyntheMed, Inc. (formerly Life Medical Sciences, Inc.)
200 Middlesex-Essex Turnpike
Suite 210
Iselin, NJ 08830
732-404-1117

Attn: Eli Pines, Ph.D.

1.1.4. PMA Number

P070005

1.2. Indication for Use

REPEL-CV is a surgical adjuvant indicated for reducing the incidence, severity and extent of post-operative adhesion formation in patients undergoing cardiac surgery via sternotomy.

1.3. Device Description

Adhesion formation is a direct result of trauma, blood coagulation and reduced fibrinolytic activity. Surgical trauma to the parietal pleura and pericardial mesothelium leads to fibrin deposition, the formation of fibrinous adhesions connecting opposing surfaces and reduced fibrinolytic activity. With the reduction in fibrinolytic activity, the resolution of the deposited fibrin and fibrinous adhesions is compromised. Fibroblasts, which proliferate and migrate towards the site of injury, will then migrate into these fibrinous bands where collagen and other components of extracellular matrix are deposited. This results in the formation of extensive, dense, cohesive and tenacious adhesions (fibrous adhesions) connecting adjacent structures. The etiology and pathogenesis are common to all cardiac surgical procedures in patients of any age.

REPEL-CV Bioresorbable Adhesion Barrier is a single use, synthetic, bioresorbable polymeric film composed of poly-lactic acid (PLA) and polyethylene glycol (PEG), polymers used extensively in implantable, absorbable medical devices.

REPEL-CV provides a temporary barrier to mechanically separate opposing surfaces from interconnecting with each other via fibrin bands (fibrinous adhesions) during the early phase of tissue repair. By placing REPEL-CV over the traumatized tissue surfaces, the formation of the interconnecting fibrinous bands between opposing surfaces is prevented and the development of fibrous adhesions is reduced or prevented.

The critical intrinsic properties of REPEL-CV are such that it maintains its barrier property during the early phase of the healing process, when fibrin is formed. Once fibrinogenesis is completed and the formation of the interconnecting fibrinous bands has been blocked, the barrier begins to fragment and degrade (resorb) over time. REPEL-CV was designed to be absorbed from the site of implantation within 28 days.

1.4. Contraindications, Warnings and Precautions

1.4.1. Contraindications

REPEL-CV is contraindicated in patients in whom a Ventricular Assist Device (VAD) is implanted**.**

1.4.2. Warnings

This device is an adjunct to good surgical technique and is not to be used to replace it.

1.4.3. Precautions

1. The safety and performance of REPEL-CV have not been established in pregnant women.
2. As with other surgically implanted foreign material, REPEL-CV should not be used in the presence of frank infection.
3. Do not use if pouch is damaged or opened prior to use.
4. Single use only.
5. Do not resterilize.

1.5. Alternative Practices and Procedures

A number of approaches have been described experimentally in an attempt to reduce postoperative adhesions after cardiac surgery. These include the use of bovine/heterologous pericardium, hydrophilic solutions, resorbable polymeric matrices, silicone rubber as well as procedural modifications such as closure of the pericardium.[1-9] To date, there is no FDA approved product indicated for reducing the formation of post-operative cardiac adhesions. However, there are 4 products that have received CE Mark in Europe for reducing the formation of post-operative cardiac adhesions.[8,9] Products include 1) Seprafilm (Genzyme); 2) Adhibit (Baxter); 3) CardioWrap (Mast Biosurgery); and 4) REPEL-CV (SyntheMed).

The clinical development program for REPEL-CV represents the first series of clinical trials approved under an IDE to clinically address the safety and effectiveness of a product indicated for reducing the formation of post-operative cardiovascular adhesions.

1.6. Marketing History

REPEL-CV has no marketing history in the U.S. 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.

1.7. Potential and Observed Adverse Effects of the Device on Health

1.7.1. Observed Adverse Effects

The REPEL-CV pivotal trial was a prospective, comparative, randomized, evaluator-masked, multicenter trial, which randomized 144 (73 REPEL-CV; 71 Control) pediatric patients undergoing staged cardiac surgical procedures to correct congenital cardiac malformations. The control treatment group had two protocol violations. These two patients were randomized and not treated. This patient population is an extraordinarily high-risk group that is routinely subjected to a variety of different postoperative complications. The majority of the patients participating in the pivotal trial required cardiac surgery when less than 14 days old, all were cyanotic both before and following surgery, and greater than 90% had a single ventricle. In addition, approximately 75% of the patients had their sternum left open for several days, as a routine procedure, prior to closure. The Table below tabulates all adverse events occurring at a frequency $\geq 2\%$ in either the treated or control arms.

Table 1: Observed Adverse Events by Descending Frequency ≥ 2% (Study LMS0103RCV) ***

		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*	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 sterntotomy)	2 (3.6%)	1 (1.4%)**
	Mediastinitis* (after 2nd sternotomy)	2 (2.7%)	0
	Wound Infection*	2 (2.7%)**	3 (4.3%)
	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%)

* Reclassified to assure consistency across study sites

***For AEs with frequency ≥ 2% and for which frequency of REPEL-CV's AE was not 0%

There were no differences in total adverse events occurring post-randomization between the REPEL-CV and the non-treatment control group (p=1.000). In the REPEL-CV treatment group, 51 patients experienced 135 AEs post-randomization, of whom six patients experienced 6 AEs that were possibly, probably or definitely treatment related. Thirty-seven (37) patients experienced 63 SAEs, of which only 4 were considered possibly, probably or definitely treatment related (none were considered definitely related). In the control treatment group, 49 patients experienced 123 adverse events post-randomization. One patient experienced one AE that was possibly, probably or definitely

a treatment related AE. Thirty-two (32) patients experienced 53 SAEs, none of these SAEs was considered possibly, probably or definitely treatment related AE.

There was no statistically significant difference between the REPEL-CV and the control treatment group in serious adverse event rates (50.7% vs. 46.4% of patients, respectively; p=0.6189).

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 (p=0.7930). The overall death rate was 16.4% (12/73) for REPEL-CV vs. 13.0% (9/69) for Control (p=0.6405) with the inclusion of three REPEL-CV deaths and two Control deaths post-second sternotomy. The mortality following cardiac surgery in a comparable pediatric population is well reported in the literature. The preponderance of papers report mortality rates approaching 20%. Several contemporary references are cited below.

B. Alsoufi, et al. Peds. 2007;119:109-117 (Table 1:several studies): Mortality >18% (59- 840 pts.)

P. Checchia, et al., J.Thoracic Cardiovasc Surg 2005;129:754-9: Mortality 22% (801 pts.)

T. Tweddell, et al., Circulation 2002;106 [Supp l]:82-89: Mortality 19% (115 pts.)

S.Daebritz, et al., J.Thoracic Cardiovasc Surg 2000;119:358-67: Mortality 21% (194 pts.)

The mortality rates reported in the submitted pivotal study are consistent with those reported in the literature for this extraordinarily high-risk patient population.

Potential Adverse Events

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

- Adhesions
- Aortic insufficiency
- Arrhythmia
- Cardiac arrest
- Cardiac tamponade
- Cerebral emboli
- Chylothorax
- Coagulopathy
- Death or irreversible morbidity
- Diaphragm paralysis to placation
- Dissection
- GI/Digestive tract complication
- Hemorrhage
- Injury to vessels or tissue

- Ischemia
- Low cardiac output
- Mediastinal wound infection (local erythema or purulence from sternal incision requiring surgical drainage and/or antibiotic)
- Mediastinitis (deep space infection, requiring sternal debridement and antibiotics)
- Myocardial infarction
- Neurological deficits
- Organ system dysfunction/failure
- Pericardial effusion
- Pleural effusion
- Pneumothorax
- 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

1.8. Summary of Nonclinical Studies

1.8.1. Safety/Biocompatibility

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 by NaMSA under USP and ISO 10993 Guidelines.

1. Cytotoxicity Test USP Elution Method - The cytotoxicity study indicated that extracts of the test article did not cause cell lysis or toxicity **(Vol. 9; Page 1980)**.

2. 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 **(Vol. 9; Page 2005, 2027)**.

3. 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 **(Vol. 9; Page 2050, 2066)**.

4. Rabbit Pyrogen Study - The material was shown to be non-pyrogenic using a protocol to determine material mediated pyrogenicity in a rabbit model **(Vol. 9; Page 2092)**.

5. 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%) **(Vol. 9; Page 2108)**.

6. 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. **(Vol. 9; Page 2118)**.

7. 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, test article was considered a non-irritant **(Vol. 9; Page 2136)**.

8. 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 **(Vol. 9; Page 2160)**.

9. Infectivity - Under the conditions of the study, the test article did not appear to potentiate mortality or abscess formation (non GLP) **(Vol. 9; Page 2209)**.

10. 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 **(Vol. 9; Page 2185)**.

11. Intraperitoneal Toxicity Study in the Rat - In the intraperitoneal toxicity study in the rat, 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 **(Vol. 9; Page 2219)**.

12. 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 **(Vol. 9; Page 2264)**.

13. 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 **(Vol. 10; Page 2282)**.

14. 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 **(Vol. 10; Page 2542)**.

15. Twenty-Eight Day Cardiac Biocompatibility Study in the Rabbit - The 28-day cardiac biocompatibility study in the rabbit of the test article indicated no untoward or gross histological reactions **(Vol. 10; Page 2567, 2594)**.

16. 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 **(Vol. 10; Page 2615)**.

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

1.8.2. Nonclinical Efficacy Studies

Studies were performed using canine and rabbit models to evaluate the efficacy of several bioresorbable films in their ability to reduce post-operative adhesion formation following cardiac surgery (Study #s: LMS 22, 26, 27, 34, 40; and 97-001). All of the prototypes were more efficacious than the no-treatment controls. However, one prototype with an EO/LA ratio of 1.5 was the most effective in reducing the formation of adhesions between the epicardium and the sternum, as well as between the epicardium and the pericardium. In addition, this prototype maintained its integrity for a longer period of time (Study No.: LMS 20, 21 and 24A.). This prototype was designated as REPEL-CV. These studies are summarized in the Table below.

Table 2: Summary of REPEL-CV® Short Term Placement and Nonclinical Efficacy Studies

Study Title	Study No.	Study Objective	Conclusions	Volume	Page
Observation of REPEL and REPEL-CV® after short term placement in animals (Rabbit)	LMS 20	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.	9	1920
Observation of REPEL and EO/LA 1.5 (REPEL-CV) after short term placement in animals (Rabbit).	LMS 21	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.	9	1921
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.	LMS 22	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.	9	1922
Observation of Repel, EO/LA 1.5 (60 μm thick) after short term placement in animals (Rabbit)	LMS 24A	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.	9	1928
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.	97-001	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.	9	1929

Study Title	Study No.	Study Objective	Conclusions	Volume	Page
Design evaluation of cardiovascular EO/LA film (1.5), Lot 082097, in the prevention of retrosternal adhesions in the rabbit cardiac model.	LMS 26	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.	9	1938
Design evaluation of REPEL-CV® cardiovascular (CV), EO/LA film 1.5, in the prevention of epicardial-pericardial adhesions in the canine cardiac model.	LMS 27	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.	9	1944
Design evaluation of REPEL-CV®cardiovascular (CV), EO/LA film 1.5, in the prevention of retrosternal adhesions in the rabbit cardiac model.	LMS 34	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.	9	1949
Design evaluation of cardiovascular EO/LA film (1.5), Lot No. I01498, in the prevention of retrosternal adhesions in the rabbit cardiac model	LMS 40	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.	9	1957

1.8.3. Bench Top Laboratory Studies

1.8.3.1. Hydrated Tensile Strength Study

Objective: Correlate the device hydrated tensile strength with its qualitative suture pull-out strength.

Experimental design: 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.

Results: With increasing hydration time the hydrated tensile strength and the suture pull-out strength decreased.

Conclusion: The minimum acceptable hydrated tensile strength for the device was 400 psi.

Note: It should be noted that the testing described was performed on REPEL, a product similar to REPEL-CV. The conclusions are applicable to REPEL-CV as well.

1.8.3.2. USP 23 Antimicrobial Preservative Effectiveness Study

Objective: Determine if the product (REPEL) could be stored without causing an increase in the bioburden for the material.

Experimental design: The inoculated samples were incubated in sealed vessels and recovery of viable organisms was performed at the cited intervals by standard plate count.

Results: 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.

Conclusion: The device did not support bacterial growth.

Note: It should be noted that 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.

1.9. Summary of Clinical Studies

A clinical trial designed to evaluate the safety and effectiveness of a medical device developed to reduce the formation of post-operative cardiac adhesion requires sequential median sternotomies that occur in a practical time window. At the time of the first sternotomy, the patients are randomized to treatment and at the second sternotomy effectiveness is assessed.

The only appropriate patient population in which the effectiveness and safety of a product designed to reduce the formation of post-operative cardiac adhesions can be assessed is neonates requiring sequential median sternotomies for surgical correction of congenital heart disease. In this population, the first sternotomy is typically performed within 1 month of life and the second sternotomy is typically performed at approximately 6 months of life. This surgical interval provides a practical time window to evaluate both the safety and effectiveness of a product developed to reduce the formation of post-operative cardiac adhesions. For the forgoing reasons, REPEL-CV was primarily evaluated in pediatric patients who required a staged series of two operations through median sternotomy for surgical corrections of congenital heart malformations.

In order to gain marketing approval of REPEL-CV, SyntheMed (formerly Life Medical Sciences), sponsored four clinical studies to support the clinical safety and effectiveness of REPEL-CV. Three studies were conducted in the US under IDE G980030 and one study was performed in Europe to support the CE Mark. In these four studies, 114 patients were enrolled into the REPEL-CV treated arms and 89 patients were enrolled into the control arms. The following is a list of the clinical trials:

Table 3: Summary of Clinical Trials

Name	IDE # G980030 supp. #	N	Description	Vol	Page
Study1. 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)	# 1 (May 13, 1998)	15 REPEL-CV 12 Control	Safety study in adult patients undergoing CABG, Valvular and LVAD procedures	11	2671
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)	# 20 (December 26, 2001)	7REPEL-CV 6 Control	Safety and effectiveness study in pediatric patients undergoing staged cardiac surgical procedures to correct congenital cardiac malformations	13	3261
Study 3. Open Label, Multicenter Study to Determine the Effectiveness of REPEL-CV™ for Reducing Post-Operative Adhesions Following Pediatric Cardiothoracic Surgery (Protocol # LMS0104RCV)	NA	19 REPEL-CV	Open safety and effectiveness study in pediatric patients undergoing staged cardiac surgical procedures to correct congenital cardiac malformations	15	3851
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)	# 27 (May 23, 2003)	73 REPEL-CV 71 Control	Safety and effectiveness pivotal study in pediatric patients undergoing staged cardiac surgical procedures to correct congenital cardiac malformations	16	3965

1.9.1. Study 1 - Protocol # LMS9802RCV

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).

Study Period: January 27, 1999 to June 19, 1999.

1.9.1.1. Objective

The objective of the study was to determine the safety of REPEL-CV as an adjunct for reducing post-operative adhesions in patients undergoing cardiothoracic surgery.

1.9.1.2. Study Design

The study was a multicenter, 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 primary inclusion criteria were patients between 18 and 65 requiring sternotomy for cardiothoracic surgery while undergoing the following procedures: Coronary Artery Bypass Graft (CABG), valvular procedure or the implantation of Left Ventricular Assist Device (LVAD) for bridge to transplantation. Patients were excluded if prior to randomization and chest closure, absorbable hemostats remained in place at the investigational surgical site.

Patients fulfilling the inclusion criteria and having none of the exclusion criteria were enrolled into the study after they 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 not to have any intra-operative exclusion criteria. Once confirmed, the patient was then randomized either to treatment with REPEL-CV or to a control group that was to receive no treatment. If the patient was randomized to REPEL-CV, the REPEL-CV was placed directly below the sternotomy site, on the epicardium and sutured to the pericardial edges. The pericardium was left open.

All patients were monitored for adverse events on an ongoing basis. Clinical laboratory tests were performed at baseline, on day five post-surgery or at the time of discharge, whichever occurred first, and at the follow-up visit (patients were scheduled for a safety follow-up visit between 2 - 6 weeks post-surgery). The study was completed when 21 patients completed this safety follow-up visit.

For the patients in the LVAD study population who proceeded to transplantation before the completion of the study, and who did not have the explant procedure or an

exploratory surgery of the treatment site within three weeks of randomization, an evaluator who was blinded to randomization assessed the adhesions at the investigational surgical site.

Safety parameters included monitoring of adverse events, physical examination, and changes in clinical laboratory tests.

1.9.1.3. Patient Disposition and Demographics

1.9.1.3.1. Patient Disposition

Twenty-seven patients were enrolled in the study: 26 at----------
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Table 4: Patient Disposition – Study 1

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

1.9.1.3.2. Demographics

Demographic variables are summarized in the table below.

Table 5: **Demographics – Study 1**

	REPEL-CV (N=15)	CONTROL (N=12)	P-VALUE[1]
Age (Years)			
Mean ± Std Dev	54.3 ± 11.99	59.3 ± 14.52	0.330
Range	27.0 – 71.0	23.0 – 72.0	
Gender			0.236
Male	9	10	
Female	6	2	
Race			0.022*
Caucasian	13	8	
African-American	2	0	
Asian	0	1	
Hispanic	0	3	

[1]P-value associated with Fisher's Exact Test of a difference between treatment groups, using two-sided tests.
* Statistically significant ($p<0.05$)

1.9.1.4. Analysis of Adverse Events

The table below summarizes all adverse events by treatment group, surgical group, body system, preferred term and severity. All adverse events were considered by the investigators "definitely not" related to the study device, with the exception of one adverse event for the LVAD patient described below which was rated as "possibly" related to the study device.

1.9.1.4.1. CABG Group

The most frequent adverse events associated with REPEL-CV were cardiovascular. Four of the 9 REPEL-CV patients experienced a total of 5 cardiovascular events, one of which was a severe arrhythmia. In the control group, 2 of the 11 patients experienced a mild or moderate cardiovascular adverse event, and 3 patients had 4 respiratory events, 2 of which were severe.

1.9.1.4.2. Valve Group

The most common adverse events in patients with REPEL-CV (n=4) were 6 cardiovascular events that occurred in 3 patients (1 event of ventricular tachycardia was rated as severe). There was one control patient in the valve group who experienced 5 adverse events. Two of these events were cardiovascular; one event of hypotension was rated as severe.

1.9.1.5. LVAD

Of the two REPEL-CV patients in this group, one patient experienced 10 adverse events (only 9 are shown in the table below: the patient had two events of coagulopathy which are counted as one event under the most severe category). Two of the events experienced by the REPEL-CV patient were severe: 1) ventricular tachycardia, which is not uncommon in the LVAD patient population, and 2) coagulopathy, which was considered by the investigator "possibly" related to the study device.

Table 6: Incidence of Adverse Events By Treatment Group, Surgical Procedure, Body System Preferred Term and Severity – Study 1*

	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
CABG								
	REPEL–CV (N=9)				**Control (N = 11)**			
Body as a Whole	0	0	0	0	0	1	0	1
Fever	0	0	0	0	0	1	0	1
Cardiovascular	1	2	1	4	1	1	0	2
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
Digestive	0	0	0	0	0	1	0	1
Nausea	0	0	0	0	0	1	0	1
Metabolic/Nutritional	0	0	0	0	0	1	0	1
Hyperglycemia	0	0	0	0	0	1	0	1
Nervous	0	1	0	1	0	0	1	1
Cerebral Infarct	0	1	0	1	0	0	0	0
Encephalopathy	0	0	0	0	0	0	1	1
Respiratory	0	1	0	1	0	1	2	3
Bronchitis	0	0	0	0	0	0	1	1
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
Urogenital	0	0	0	0	0	1	0	1
Urinary Retention	0	0	0	0	0	1	0	1
VALVE								
	REPEL–CV (N = 4)				**Control (N = 1)**			
Body as a Whole	0	0	0	0	1	0	0	1
Fever	0	0	0	0	1	0	0	1
Cardiovascular	0	2	1	3	0	0	1	1
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
Syncope	0	1	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
Metabolic/Nutritional	0	0	0	0	0	0	1	1
Acidosis	0	0	0	0	0	0	1	1
Respiratory	0	1	0	1	0	0	0	0
Pleural Effusion	0	1	0	1	0	0	0	0
Urogenital	0	0	0	0	1	0	0	1
Urinary Tract Infection	0	0	0	0	1	0	0	1
LVAD								
	REPEL–CV (N = 2)				**Control (N = 0)**			
Body as a Whole	1	0	0	1	-	-	-	-
Fever	1	0	0	1	-	-	-	-
Infection	1	0	0	1	-	-	-	-
Cardiovascular	0	0	1	1	-	-	-	-
Ventricular Tachycardia	0	0	1	1	-	-	-	-
Hemic/Lymphatic	0	0	1	1	-	-	-	-
Coagulation Disorders	0	0	1	1	-	-	-	-
Leukopenia	1	0	0	1	-	-	-	-
Metabolic/Nutritional	1	0	0	1	-	-	-	-
Edema	1	0	0	1	-	-	-	-
Hypokalemia	1	0	0	1	-	-	-	-
Respiratory	1	0	0	1	-	-	-	-
Pleural Effusion	1	0	0	1	-	-	-	-
Pulmonary Hypertension	1	0	0	1	-	-	-	-

*Multiple events for the same subject within the same body system or preferred level are counted once, using the most severe event.

1.9.1.6. Clinical Laboratory Test Results

The two treatment groups were similar with respect to the number of patients with abnormal laboratory results at screening, post-operative day 5 (or day of discharge) and follow-up visit (Table 6, Appendix 16.1.9 of said Clinical Study Report). There were no statistically significant differences between the REPEL-CV and control patients in the CABG and valve groups with respect to the means of the individual patient changes over time in laboratory test values. Since there were no control LVAD patients, between-treatment comparisons could not be performed for the LVAD group.

1.9.1.7. Safety Conclusions

1.9.1.7.1. Adverse Events

The adverse events profile in both treatment groups was expected and consistent with the clinical experience for this study population. All adverse events were considered by the investigators "definitely not" related to the study device, with the exception of one serious adverse event of coagulopathy in a LVAD patient who received REPEL-CV. This serious adverse event was considered by the investigator "possibly" related to the study device. However, it should be noted that the patient who experienced this event had a history of coagulopathy, and had several risk factors for coagulopathy, including sepsis, re-explorative surgery, and the administration of heparin subcutaneously, all of which are predisposing factors for coagulopathy and/or exacerbate the coagulopathy. Moreover, coagulopathy is not uncommon in the LVAD patient population. Finally, the event occurred approximately 3½ months after the placement of REPEL-CV, when the device was completely resorbed. Given the patient's history and status, it is the opinion of the sponsor that REPEL-CV was most likely not a causative factor for this serious adverse event of coagulopathy.

1.9.1.7.2. Clinical Laboratory Test Results

Changes in laboratory test results were not statistically different between the two treatment groups. Changes in concomitant medication use in both treatment groups were expected and consistent with the clinical experience for this study population.

1.9.1.8. Discussion and Overall Conclusions

Based on the clinical and laboratory safety measures monitored in this study, REPEL-CV does not present additional risk to patients undergoing cardiothoracic surgery.

One key observation noted during the placement of REPEL-CV at the investigational surgical site in the LVAD implanted patients is that the dynamic mechanical stresses generated by the large pulsating outflow graft of the LVAD, which is positioned either above or below REPEL-CV, prematurely disrupted (fragmented) the integrity of REPEL-

CV. This premature disruption of the integrity and barrier properties of REPEL-CV by the outflow graft of the LVAD preclude the expected clinical response of adhesion reduction associated with the use of REPEL-CV in non-VAD implanted cardiac procedures were the integrity and barrier properties of REPEL-CV are maintained for the desired time, i.e., the LVAD patient population is not an appropriate clinical population for assessing the effectiveness of a resorbable adhesion barrier film.

1.9.2. Study 2 - Protocol # LMS0001RCVP

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).

Study Period: March 2002 - February 2003

1.9.2.1. Objective

The objectives of the study were to determine the safety and effectiveness of REPEL-CV for reducing post-operative adhesions in pediatric patients undergoing cardiothoracic surgery.

1.9.2.2. Study Design

The study was a multicenter, pilot, comparative, evaluator-blinded, randomized, parallel, single center clinical trial. The clinical safety and effectiveness of REPEL-CV was evaluated in neonate patients (7 REPEL-CV patients; 6 Control patients) who required a staged series of surgical corrections of congenital heart malformations through median sternotomy.

Pediatric patients 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). Four visits were scheduled after the screening visit, first sternotomy procedure (Visit 1), chest closure (Visit 2), safety follow-up evaluation (Visit 3) and second sternotomy procedure (Visit 4). The expected duration of patient participation, from the time of initial sternotomy to the second sternotomy procedure, was between 2 to 8 months.

The primary inclusion criteria were male or female---------- requiring staged cardiovascular sternotomy procedures. Patients had to be on Heart-Lung Bypass Machine during the first procedure with anticipation that the chest would be closed (delayed chest closure) at least 24 hours after the initial surgery, and that the second sternotomy procedure was to be performed 2-8 months after the initial sternotomy procedure. The primary exclusion criteria prior to chest closure were 1) an untoward response associated with the initial placement of REPEL-CV, and 2) any adverse event showing evidence of thick, discolored or malodorous discharge in the wound; and 3) any friable tissue underlying the sternum.

At the time of the first sternotomy (Visit 1), just prior to dressing the sternotomy site, the patient was reviewed to confirm the absence of 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 non-treatment control group. If the patient was randomized to

receive REPEL-CV, the REPEL-CV was placed at the investigational surgical site directly below the sternotomy site and sutured to the pericardial edges. The pericardium was left open.

At the time of chest closure (Visit 2), the extent of fibrinous adhesions was determined. For patients treated with REPEL-CV at Visit 1, all of the REPEL-CV was removed. If in the opinion of the investigator there was no adverse event associated with the initial placement of REPEL-CV, then just prior to chest closure, a new piece of REPEL-CV was placed on the investigational surgical site and sutured to the pericardial edges.

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

The second sternotomy procedure (Visit 4) was performed between 2 and 8 months after the first sternotomy. At that time, an evaluator, masked to the randomization code, assessed the severity and extent (% area) of adhesions at the investigational surgical site. Severity was graded as per the table below.

Table 7: Adhesion Severity Grading – 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)

All patients were monitored for adverse events on an ongoing basis. 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 safety follow-up visit (Visit 3) as clinically indicated.

1.9.2.3. Patient Disposition and Demographics

Patient Disposition: The table below summarizes patient disposition by treatment group. ---------- tients were enrolled into the study at---------- ----------
----

Table 8: Patient Disposition – Study 2

	REPEL-CV	Non-Treatment Control
Screened	7	6
Randomized	7	6
Completed	3	4
Discontinued for:		

	REPEL-CV	Non-Treatment Control
Investigator's decision/exclusion criteria	1	0
Serious Adverse events	2	2
Protocol Violation	1	0
Deaths	3	2

Patient Demographics: Demographic variables are summarized in the table below.

Table 9: Demographics – Study 2

	REPEL-CV	Non-Treatment Control	p-value
	N=7	N=6	
Age (days)			0.007
Mean ± SD	5.6 ± 1.4	3.0 ± 1.4	
Range	3.0 - 7.0	1.0 - 5.0	
Gender			1.000
Male	3	3	
Female	4	3	
Race			0.164
Caucasian	1	4	
Asian	1	0	
Hispanic	5	2	

1.9.2.4. Analysis of Effectiveness

For the seven patients (3 REPEL-CV treated, 4 non-treatment control) who underwent the second sternotomy procedure (Visit 4) the following are noted:

1 None of the three REPEL–CV treated patients had "dense" adhesions (Grade 2) at the investigative site. In contrast, three of the four non-treatment control patients had extensive "dense" adhesions at the investigative site.

2 The average percentage of the study-defined surface area (the investigational surgical site) with "dense" adhesions (Grade 2) at the second sternotomy was none (0%) for the REPEL-CV treatment group and 66.6% for the non-treatment control group ($p = 0.062$, Statistical Table 8, Appendix 16.1.9).

3 Two of three REPEL-CV treated patients had 35% and 50% of the surgical area with no adhesions (Grade 0).

The table below summarizes the findings for individual patients.

Table 10. Investigational Surgical Site Adhesion Assessments at Visit 4

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 Grade "1" - **Filmy** Adhesions Grade "2" - **Dense** Adhesions			

1.9.2.5. Analysis of Adverse Events

The table below summarizes all adverse events by treatment group, SOC, Preferred Term (PT) and severity.

Table 11. Incidence of Adverse Events by Treatment Group, System Organ Class, Preferred Term and Severity

Med DRA Term	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
System Organ Class/ Preferred Term	**REPEL–CV (N=7)**				**Non-Treatment Control (N = 6)**			
Cardiac Disorders	**1**	**0**	**3**	**3**	**0**	**0**	**3**	**3**
Cardiac arrest neonatal	0	0	2	2	0	0	2	2
Cardiac function disturbance postoperative	-	-	-	-	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	**1**	**4**	**1**	**4**	**0**	**1**	**1**	**2**
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	-	-	-	-
Injury, Poisoning and Procedural Complications	**0**	**1**	**0**	**1**				

Med DRA Term	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
System Organ Class/ Preferred Term	REPEL–CV (N=7)				Non-Treatment Control (N = 6)			
Wound dehiscence	0	1	0	1				
Nervous System Disorders	**0**	**1**	**0**	**1**	-	-	-	-
Atonic seizures	0	1	0	1	-	-	-	-
Renal and Urinary Disorders	**0**	**0**	**1**	**1**	-	-	-	-
Oliguria	0	0	1	1	-	-	-	-
Respiratory, Thoracic and Mediastinal Disorders	**2**	**4**	**2**	**5**	**0**	**0**	**2**	**2**
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 NOS	-	-	-	-	0	0	1	1
Respiratory distress	0	2	1	3	-	-	-	-
Surgical and Medical Procedures	**0**	**0**	**1**	**1**	-	-	-	-
Cardiac operation NOS	0	0	1	1	-	-	-	-
Vascular Disorders	**0**	**0**	**1**	**1**	**0**	**0**	**1**	**1**
Hemodynamic instability	0	0	1	1	-	-	-	-
Vena cava thrombosis	-	-	-	-	0	0	1	1

1.9.2.5.1. Analysis of Serious Adverse Events and Withdrawals

Three patients in the REPEL-CV treatment group had three SAEs (*enterococcus fecalis* sepsis and cardiac arrest n = 2) resulting in three deaths. The three SAEs were rated as definitely not related to the device by the investigator. Two patients in the non-treatment control group had three SAEs (candida sepsis and cardiac arrest; cardiac arrest) resulting in two deaths. One REPEL-CV patient was discontinued from the study because of a protocol violation. The violation involved a surgeon, who inadvertently neglected to place REPEL-CV in the patient prior to chest closure.

1.9.2.5.2. Clinical Laboratory Test Results

The changes in laboratory test results were not statistically different between the two treatment groups with respect to the means of individual patient changes over time. The abnormal laboratory results for all patients were considered by the investigators to be not related to the study device.

1.9.2.5.3. Concomitant Medications

The average number of medications used during the study was similar for both the REPEL-CV and non-treatment control patients. The number of medications used prior to surgery was also similar for the REPEL-CV and non-treatment control groups.

1.9.2.6. Safety Conclusions

The adverse event profile for both treatment groups was expected and consistent with this patient population. All adverse events, including the serious adverse events were considered by the investigators "definitely not" related to the study device.

The majority of the changes in laboratory test results were not statistically different between the two treatment groups. All the abnormal laboratory results were considered by the investigators to be not related to the study device.

Concomitant medications used in both treatment groups were expected and consistent with this patient population.

1.9.2.7. Effectiveness Conclusions

The effectiveness data available from this pilot study suggest that REPEL-CV reduces the incidence of dense 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 ($p = 0.062$).

1.9.2.8. Discussion and Overall Conclusions

Based on the safety measures in this study, REPEL-CV does not present an additional risk to pediatric patients undergoing cardiothoracic surgery. The observed mortality rate was expected for this high-risk patient population.

The effectiveness data available from this feasibility study suggest benefits attributable to REPEL-CV outweigh any risk. The results from this study provided the basis to proceed to the European and U.S. Pivotal trials.

1.9.3. Study 3 - Protocol # LMS0104RCV

Open Label, Multicenter Study to Determine the Effectiveness of REPEL-CV™ for Reducing Post-Operative Adhesions Following Pediatric Cardiothoracic Surgery (Protocol # LMS0104RCV).

Study Period: May, 2005 - June, 2006

1.9.3.1. Objective

The objective of the study was to evaluate REPEL-CV for reducing post-operative adhesions in pediatric patients undergoing staged cardiothoracic surgery via sternotomy.

1.9.3.2. Study Design

This was an open-label, multi-center human clinical study performed in Europe to evaluate the performance of REPEL-CV for the purpose of reducing the severity and extent of post-operative adhesions after cardiothoracic surgery. As in study 2, 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.

In order to evaluate device performance in these staged procedures, at the time of the second sternotomy, the severity and extent of adhesions at the investigational surgical site were assessed. In addition, serious adverse events were monitored throughout the study.

Patients fulfilling the inclusion criteria and having none of the clinical exclusion criteria were enrolled into the study after their legal representatives had signed the informed consent form. Upon enrollment, but prior to surgery, patients underwent the required screening evaluations. Just prior to chest closure, the patient's history was reviewed and it was confirmed that the patient did NOT have any exclusion criteria during the first sternotomy procedure and/or at the time of chest closure (Visit 1). If the patient met all the inclusion criteria and had none of the exclusion criteria, then the patient was treated with REPEL-CV. REPEL-CV was placed directly below the sternotomy site and sutured to the pericardial edges. The pericardium was left open.

Patient assessments were performed through the second surgical (sternotomy) procedure, which was anticipated to occur 2-8 months following treatment. All patients were monitored for SAEs on an ongoing basis. At the time of the second sternotomy procedure, an evaluator, who was a cardiac surgeon, assessed the severity and extent of adhesions at the investigational surgical site.

The primary inclusion criteria were: pediatric patients undergoing staged cardiothoracic surgery via sternotomy; and it was anticipated that the second sternotomy procedure would to be performed 2-8 months after the initial sternotomy procedure. The primary exclusion criteria were: absorbable hemostats remaining at the investigational surgical

site just prior to treatment with REPEL-CV and chest closure; and evidence of thick, discolored or malodorous discharge in the wound or other gross evidence of mediastinitis.

1.9.3.3. Patient Disposition and Demographics

Patients disposition: Nineteen (19) patients enrolled---------- fifteen (15) completed; one (1) discontinued for SAE---------- ---------- discontinued for SAE resulting in death.

Patient Demographics: Demographic variables are summarized in the table below.

Table 12: Demographics

	REPEL-CV N=19
Age (days) at time of chest closure	
Mean ± SD	12.9 ± 5.4
Median	10
Range	4 - 54
Gender	
Male	11
Female	8

1.9.3.4. Safety Analyses

1.9.3.4.1. Serious Adverse Events

Five serious adverse events (SAE) were reported. There were three deaths: 1. bradycardia with accompanying extreme cyanosis, 2. arrhythmia and decreased ventricular function, 3. cyanosis and cardiac arrest. There were also one shunt revision and one cerebral cramp. All five SAEs were anticipated events (*i.e.*, they were identified in the investigators brochure and the protocol) and were considered by the investigators "definitely not related" to the study device.

1.9.3.5. Effectiveness Analyses

The patients who completed the study had their adhesions assessed at the time of the second sternotomy. The severity of the adhesions, if any, at the investigational surgical site was graded as presented in the table below.

Table 13. Adhesion Severity Grading – Study 3

Adhesion Grade	Description
0	No adhesions
1	Mild Adhesions (filmy, non-cohesive adhesions requiring blunt dissection to separate the space between the epicardium and sternum)
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)
3	Severe adhesions (dense, cohesive adhesions requiring extensive sharp dissection to separate the space between the epicardium and the sternum)

The surgical investigative site was defined as: the area between the pericardial edges, *i.e.*, the area directly below the sternotomy site between the epicardium and the sternum (mediastinal space) and extending laterally to the pericardial edges.

The table below captures the extent and severity of the adhesions present at the time of the second sternotomy. Grade 3 (severe, dense, cohesive) adhesions are the most clinically challenging to the surgeon. The incidence and extent of Grade 3 adhesions have been, therefore, selected as the performance (effectiveness) clinical endpoint.

Table 14: REPEL-CV. Adhesion Severity and Extent (% area)

Patient #	Grade 0	Grade 1	Grade 2	Grade 3
----------	0	0	0	100
----------	0	100	0	0
----------	20	20	60	0
----------	0	50	50	0
----------	0	0	40	60
----------	0	100	0	0
----------	0	100	0	0
----------	0	100	0	0
----------	0	50	50	0
----------	0	100	0	0
----------	60	40	0	0
----------	30	50	20	0
----------	10	60	30	0
----------	0	100	0	0
----------	20	40	40	0
Mean (% Area)	10	60	20	11

As shown above:

1 Only two (2) of fifteen (15) patients (13.3%) treated with REPEL-CV had any Grade 3 (severe, dense, cohesive,) adhesions at the investigational surgical site.
2 The mean percentage of the investigational surgical site involved with Grade "3" adhesions in the REPEL-CV group was 11%.
3 The mean percentages of the investigational site involved with Grade 0, 1 and 2 are 10%, 60% and 20% respectively in the REPEL-CV group.

1.9.3.6. Discussion and Conclusions

The REPEL-CV treated patients had minimal Grade 3 (severe) adhesions in this study. As shown in study 4 below, in the absence of intervention to reduce the formation of post-operative adhesions (untreated "control") this patient population has extensive Grade 3 (severe) adhesions. Based on the data presented in this clinical trial, the benefits from the use of REPEL-CV outweigh the potential risks from the use of the product.

1.9.4. Study 4 - Protocol # LMS0103RCV

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).

Study Period: March 2004 - August 2006

1.9.4.1. Objectives

The objectives of the 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 cardiovascular surgery

1.9.4.2. 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 cardiovascular surgery. Pediatric patients from 15 clinical 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).

Three visits were scheduled after the screening visit, 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 was between 2 to 8 months.

At the time of the first sternotomy and just prior to chest closure (Visit 1), the patient's history was reviewed to confirm that there were no exclusion criteria associated with the first sternotomy procedure and/or at the time of chest closure. The patient was then allocated in a randomized fashion, to receive one of the following two treatment regimens at the time of chest closure: (1) REPEL-CV or (2) no treatment. If the patient was randomized to receive REPEL-CV, it was placed at the investigational surgical site directly below the sternotomy site and sutured to the pericardial edges. The pericardium was left open.

A safety follow-up visit was scheduled 3 - 8 weeks post chest closure (Visit 2). Clinical laboratory tests were performed 3 days post chest closure or at the time of discharge from hospital, whichever was sooner, and if clinically indicated at the time of Visit 2. All patients were monitored for adverse events on an ongoing basis including at all of the above visits.

At the time of the planned second sternotomy procedure (Visit 3), an evaluator, masked to the randomization code, assessed the severity and extent (% area) of adhesions at the investigational surgical site. If the implanted test material or fibrous capsule was visible or any abnormal tissue was present, it was sent for histopathologic evaluation.

The severity and extent of adhesions were evaluated as in Study 3, severity was graded as follows:

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)

Each study center was to enroll a sufficient number of patients until 50 patients per treatment group (per-protocol patients) completed the study.

The primary inclusion criteria were pediatric patients with weight > 2.5 kg and requiring a first-time staged cardiovascular sternotomy procedures. In addition, it was planned that the second sternotomy procedure would be performed two to eight months subsequent to the initial sternotomy procedure. As in studies 2 and 3, the primary exclusion criteria were: absorbable hemostats remaining at the investigational surgical site just prior to randomization and chest closure; and evidence of thick, discolored or malodorous discharge in the wound or other gross evidence of mediastinitis.

Just prior to chest closure, REPEL-CV was applied to the investigational surgical site and sutured to the pericardial edges. The piece of REPEL-CV was applied to the area directly below the sternotomy site, between the epicardium and the sternum, extending laterally sufficiently beyond the pericardial edges to the area between the epicardium and the pericardium, so that the tack sutures could be properly placed. The area between the epicardial edges was completely covered with one continuous piece of REPEL-CV. The pericardium was left open.

1.9.4.3. Measurement of Effectiveness and Safety

The primary effectiveness endpoint was the percentage of the study-defined investigational surgical site (ISS), with severe adhesions (Grade 3) at the second sternotomy procedure (Visit 3).

The secondary effectiveness endpoints 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 was clarified in the CRF as dissection time of adhesions at the investigational surgical site).
4 The percentage of patients by worst degree of adhesions within the investigational surgical site.

Safety was assessed by comparing events common, adverse events, serious adverse events, hematology and blood chemistry values, mortality, concomitant medications and common medications for the treatment groups. Events common was a category of events that were prospectively defined in the protocol as adverse events commonly associated with this patient population. Common medications included classes of medication that were prospectively defined in the protocol as commonly associated with this patient population.

Three patient populations were used for these evaluations:

1. The Intent-to-Treat (ITT) population consisted of all randomized patients who underwent the adhesion evaluations at the time of the planned second sternotomy. The ITT population was used to evaluate effectiveness and investigational surgical site observations at the second sternotomy.

2. 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 ITT group, as the results for the PP population were similar and the conclusions confirmatory.

1.9.4.4. Patient Disposition and Demographics

Patient Disposition: Patients were randomized at 15 study sites. The table below 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 (Randomization No.---------- and these subjects were discontinued from the study. These two pa---------- --------- mized and not treated: Patient--------surgeon elected to place Goretex membrane at investigational site and patient was not treated per

randomization code on 29Dec2003; Patient--------PI decided to not treat at the time of chest closure due to conduit location.

Table 15: Patient Disposition – Study 4

		REPEL-CV	Non-Treatment Control
Randomized		73	71
Safety Population***		73 (100%)	69 (97.2%)
ITT 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

* ITT 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.

Patient Demographics: The demographic variables for the ITT population are summarized in the table blow. The majority of the patients were Caucasian or African American. There were no statistically significant differences in age, gender, race, chest closure delay and type of surgical procedure. 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 16: Demographics (ITT) – Study 4

	REPEL-CV	Non-Treatment Control	p-value
	N=56	N=54	
Age (days)			0.374
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			0.118
Male	31 (55.4%)	38 (70.4%)	
Female	25 (44.6%)	16 (29.6%)	
Race			0.267
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)			0.003
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)			0.001
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			0.197
Norwood	38 (67.9%)	43 (79.6%)	
Non-Norwood	18 (32.1%)	11 (20.4%)	
Use of Heart-Lung Bypass Machine			0.043
Yes	45 (80.4%)	51 (94.4%)	
No	11 (19.6%)	3 (5.6%)	
Chest Closure Delay			0.379
Delay	40 (71.4%)	43 (79.6%)	
No Delay	16 (28.6%)	11 (20.4%)	

1.9.4.5. Primary Effectiveness Results

The REPEL-CV group achieved the clinically meaningful objectives sought for the primary endpoint. The differences consistently achieved statistical significance in both the ITT and PP populations. Results are presented for primary clinical endpoint: mean percent of the investigational surgical site (area) with Grade 3 (severe) adhesions in the table below (bold font) for the ITT population.

Table 17. Investigational Surgical Site Adhesion Assessments at Visit 3 (ITT)

Extent of Severity (% Area)		REPEL-CV (N=56)	Control (N=54)	p-value*
% Area with Grade 3 (Severe) Adhesion	**Mean ± SD**	**21.3 ± 36.50**	**47.3 ± 42.73**	**0.0008**
	Median	**0.0**	**35.0**	**0.0001**
% Area with Grade 2 (Moderate) Adhesion	Mean ± SD	44.8 ± 36.26	35.5 ± 35.36	0.1778
	Median	45.0	25.0	0.1650
% Area with Grade 1(Mild) Adhesion	Mean ± SD	31.0 ± 35.79	16.2 ± 26.79	0.0153
	Median	20.0	0.0	0.0351
% Area with Grade 0 (No) Adhesion	Mean ± SD	2.9 ± 13.75	0.9	0.3217
	Median	0.0	0.0	0.3296

*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). The 26.0% mean differences for the ITT populations exceeded the 20% criteria for a clinically meaningful change.

1.9.4.6. Secondary Effectiveness Results

In terms of secondary effectiveness endpoints:

1. REPEL-CV reduced the percentage of patients with Grade 3 adhesions as worst degree of adhesions (see table below [bold font]). For REPEL-CV, 30.4% (17/56) of the ITT population had Grade 3 adhesions. In comparison, 72.2% (39/54) of the Control group had Grade 3 adhesions ($p<0.0001$). The distribution of the worst degree of adhesions also favored REPEL-CV. There was a one-grade shift downwards favoring REPEL-CV ($p<0.0001$).

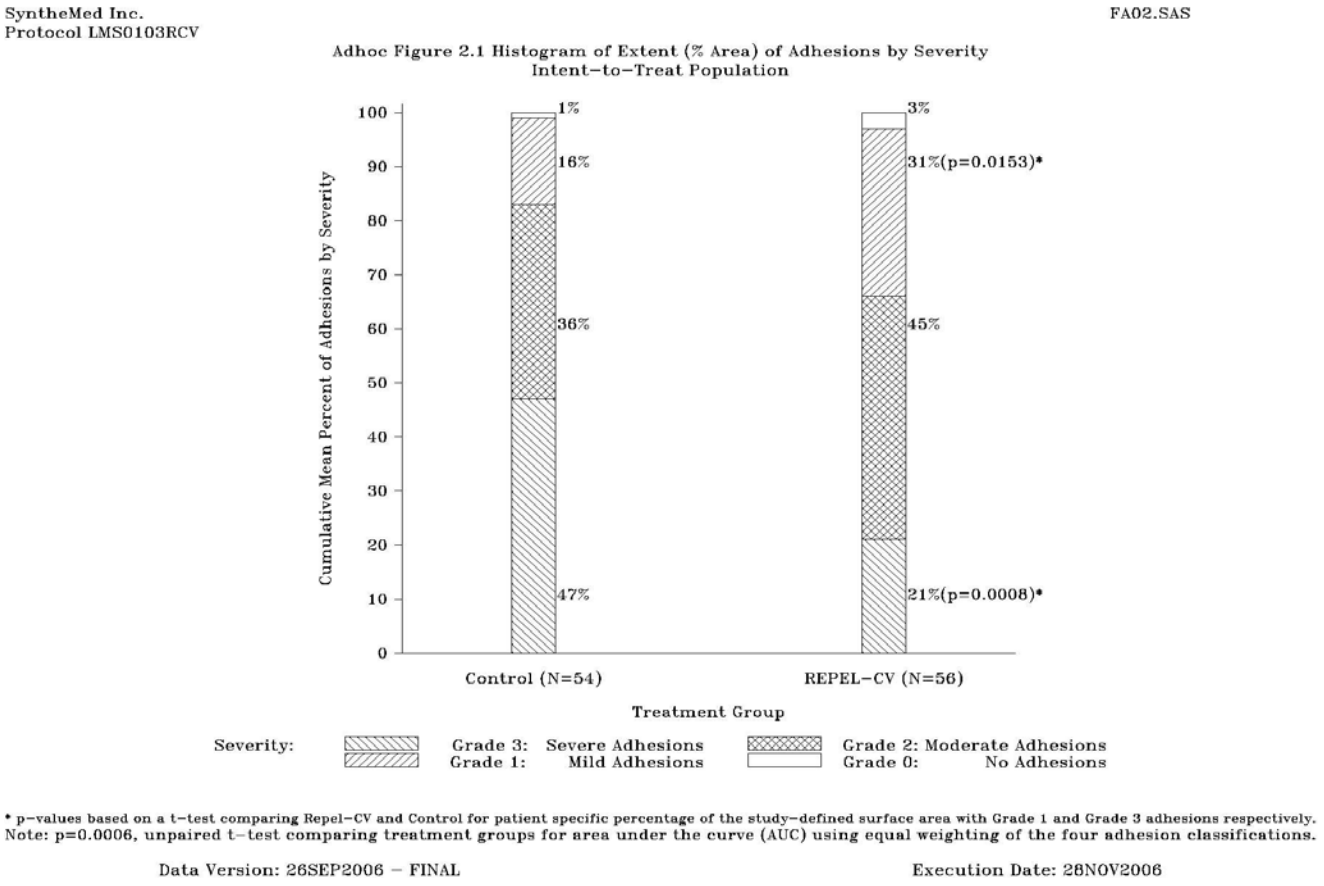
Table 18. Worst Degree of Adhesions Within the Investigational Surgical Site (ITT).

	REPEL-CV	Control	p-value
	(N=56)	(N=54)	
Patients (Percentage) with Grade 3: Severe Adhesions*	**17 (30.4%)**	**39 (72.2%)**	**<.0001**
Patients by Worst Degree of Adhesions**			<.0001
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. As described in Table 17, the mean percent of the study-defined surface area with severe (Grade 3) adhesions at the time of the second surgery was significantly lower for REPEL-CV treatment group as compared to the Control group. In addition, the mean percent of the study-defined surface area with mild (Grade 1) adhesions was significantly 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; p=0.0153 for the mean and p=0.0351 for the median).

3. Figure 1 below displays the mean extent (% area) of adhesions by severity in the ITT population. An ad hoc analysis was performed to compare the area under the curve (AUC) for REPEL-CV and Control using an unpaired t-test with equal weighting of the four adhesion classifications. The area under the curve was significantly lower for the REPEL-CV with an AUC of 184.5 units as compared to the Control group with an AUC of 229.3 units (n=110; 56 REPEL-CV, 54 Control; p=0.0006).

Figure 1. Histogram of Extent (% Area) of Adhesions by Severity



4. Adhesion dissection time was not influenced by REPEL-CV. For both the ITT and the PP populations, there was no significant difference in the mean dissection time (ITT: REPEL-CV=25.9 minutes (n=55), Control =25.0 minutes (n=53); p=0.8365.

An ad hoc analysis was performed to examine the relationship between dissection times for each treatment group and for both groups combined (overall) as a function of presence (severe adhesions present) or absence (no severe adhesion present) of severe (Grade 3) adhesions (see table below).

For both REPEL-CV and Control, the dissection time was reduced for those without severe adhesions vs. those with severe adhesions. In the ITT population, mean dissection time was reduced for those without severe adhesions by 10.4 minutes (corresponding to a 46% relative reduction) for REPEL-CV and 10.5 minutes (corresponding to a 60% relative reduction) for Control. Statistical significance is borderline in each treatment group, suggesting that the mean dissection time is greater when severe adhesions are present.

The impact of the presence vs. absence of severe adhesions, independent of treatment, was also assessed in the overall (combined) ITT population. Dissection time was significantly reduced for the ITT population from 29.6 to 21.2 minutes (an 8.4 minute difference corresponding to a 40% relative reduction) for those with vs. without severe adhesions. Although this overall reduction of 8.4 minutes was less than the reduction of 10.4 and 10.5 minutes for REPEL-CV and Control groups, respectively, significance was attained (p=0.0408 for the mean and p=0.0114 for the median). The combined reduction was slightly lower overall than within each treatment group reduction because of the imbalance between the numbers of patients with severe adhesions within each treatment group.

Table 19: Dissection Time of Adhesions by Severe Adhesion Status

	ITT Population		
	Overall	REPEL-CV	Control
Severe Adhesions Present			
N	55	17	38
Mean ± SD	29.6 ± 21.8	33.1 ± 19.1	28.0 ± 23.0
Median	27.0	38.0	23.0
No Severe Adhesions Present			
N	53	38	15
Mean ± SD	21.2 ± 20.1	22.7 ± 21.4	17.5 ± 16.9
Median	14.0	13.0	14.0
Differences in Means**	8.4	10.4	10.5
p-value*: t-test	0.0408	0.0918	0.1127
p-value*: Wilcoxon rank sum	0.0114	0.0556	0.0504

*Within treatment comparisons comparing dissection times for patients with severe adhesions present versus without severe adhesions present

**Differences in mean dissection time between subjects with severe adhesions present and subjects without severe adhesions present

1.9.4.7. Subgroups analyses: Evaluation Type

It was recognized from the beginning of the program that this would be a novel, complex and challenging study in a difficult patient population. Surgery is scheduled when key personnel (*e.g.*, masked assessor) may be out of town or unavailable, *i.e.*, limited number of cardiac surgeons who may be unavailable for multitude of reasons, to include being in the midst of their own case and hence unavailable. In some instances, the surgeon who randomized the patient also assessed the adhesions at the second sternotomy. These observations were classified as unmasked evaluations since performing both could have biased the surgeon's assessment. The primary effectiveness endpoint was separately evaluated for patients undergoing masked and unmasked assessments.

The Table below presents the data for the masked and unmasked evaluations.

Table 20. Percent Area with Severe (Grade 3) Adhesions for the Masked and Unmasked Evaluations

Group	REPEL-CV	Control	p-value*	Delta
Intent-to-Treat				
Overall (ITT; N=110)	56	54		
Mean ± SD (%)	**21.3 ± 36.5**	**47.3 ± 42.7**	**0.0008**	**26.0**
Evaluation Type				
Masked Evaluation (N=84)	43	41		
Mean ± SD (%)	24.0 ± 38.6	50.4 ± 44.0	0.0045	26.4
Unmasked Evaluation (N=26)	13	13		
Mean ± SD (%)	12.5 ± 27.9	37.7 ± 38.1	0.0662	25.2

* two-sided unpaired t-test

There were 84 (REPEL-CV: N=43; Control: N=41) cases where the masking was preserved vs. 26 cases (REPEL-CV: N=13; Control: N=13) where unmasking occurred. Among the 84 masked cases, there was a significant difference in the Severe (Grade 3) adhesions mean (REPEL-CV=24.0%, Control=50.4%; p=0.0045); the 26.4% advantage was consistent with the overall result. Similarly, for the 26 unmasked cases, the mean difference was 25.2% (REPEL-CV=12.5%, Control=37.7%; p=0.0662) (Statistical Table 16.1). It should be emphasized that the power of the study was not appropriate for inference-based subgroup analyses. The focus in the subgroups analyses was on the magnitude and the consistency of the REPEL-CV advantage *vs.* control. A reduction in the extent of Severe (Grade 3) adhesions for the REPEL-CV group occurred for both masked and unmasked evaluation types. Statistical significance (p=0.0045) was achieved for the critical masked evaluations where the evaluator did not know the original treatment group assignment.

1.9.4.8. Safety Results

1.9.4.8.1. Adverse Events

This REPEL-CV multicenter trial involved patients in an extraordinary high-risk group which are routinely subjected to a variety of different postoperative complications. The majority of the patients required cardiac surgery when less than 14 days old, all were cyanotic both before and following surgery, and greater than 90% had a single ventricle. In addition, approximately 75% of patients had their sternum left open for several days as a routine prior to closure.

The Events Common to this study population that occurred post-randomization are presented in Statistical Table 20 of the Clinical Study Report. The most frequent Events

Common that occurred at Visit 1 post-randomization included pain (REPEL-CV, 81.7% patients; Control, 84.8% patients), hemodynamic instability requiring inotropic support (REPEL-CV, 74.6% patients; Control, 74.2% patients), and electrolyte disturbances (REPEL-CV, 73.2% patients; Control, 72.7% patients). These post-randomization Events Common were similar to the Events Common that occurred prior to randomization.

The table below summarizes the adverse events and death. There were no differences in adverse events occurring post-randomization between the REPEL-CV and the non-treatment control group (p=1.000). In the REPEL-CV treatment group, 51 patients experienced 135 AEs post-randomization, of whom six patients experienced 6 AEs that were possibly, probably or definitely treatment related. Thirty-seven (37) patients experienced 63 SAEs, of which 4 were considered possibly, probably or definitely treatment related (none were considered definitely related).

In the control treatment group, 49 patients experienced 123 adverse events post-randomization, of which one patient experienced one AE that was possibly, probably or definitely treatment related (considered possibly related). Thirty-two (32) patients experienced 53 SAEs; none of these SAEs was considered possibly, probably or definitely a treatment related SAE.

Table 21 Summary of Adverse Events and Death – Safety Population

	REPEL-CV (n=73)		Control (n=69)		p-value (Fisher's exact test)
	Patients	Events	Patients	Events	
Number of Patients (percent) With at Least One Adverse Event	51 (69.9%)	135	49 (71.0%)	123	1.0000
Possibly, Probably or Definitely Treatment Related Adverse Events	6 (8.2%)	6	1 (1.4%)	1	0.1167
Number of Patients (percent) With at Least One Serious Adverse Events	37 (50.7%)	63	32 (46.4%)	53	0.6189
Number of Possibly, Probably or Definitely Treatment Related Serious Adverse Events	4 (5.5%)	4	0	0	0.1203
Number (percent) of Deaths (following the 1st and 2nd sternotomies)	12 (16.4%)	-	9 (13.0%)	-	0.6405

In the REPEL-CV treated group, the most frequently observed post-randomization adverse events were (Statistical Table 23.2 of the Clinical Study Report): 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. The numbers of events in less frequent SOCs are too infrequent to draw meaningful conclusion. It should be noted: 1) that 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 was expected and consistent with the clinical experience for this study population and they were identified as anticipated adverse events in the Protocol.

The adverse events as reported by the investigators with an incidence ≥ 2% are displayed in Table 22 below. In addition, and in order to impose consistency across investigator sites, the investigators reported adverse events associated with wound infection, medistinitis, medistinal infection, dehiscence and postoperative thoracic surgery complications (which included dehiscence and wound secretion) were reclassified to establish consistency across investigator sites. Table 23 displays the reclassified adverse events with an incidence ≥ 2% (Note: This Table was included in Section 3.7.1 (SSED); page 19 of the original PMA Submission). In both tables, there were few events in each category and no pattern of events indicating a safety signal when comparing REPEL-CV treatment against the non-treatment control.

Table 22. Incidence of Adverse Events ≥ 2% by Treatment Group, System Organ Class, Preferred Term

MedDRA Terms		REPEL-CV (n=73)	Control (n=69)
System Organ Class and Preferred Term		N (%)	N (%)
Cardiac Disorders			
	Ascites	3 (4.1%)	0
	Cardiac Arrest	3 (4.1%)	4 (5.8%)
	Cardio-Respiratory Arrest	4 (5.5%)	2 (2.9%)
	Cardiovascular Disorder	0	2 (2.9%)
	Cyanosis	2 (2.7%)	1 (1.4%)
Congenital, Familial and Genetic Disorders			
	Coarctation of the Aorta	2 (2.7%)	3 (4.3%)
Gastrointestinal Disorders			
	Abdominal Distension	0	2 (2.9%)
	Gastrooesophageal Reflux Disease	0	2 (2.9%)
	Haematochezia	0	2 (2.9%)
	Necrotising Colitis	2 (2.7%)	3 (4.3%)
General Disorders			
	Death	0	2 (2.9%)
	Pyrexia	1 (1.4%)	2 (2.9%)
Infections and Infestations			
	Bacteraemia	2 (2.7%)	2 (2.9%)
	Bronchiolitis	3 (4.1%)	0
	Central Line Infection	0	3 (4.3%)
	Fungal Sepsis	0	2 (2.9%)
	Gastroenteritis	1 (1.4%)	2 (2.9%)
	Mediastinitis	2 (2.7%)	1 (1.4%)*
	Respiratory Syncytial Virus Infection	2 (2.7%)	0
	Sepsis	0	2 (2.9%)
	Viral Infection	0	2 (2.9%)
	Wound Infection	3 (4.1%)*	3 (4.3%)
Injury, Poisoning and Procedural Complications			
	Postoperative Thoracic Procedure Complication	2 (2.7%)	3 (4.3%)*
	Wound Dehiscence	2 (2.7%)	0
Investigations			
	Cardiac Output Decreased	3 (4.1%)	1 (1.4%)
	Oxygen Saturation Decreased	1 (1.4%)	7 (10.1%)
Metabolism and Nutrition Disorders			
	Feeding Disorder Neonatal	2 (2.7%)	2 (2.9%)
Nervous System Disorders			
	Convulsion	2 (2.7%)	7 (10.1%)
Respiratory, Thoracic and Mediastinal Disorders			
	Atelectasis	2 (2.7%)	0
	Chylothorax	1 (1.4%)	2 (2.9%)
	Diaphragmatic Paralysis	2 (2.7%)	1 (1.4%)
	Hypoxia	3 (4.1%)	2 (2.9%)
	Pleural Effusion	4 (5.5%)	3 (4.3%)
	Pulmonary Artery Stenosis	3 (4.1%)	1 (1.4%)
	Respiratory Distress	2 (2.7%)	3 (4.3%)
Skin and Subcutaneous Tissue Disorders			
	Dermatitis Diaper	2 (2.7%)	0
Surgical and Medical Procedures			
	Life Support	2 (2.7%)	0
Vascular Disorders			
	Haemodynamic Instability	2 (2.7%)	0

Table 23: Observed Reclassified Adverse Events by Descending Frequency ≥ 2% (Study LMS0103RCV)***

		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*	**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**
	Wound Infection *	**2 (2.7%)****	**3 (4.3%)**
	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%)

1.9.4.8.2. Deaths and Other Serious Adverse Events

As per Table 20, there was no statistically significant difference between the REPEL-CV and the control treatment groups in serious adverse event rates (50.7% vs. 46.4% of patients, p=0.6189).

The table below summarizes the significance associated with deaths following the first sternotomy and overall (following 1st and 2nd sternotomies). The death rate following the first sternotomy was 12.3% (9/73) for REPEL-CV vs. 10.1% (7/69) for Control (p=0.7930, two-sided Fisher Exact test). The overall death rate was 16.4% (12/73) for REPEL-CV vs. 13.0% (9/69) for Control (p=0.6405, two-sided Fisher Exact test) with the inclusion of three REPEL-CV deaths and two Control deaths following the second sternotomy. The 90% confidence intervals were (-11.6%, 7.0%) following first sternotomy and (-13.5%, 6.8%) overall. The 90% lower bounds for the REPEL-CV – Control difference are -11.6% following first sternotomy and -13.5% overall. Results are shown below. The sample size is adequate to rule out a 18% disadvantage (15% vs. 33%, 2.8 odds ratio) with 80% power and one-sided 5% Type I error. This conclusion is totally consistent with the underlying study hypnosis for mortality with the exception that the mortality was more favorable (~ 15 %) than expected.

Table 24. Study Phase Death Rates For Each Treatment Group – ITT Population

Time	**REPEL-CV**	**Control**	**P-value***
Post-First Sternotomy	12.3% (9/73)	10.1% (7/69)	0.7930
90% CI	(-11.6%, 7.0%)		
Overall	16.4% (12/73)	13.0% (9/69)	0.6405
90% CI	(-13.5%, 6.8%)		

* Two-sided Fisher Exact test

The mortality following cardiac surgery in a comparable pediatric population is well reported in the literature. The preponderance of papers report mortality rates approaching 20%. Several contemporary references are cited. [14,15,16,17]

B. Alsoufi, et al. Peds. 2007;119:109-117 (Table 1:several studies): Mortality >18% (59- 840 pts.)

P. Checchia, et al., J.Thoracic Cardiovasc Surg 2005;129:754-9: Mortality 22% (801 pts.)

T. Tweddell, et al., Circulation 2002;106 [Supp l]:82-89: Mortality 19% (115 pts.)

S.Daebritz, et al., J.Thoracic Cardiovasc Surg 2000;119:358-67: Mortality 21% (194 pts.)

The mortality rates reported in the submitted pivotal study are consistent with those reported in the literature. The distribution of 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.

1.9.4.8.3. Adverse Events of Special Interest

Application of a foreign substance to the surgical site could result in an increased risk of infection or wound complications. Therefore, it was of interest to evaluate specific adverse events related to infections and complications involving the surgical site. The adverse events involving the surgical site are presented (in bold font) in Table 23 (wound dehiscence: REPEL-CV = 4 (5.5%), Control = 3 (4.3%); medistinitis after 1st sternotomy: REPEL-CV = 2 (2.7%), Control = 1 (1.4%); Mediastinitis after 2nd sternotomy: REPEL-CV = 2 (3.6%), Control = 0 (0%); wound infection: REPEL-CV = 2 (2.7%), Control = 3 (4.3%). In view of the small numbers of events and the potential of chance occurrence, there is no apparent difference between treatment groups with respect to these adverse events of special interest with the possible exception of mediastinitis, which is further discussed below. These events are commonly associated with the surgical procedures in this patient population and were listed in the protocol (protocol Appendix 5) as expected (anticipated) adverse events.

Mediastinitis was of specific interest. In order to impose consistency across investigator sites, events that could be classified as mediastinitis (coded as Mediastinal Infection, Mediastinitis, Wound Infection [non superficial] and Dehiscence) were more closely examined to evaluate the incidence of mediastinitis, which is potentially a more significant complication. Mediastinitis was defined as infection involving the mediastinum or sternum that required re-exploration and debridement regardless of the reported AE description.

The REPEL-CV multicenter trial involved patients in an extraordinary high-risk group that are routinely subjected to a variety of different postoperative complications. The majority of the patients required cardiac surgery when less than 14 days old, all were cyanotic both before and following surgery, and greater than 90% had a single ventricle. In addition, approximately 75% of patients had their sternum left open for several days as a routine prior to closure.

Delayed sternal closure in the postoperative period has been found to benefit some neonatal patients as the capillary leak and edema associated with cardiopulmonary bypass in the newborn continues into the postoperative period, potentially compromising myocardial and pulmonary function. Delayed sternal closure has also been an independent risk factor for mediastinitis (odds ratio, 9.3; 95% confidence interval, 1.5-56.8; P = 0.016).[10] The overall incidence of mediastinitis following cardiac surgery in diverse pediatric populations has been reported between 1.4% - 6.7% of patients undergoing median sternotomy.[10,11,12, 13] In the largest review of mediastinitis in pediatric

patients, the median time of onset following surgery for mediastinitis to occur in over 3,000 patients was 11 days (range 4-34 days).[10] When there was more than one sternotomy, all infections are described as being related to the most recent surgery.

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%).

Mediastinitis Following the First Operation:

1 Patient--------- developed mediastinitis (reported AE description = Wound infection) following a catheterization procedure in preparation for the second operation, the Glenn Shunt. This time frame was remote from randomization (~ 4 months subsequent to randomization, the first operation). As quoted in the SAE report, "The PI feels that this event is more likely due to complications following the cardiac catheterization than the study device, especially given the timing of the events and the other associated complications." The PI at the study site rated the event as "Possibly Related" to the study device.

2 Patient--------- underwent a Norwood procedure with delayed chest closure (23 March 2005). Two days later at the time of chest closure the patient was randomized to the REPEL-CV group (25 March 2005). The patient was readmitted with mediastinitis (reported AE description = Mediastinitis – bacteria culture found staph aureus) on 6 April 05 (14 days after the initial surgery). The patient underwent mediastinal exploration, debridement and primary closure. The PI rated the event as "Possibly Related" to the study device. The patient was discharged home in stable condition and received 6 weeks of antibiotics to complete therapy.

CONTROL:

1. Patient---------, female, born on---------- with double outlet right ventricle, ventricular septal defect and hypoplastic left ventricle, underwent a pulmonary artery banding procedure on 17June2005 (in original CSR and Amendment 11 the date of procedure was stated incorrectly as 9June2005). On 21Jun2005 (4 days after chest closure), the patient developed a *Staphylococcus epidermidis* infection in the chest wound and was treated with intravenous antibiotics. On 29Jun2005 (12 days after chest closure) as a result of a deep (just below the sternum) sternal dehiscence (Coded Postoperative Thoracic Procedure Complication = Sternal dehiscence), the patient's chest was opened and needed debridement; sternal reclosure and bilateral pectoralis flap mobilization were performed.

Mediastinitis following the second operation:

1 Patient---------- underwent a Norwood operation (2 Feb. 2004) with delayed sternal----------4 Feb. 2004). This patient required an additional sternotomy to create a new source of pulmonary blood flow with a Blalock-Taussig shunt on 24 March 2004 (50 days later). The additional shunt in this setting suggests undue cyanosis, which, along with this patients second Sternotomy in 50 days, can impair wound healing and promote infection. In addition, this patient had a percutaneous gastrostomy tube placed (15 April 2004). This tube often sits very close to the sternotomy site allowing GI and skin organisms to leak into the mediastinal incision and potentially increases the incidence of infection. The PI at this study site commented on this patient, "His risk for mediastinitis (23 April 2004) was increased by his multiple surgeries, not by the potential application of the bioresorbable adhesion reduction barrier that would have been placed almost 3 months (78 days) prior to the infection." The PI at the site rated the event (reported AE description = Mediastinal infection) as "Not Related" to the study device. This patient received 42 days of antibiotic therapy, and was discharged in stable condition.

2 Patient---------- had the initial sternotomy on 30 Dec. 2005 and delayed chest closure and randomization on 31 Dec. 2005. On 10 Jan. 2006, the patient underwent cardiac catheterization and stent placement in shunt narrowing. Six months later (15 June 2006), the patient underwent the second surgery (Glenn Shunt). On 19 June 2006 (4 days later), the patient developed serous drainage from the incision which grew *S. aureus* (mediastinitis) (reported AE description = Mediastinitis after 2nd sternotomy). The PI at the site rated the event as "Possibly Related." The patient received open debridement, and antibiotic therapy. In the opinion of the Sponsor, this case of mediastinitis, as described in the clinical papers on the topic, [10,11,12,13] would be considered related to the operation that preceded it, the Glenn Shunt, and not the operation 6 months prior.

The Table below shows the incidence of mediastinitis after the first sternotomy for REPEL-CV (2.7%) and the Control (1.4%). This difference is not statistically significant (p=1.000, two-sided Fisher Exact test).

Table 25. Incidence of Mediastinitis

Treatment at First Sternotomy	Randomization #	Onset of Mediastinitis (Days After 1st Sternotomy)	Incidence of Mediastinitis
REPEL-CV	03-03	~ 120	2.7% (2/73)
	13-09	14	
CONTROL	01-10	12*	1.4% (1/69)
		Onset of Mediastinitis (Days After 2nd Sternotomy)	
REPEL-CV	07-04	30	3.6% (2/56)
REPEL-CV	16-08	4	

*In amendment 11 it was improperly reported as 20 days post chest closure

As per page 4017 of the PMA Submission and references cited therein, when there are sequential sternotomies, surgical-site (sternotomy) related adverse events should be attributed to the most recent sternotomy. Therefore, the incidence of mediastinitis (3.6%; 2/56) following the 2nd sternotomy (Table above) should be attributed to the procedure rather than to REPEL-CV. Moreover, the risk for mediastinitis is known to increase by sequential surgeries, and especially when they occur as closely in time as they did in these instances.

In conclusion: (i). the patient population in the REPEL-CV Pivotal Study (neonates, cyanotic, delayed sternal closure) is predisposed to a higher infectious risk and (ii). the overall incidence of mediastinitis following cardiac surgery in a comparable pediatric population is well reported in the literature. [10,11,12,13] Based on these considerations, it is concluded that REPEL-CV does not pose an additional mediastinitis risk to patients undergoing cardiac sternotomy procedures.

1.9.4.8.4. Observations at the Second Sternotomy

The implanted test material or a fibrous capsule, or other abnormal tissue was present for 30.4% (17/56) of patients in the REPEL-CV group versus 1.9% (1/54) of patients in the Control group. This difference was significant ($p<0.0001$). Specimens from 13 of the 17 observations in the REPEL-CV group were obtained and processed for histological evaluation. The one control specimen was processed and evaluated.

Overall, 13 (12 from REPEL-CV treated patients; 1 from Control patient) of the 14 cases received showed foreign material with a focal foreign body reaction and fibrous encapsulation. The focal foreign body reaction was characterized by the presence of macrophages and some foreign body giant cells at the particulate material/tissue interface. The findings of foreign body reaction and fibrous encapsulation varied in degree and extent from case to case, but the general finding in the 13 of 14 cases was foreign body reaction. Fibrous encapsulation and fibrosis with fibroblasts and fibrocollagenous tissue were identified. Several cases showed focal granulation tissue

that is the healing response leading to fibrous encapsulation and fibrosis. Granulation tissue is characterized by the presence of capillaries and proliferating fibroblasts. Two cases also demonstrated focal microscopic dystrophic calcification and another single case showed fragments of a fibrin thrombus.

No acute inflammation and no chronic inflammation were identified in any of the 13 cases. Amorphous tissue fragments with no cellularity s---------t for diagnosis were identified in the one remaining case (Randomization No--------- a REPEL-CV treated patient).

The histological finding of a focal foreign body reaction with fibrous encapsulation is consistent and expected with a slowly degrading biomaterial. No pathology or adverse reactions were identified in the 13 of 14 cases and in these 13 cases, the material was considered biocompatible. It should be noted that the observed histological finding is comparable and consistent with that observed for commercially available synthetic resorbable sutures, which were used to secure REPEL-CV to the pericardium in the current study.

1.9.4.8.5. Laboratory Values Over Time

Laboratory chemistry and hematology test results by visit, Visit 0 (screening), Visit 1 (3 days post-chest closure or day of discharge) and Visit 2 (safety follow-up evaluation as clinically indicated) were summarized in Statistical Tables 27 and 28 of the Clinical Study Report.

There was no evidence of changes in laboratory values associated with treatment with REPEL-CV.

1.9.4.8.6. Vital Signs/Physical Examination

Vital signs and physical examination at baseline for individual patients are provided in Appendix 15.2 Data Listings 6 and 7, respectively of the Clinical Study Report. The summary of vital signs and the physical exam results at baseline are provided in Appendix 15.1.9, Statistical Tables 4 and 6, respectively of said Clinical Study Report.

There was no evidence of adverse effects on vital signs or physical examination associated with treatment with REPEL-CV.

1.9.4.8.7. Concomitant Medications and Common Medications

Concomitant medication and common medications include medications associated with the patients' surgical procedures and clinical conditions. Data Listing 18 of the Clinical Study Report presents concomitant medications by individual patient. The common medications used during the study by visit are summarized in Statistical Table 7 of said Clinical Study Report.

The number of concomitant and common medications used was similar for both the REPEL-CV and control patients.

1.9.4.9. Conclusions

1.9.4.10. Effectiveness Conclusions

The study results for the ITT population demonstrated a statistically significant reduction (26.0%) in the mean percentage of the study defined surface area with severe (Grade 3) adhesions favoring the REPEL-CV treatment (21.3% vs. 47.3%, p=0.0008). In addition, the percentage of patients with Grade 3 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 (p<0.0001). The percentage of patients by worst degree of adhesions favored REPEL-CV (p<0.0001). The distribution of the worst degree of adhesion showed a one-grade shift downwards that also favored REPEL-CV.

The study met the desired study objectives for the primary effectiveness measure. Results were established in both the ITT and PP populations. Multiple prospectively defined statistical analyses were confirmatory of significance for the ITT and PP populations.

1.9.4.11. Safety Conclusions

There were no statistically significant differences observed between the REPEL-CV and the control treatment groups in number of adverse events and number of patients with at least one adverse event (p=1.000), number of serious adverse events and number of patients with at least one SAE (p=0.6189), and mortality (p=0.6405).

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.

1.9.4.12. Overall Conclusions

The REPEL-CV multicenter trial involved patients in an extraordinary high-risk group that are routinely subjected to a variety of different postoperative complications. The majority of the patients required cardiac surgery when less than 14 days old, all were cyanotic both before and following surgery, and greater than 90% had a single ventricle. In addition, approximately 75% of patients had their sternum left open for several days as a routine prior to closure.

The study met the desired study objectives for the primary effectiveness measure. Multiple prospectively defined statistical analyses were confirmatory of significance for the ITT and PP populations. The adverse event profiles for both treatment groups were consistent with this patient population and the observed mortality rate was expected for this high-risk patient population. Based on the safety measures (adverse events and clinical laboratory) in this study, REPEL-CV does not present an additional risk to pediatric patients undergoing cardiac surgery.

1.10. Risk Benefit Analysis

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 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.

It is well recognized and accepted that 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 extensive severe, dense, vascular and cohesive post-operative cardiac adhesions. The risks inherent in the dissection of these adhesions, which obscure cardiac architecture and landmarks, make a repeat sternotomy more challenging and dangerous.

The clinical complications associated with these adhesions can include the following which can result in significant attendant morbidity and mortality:

1. Prolonged surgical time and excessive bleeding

2. Inadvertent entry into a critical structure or vessel (*e.g.*, the right ventricle, aorta, right atrium and any aortocoronary bypass graft, *etc.*) is increased which can result in severe hemorrhage

SyntheMed has sponsored four clinical studies, which assessed the use of REPEL-CV in both the adult and pediatric cardiothoracic patient population. Safety was measured across these four studies via assessment of:

1. Adverse events

2. Concomitant Medication

3. Laboratory Results

4. Patient Monitoring

These assessments have shown that REPEL-CV does not present an additional risk to pediatric or adult patients undergoing cardiothoracic surgery. The adverse events profile in both treatment groups was expected and consistent with the clinical experience for these study populations.

Effectiveness was evaluated in three studies at the time of resternotomy. In all three studies, it was concluded that REPEL-CV decreased the extent (area) of severe adhesions as compared to those patients (controls and historical controls) who did not receive the

product. By extension, the benefit accruing to the patient could include less clinical complications such as increased operating time, increased hemorrhage, and increased morbidity and mortality.

It is against these clinical complications that the safety and effectiveness profile of REPEL-CV must be weighed. Based on the four clinical studies, but primarily the larger multi-center US Pivotal trial that this submission is based on, the following conclusions have been reached:

1. There is no significant additional risk to the patient, *i.e.* the risk is as low as reasonably possible

2. The device met its primary clinical effectiveness endpoint, *i.e.*, the incidence and extent of severe (dense and cohesive) post-operative adhesions following cardiac surgery was significantly reduced ($p<0.001$).

3. The claims made in the device labeling are substantiated by the clinical investigations taken together with the preclinical data presented earlier.

4. This risk-benefit analysis has demonstrated that any risks associated with this device are acceptable when balanced against the benefits to the patient associated with the reduction in the incidence and extent of severe (dense and cohesive) post-operative adhesions following cardiac surgery.

1.11. Summary

The above information provides a reasonable assurance that REPEL-CV is safe and effective when used in accordance with the labeling.

1.12. FDA Decision

1.13. Approval Specifications

1.13.1. Bibliography/References

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