FDA EXECUTIVE SUMMARY

Prepared for the

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Circulatory System Devices Panel

P070005
Synthemed Inc.
REPEL-CV

Introduction

This is an Executive Summary for the REPEL-CV (P070005). The device has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration.

The Executive Summary begins with a brief discussion of the regulatory history of this device, followed by a summary of FDA's review of the device description, preclinical, and clinical information.

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1. Regulatory History

- **July 23, 2003** – Pivotal investigational device exemption (IDE) study approved for REPEL-CV (G980030/S28)
- **January 29, 2007** – Pre-market application (PMA) (P070005) was originally submitted
- **May 1, 2007** – Day 100 Meeting with sponsor – discussed major deficiencies
- **May 11, 2007** – Major Deficiency letter issued to the sponsor due to issues regarding the indications for use, as well as the animal, statistical, and clinical data
- **May 29, 2007** – Sponsor submitted response to major deficiency letter

2. Proposed Indications 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.

Contraindications

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

3. Device Description

The REPEL-CV is a single use, bioresorbable adhesion barrier composed of 52% by weight poly-lactic acid (PLA) and 47% by weight polyethylene glycol (PEG). The device is designed to provide a temporary barrier between two opposing surfaces lacking pericardial coverage. The barrier is intended to inhibit fibrinolytic activity and prevent interconnection as a result of the fibrin bands that develop during the course of normal healing. This device is intended to be used during cardiac surgery to prevent adhesions in the case of a second or third reoperation.

The device is supplied as a sterile, single-use micron film, packaged in a sterile foil pouch. The size of the device is: 18 cm x 13.5 cm x 137 microns. The device is stored between 2-8 degrees Centigrade.

At the first surgery, one continuous piece of the REPEL-CV is placed to the area directly below the sternotomy site, between the epicardium and the sternum and extending laterally sufficiently beyond the pericardial edges, between the epicardium and the pericardium. The material should extend at least 1.5 cm laterally beyond the pericardial edges between the pericardium and the heart to facilitate suturing to the pericardium.

Please refer to the device description provided in the proposed Summary of Safety and Effectiveness Data (SSED, Section 7), enclosed by the sponsor, for further details.

4. Preclinical Studies

FDA conducted a thorough engineering review of the preclinical testing. This device is a biodegradable film made of PLA and PEG. The following areas of review were included in FDA's engineering review:

- Mechanical properties
- Biocompatibility
- Sterilization
- Device packaging and shelf-life

FDA does not have any remaining concerns with the preclinical study data.

5. Animal Study

The sponsor has submitted summaries for the safety and effectiveness studies in canine and rabbit models. The sponsor's studies were previously reviewed in the original IDE G980030. The study summary results describe reproducible favorable results, indicating very good inhibition of adhesion in all animal models using the 47:52 PEG/LA.

FDA does not have remaining concerns regarding the animal data.

6. Clinical Study - Feasibility

This section presents the feasibility study trial design and clinical data. The sponsor conducted 3 feasibility studies prior to initiation of the pivotal trial. A summary of the studies is shown in Table 1. Each feasibility study is briefly discussed below and a more detailed description can be found in Section 7, beginning on page 16.

Table 1. 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

6.1 Study 1

This study was conducted in 1998 as a randomized trial at a two-hospital, single center and included adult patients. Although designed as a feasibility study for safety, assessment of adhesion extent at the time of re-explorative cardiac surgery was also conducted by a masked evaluator. Twenty-seven (27) patients were randomized who underwent operation for CABG (9 REPEL-CV, 11 Control), valve operations (4 REPEL-CV, 1 Control), and 2 cases (REPEL-CV) of LVADs implanted for bridging to transplant. One of the patients with an LVAD suffered from coagulopathy, noted as possibly related to the device.

6.2 Study 2

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

Table 2. Surgical site fibrinous adhesion assessments at Visit 2

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

There were a total of 7 patients who completed the study. Of the 7, three received the REPEL-CV. While the differences between the adhesion results for the patients were not significant for the sample size, there was a suggestion of effectiveness that prompted the sponsor to conduct a third feasibility study, and later, initiate a pivotal trial.

Serious adverse events (SAE) occurred in 3 patients in each cohort. These were listed as cardiac in all cases except for a single infection in a Control patient. There were 4 additional infections in REPEL-CV patients listed as moderate in severity. Mediastinal events, not further described, were listed for REPEL-CV patients, 2 as severe, and none for the Controls.

6.3 Study 3

This study was an Open Label, outside United States (OUS), single arm study that enrolled 19 REPEL-CV patients undergoing staged congenital cardiac procedures in a multi-center trial. The objective of this study was to gain European clinical experience with the REPEL-CV. The performance (effectiveness) endpoints were the percent of patients with any Grade 3 (severe) adhesions and the patient-specific percentage of the study-defined surface area of the investigational surgical site with Grade 3 adhesions at the time of the 2nd sternotomy.

The grading scale used for this study is shown in Table 3.

Table 3. Adhesion severity scale for Study 3

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

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

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

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

The results from the aforementioned pilot studies provided the sponsor with enough feasibility data to support an IDE application for a pivotal study. FDA had no major concerns with the feasibility data provided and approved the start of the pivotal study.

7. Clinical Study – Pivotal (Study 4)

Study 4, the pivotal study, was a multi-center, randomized, evaluator-masked, parallel comparative study at 15 study sites. 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.

This trial was conducted in 15 centers with a total of 144 pediatric patients. Two of the 15 centers had only 1 to 4 patients. Four centers had 14 to 19 patients. There were a total of 142 patients enrolled in the study after 2 patients were not enrolled due to protocol violations.

The following rationale for sample size, shown below, was taken from the sponsor's clinical protocol LMS0103RCV, January 26, 2004, in the PMA:

The null hypothesis is that there is no treatment difference in the success rates between treatments, while the alternative hypothesis is that there is a 20% improvement. Assuming a 35% standard deviation for the percent of the study-defined surface area with severe adhesions, to detect the 20% difference, a sample size of 50 patients per group (per-protocol patients) will be required for 80% power and overall 5% Type I error for a two-sided hypothesis test. Because of the high mortality associated with this patient population, the study will randomize up to 78 patients per group to allow for a loss of 28 patients/group due to early deaths or early surgeries.

FDA acknowledges that finding a feasible population for study of this device in a reasonable time span is a major challenge. The use of a pediatric population where multiple, staged, cardiac surgeries were planned was a reasonable model. The multiple staged surgeries were typically required within a window of 2-8 months and allowed for an assessment of short-term device safety and effectiveness.

Seventy three (73) patients received REPEL-CV; 71 patients were in the Control group. An accounting summary of the patient data is provided in Table 4. There were multiple analyses presented in the PMA regarding the intent-to-treat (ITT) and per-protocol patients (PP). There were 2 effectiveness analyses (ITT and PP) and 1 safety analysis (safety population) performed, as proposed by the sponsor in the original protocol. The PP analysis was used to confirm the ITT analysis. The patient enrollment differences between the 3 groups are shown in Table 4. For specific demographic data for the ITT patients, please see Table 6 in Section 9, page 34.

The 2 protocol violations were related to the Control group. Randomized patients ---------- and ------- were-------- tinued from the study. These two patients were randomized and not treated. For patient -------- the surgeon elected to place Gortex membrane at the investigational surgical site and the patient was not treated per randomization code. For patient ------- the principal investigator decided to not treat at the time of chest closure due to condu------- tion. However, the randomization envelope was already opened.

Table 4. Patient Accounting Summary

		REPEL-CV	Non-Treatment Control
Randomized		73	71
Completed Study		53	53
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 05-05, 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.

Ref.: Statistical Tables 1.1B and 2, Section 13.1; Data Listing 23, Appendix 15.2

7.1 Inclusion and Exclusion Criteria

Inclusion Criteria

Patients had to meet all of the following criteria to be entered into the study:
1. Requiring staged cardiovascular sternotomy procedures
2. No previous sternotomy
3. Weight greater than 2.5 Kg
4. It was anticipated that the second sternotomy procedure to be performed two to eight months subsequent to the initial sternotomy procedure
5. Patient was not a participant in another invasive device or drug study during the course of the study
6. Willing to participate in the study and abide by its requirements
7. Patient's legal representative was willing and able to provide informed consent

Exclusion Criteria

The patient was excluded if any of the following criteria existed:
1. Use of approved or unapproved treatment to prevent adhesions during the study

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

7.2 Safety Endpoints

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

To determine if REPEL-CV increases the mortality rate, use of a binomial test was proposed to test the null hypothesis. The proposed test was documented in the PMA as follows, in LMS0103RCV, January 26, 2004:

> An evaluation of whether REPEL-CV significantly increases the death rate (mortality rate) will be a safety objective of the trial. Using a sample size of 156 patients would achieve 80% power at a 5% significance level using a 1-sided equivalence test of proportions when mortality is 35% and the maximum allowable difference between the REPEL-CV and the control is 19%.

7.3 Effectiveness Endpoints

<u>Primary Effectiveness</u>

The primary effectiveness endpoint was the percent of the study-defined investigational surgical site (ISS) with severe (Grade 3) adhesions at the second sternotomy procedure. The following grading scale, from the sponsor's clinical protocol (LMS0103RCV, January 26, 2004) was used for the pivotal study:

> **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 null and alternative hypotheses for the primary endpoint are:

$$H_0: \mu_t \geq \mu_c$$

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

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

Secondary Effectiveness

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 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. [Note: 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.

7.4 Assessments

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

Table 5. Frequency of assessments

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

Each assessment was supposed to be performed by a masked evaluator. The evaluator was a cardiac surgeon that was a member from the site's surgical team and was involved with care of the patient and may have been completely blinded to the technique used in the original surgery. The evaluators independently assessed the adhesions. All other personnel in the operating room were instructed to make no comments about the extent and severity of the adhesions.

7.5 Study Results – Safety

The safety population includes all patients randomized. The results of the data analysis including the number of adverse events and mortality are shown in Table 6. Other than for mortality, there were no pre-specified performance criteria or statistical hypothesis. Please use caution when interpreting p-values. The mortality rate for patients in the REPEL-CV group was 16.4% compared to a rate of 13% in the Control group.

Table 6. Summary of safety population

	REPEL-CV (n=73)		Control (n=69)		p-value*
	Patients	Events	Patients	Events	
Number of Patients 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 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 of Deaths	12 (16.4%)	-	9 (13.0%)	-	0.6405
Ref.: Statistical Table 21, Section 13.1 * Fisher's exact test					

FDA acknowledges that the non-inferiority hypothesis test as stated by the sponsor was not performed as specified in the clinical protocol. Instead, the sponsor used the Fisher Exact test result and the 90% confidence interval on the treatment difference regarding the death rate (REPEL-CV – Control). After reviewing the results of the trial, FDA has no major concerns regarding the mortality rate in this patient population. Literature review supports the argument that the rates reported by the sponsor are expected based on mortality rates for the population studied in this trial.

Initially, there were four cases of mediastinitis/mediastinal infection in the REPEL-CV group and no cases in the Control group, as shown in Table 7. Mediastinitis was defined as infection involving the mediastinum or sternum that required re-exploration and debridement regardless of the reported adverse event description. Further details about adverse events can be found in the sponsor's safety evaluations beginning on page 45 in Section 7. Pages 47-48 present a detailed table of adverse events.

Table 7. Adverse events

MedDRA		REPEL-CV (n=73)		Control (n=69)	
Preferred Term		N (%)		N (%)	
		All AEs	SAEs	All AEs	SAEs
	Mediastinal Infection	1 (1.4%)	1 (1.4%)	0	0
	Mediastinitis	2 (2.7%)	2 (2.7%)	0	0
	Postoperative Wound Infection	1 (1.4%)	0	0	0
	Wound Abscess	0	0	1 (1.4%)	1 (1.4%)
	Wound Infection	4 (5.5%)	1 (1.4%)	3 (4.3%)	2 (2.9%)
	Wound Infection Staphylococcal	1 (1.4%)	0	1 (1.4%)	1 (1.4%)
	Cardiac Procedure Complications	1 (1.4%)	1 (1.4%)	0	0
	Postoperative Thoracic Procedure Complication	2 (2.7%)	0	4 (5.8%)	1 (1.4%)
	Wound Dehiscence	2 (2.7%)	0	0	0
	Wound Secretion	1 (1.4%)	1 (1.4%)	1 (1.4%)	0
Ref: Statistical Tables 23.2 and 26.2, Section 13.1					

After the sponsor completed a post hoc re-adjudication of events, one case of wound dehiscence in the Control group was reclassified as a case of mediastinitis in the Control group. The re-adjudication is shown in Table 8.

Table 8. Incidence of mediastinitis – post hoc

Treatment at First Sternotomy	Randomization #	Onset of Mediastinitis (Days After 1st Sternotomy)	Incidence of Mediastinitis
REPEL-CV		~ 120	2.7% (2/73)
		14	
CONTROL		20	1.4% (1/69)
		Onset of Mediastinitis (Days After 2nd Sternotomy)	
REPEL-CV		30	3.6% (2/56)
REPEL-CV		4	

Summary of Safety Results

There was a general trend for more patients with adverse events, more serious adverse events, and more deaths in the REPEL-CV than the Control arm. FDA reviewed the individual cases of mediastinitis and agrees with the sponsor's analysis of the adjudication of the mediastinitis.

7.6 Study Results - Effectiveness

Primary Effectiveness

The primary effectiveness endpoint was the percent of the study-defined investigational surgical site (ISS) with severe (Grade 3) adhesions at the second sternotomy procedure. These data are shown in Table 9. The observed average percent for the most severe adhesions (Grade 3) was 21.3% ± 36.5% (n=56) for the REPEL-CV group, and 47.3% ± 42.7% (n=54) for the Control group. Table 9 further details the patient assessments.

Table 9. % Adhesions for the ITT population

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	35.6 ± 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
Ref.: Statistical Table 10.1, Section 13.1; Data Listing 15, Appendix 15.2 A t-test was used to compare treatment means and the Wilcoxon rank sum test for the medians				

A two-sample t-test performed by the sponsor showed a significant difference in the primary effectiveness endpoint between the REPEL-CV and the Control groups ($p < 0.001$). For the per protocol (PP) population, the mean percent of study-defined surface area with Grade 3 adhesions was 21.1% for the REPEL-CV group and 49.5% for the Control group. The two-sample t-test p-value was less than 0.001.

Analysis of variance (ANOVA) models were used by the sponsor to test for treatment difference between REPEL-CV and Control group while controlling for study site. Neither the site by treatment interaction effect nor the site effect was found to be statistically significant for either the ITT or PP populations.

FDA notes that the percentage area of Grade 1 and 2 is higher in the REPEL-CV compared to the Control group. This is because the percentage of Grade 3 adhesions is lower. As the percentage of area of Grade 3 adhesions goes down, Grades 1 and 2 adhesions increase. The total percentage of area evaluated must add up to 100%.

An example follows for the calculation of the mean adhesion percents. Suppose there are two patients with adhesion percents as follows:

Patient 1: 50% Grade 3, 20% Grade 2, 0% Grade 1, and 30% Grade 0
Patient 2: 0% Grade 3, 60% Grade 2, 0% Grade 1, and 40% Grade 0.

The means become 25% Grade 3 (average of 0% and 50%), 40% Grade 2 (average of 20% and 60%), 0% Grade 1 (average of 0% and 0%), and 35% Grade 0 (average of 30% and 40%). Note that the means for Grades 0-3 also add to 100% and that all patients are used in the calculations of the means. This explains why the significant advantage for REPEL-CV in reduced Grade 3 adhesion extent must be offset by increased mean adhesion extent in the lower grades. This represents a shift to less severe adhesions for REPEL-CV versus the Control group.

In this study, evaluators were supposed to be masked to the primary effectiveness endpoint evaluation. However, the same surgeon who did the surgery also assessed the primary effectiveness endpoint for 26 subjects. There were 13 unmasked evaluations in the REPEL-CV group and 13 unmasked evaluations in the Control group. The effects of the unmasked evaluation are shown below. It should be noted that the p-values in Table 10 were calculated without adjusting for multiple comparisons.

Table 10. Percent area of severe adhesions (Grade 3) for the masked and unmasked patients.

Group	REPEL-CV	Control	p-value*	Delta
Intent-to-Treat				
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

By assuming that the unblinding cases happened at random (in other words, the chance to happen is equal between the REPEL-CV and the Control groups), the primary effectiveness endpoint results could be analyzed using only the masked observations. Excluding the unmasked observations, a two-sample t-test performed by the sponsor showed a significant difference in the primary effectiveness endpoint between the REPEL-CV and the Control groups (p=0.0045) for the ITT population.

FDA notes that the magnitude of the effectiveness endpoint appears to be different for patients with unmasked evaluation and for patients with masked evaluation for both the REPEL-CV and the Control group. It appears that the differences between REPEL-CV and the Control group under the masked and unmasked evaluation are similar.

Secondary Effectiveness Endpoints

No hypothesis tests were planned at the IDE stage. Nevertheless, the sponsor presented a number of post hoc statistical test results that need to be interpreted with the usual caveats.

Use of REPEL-CV reduced the percentage of patients with Grade 3 adhesions as worst degree of adhesions, as shown in Table 11.

Table 11. Number of patients with varying degrees of adhesions at ISS

	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			

FDA also notes that a combination of Grades 2 and 3 in both the REPEL-CV and Control groups show a similar number of patients for each arm. The REPEL-CV group contains a total of 49 patients with Grades 2 and 3 adhesions and the Control group consists of a total of 52 patients with Grades 2 and 3 adhesions.

The dissection times for patients in the REPEL-CV and Control group are presented in Table 12.

Table 12. Dissection time (minutes)

	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 p-value*: Wilcoxon rank sum	0.0408 0.0114	0.0918 0.0556	0.1127 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

The influence of REPEL-CV on the dissection time is unclear. Patients in the REPEL-CV group with severe adhesions had longer dissection times compared to patients with severe adhesions in the Control group. FDA acknowledges that there are fewer patients with severe adhesions as a result of the REPEL-CV. Patients in the REPEL-CV group with no severe adhesions also had an increased dissection time compared to patients in the Control group and the number of patients with no severe adhesions is greater in the REPEL-CV group compared to the Control. Finally, as expected, FDA notes that a comparison of the mean dissection times for the overall group of patients shows that the dissection time is greater in patients with severe adhesions compared to patients with no severe adhesions.

Summary of Effectiveness Results

A two-sample t-test performed by the sponsor showed a significant difference in the primary effectiveness endpoint between the REPEL-CV and the Control groups ($p<0.001$). FDA acknowledges that the analysis shows that the sponsor has met the pre-specified primary effectiveness endpoint. Secondary endpoint tests should be interpreted cautiously as a limited number of hypotheses were not prospectively planned.

8. Post-Approval Study

The FDA review team, which includes an epidemiologist, has made the recommendation that if the REPEL-CV is approved, a post-approval study should be considered as a condition of approval for this first-of-a-kind device. FDA recognizes that the sponsor has proposed such a post-approval study and we will be asking the panel for their advice on its development. The components of a post-approval study which we will be seeking panel input on include the specific patient population, objectives/endpoints, and duration. For example, a post-approval study may be designed to evaluate the *long-term* safety and effectiveness of the REPEL-CV.

Note: We would like to remind you that the presence or content of a post-approval study is not a substitute for the requirement of demonstrating a reasonable assurance of safety and effectiveness prior to pre-market approval. The proposed post-approval study population should be consistent with the population in which the device is indicated for use.

9. Conclusions

The data presented in the PMA characterize the safety and effectiveness of the REPEL-CV. The sponsor has met the primary effectiveness endpoint in the specific pediatric population studied, based upon their pre-specified hypothesis. However, the safety endpoints are difficult to interpret. FDA requests input from the Advisory Panel in interpreting these data and rendering an approvability recommendation. Furthermore, FDA also requests input on the development of the proposed post-approval study.