1. Title Page

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"

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PREPARED BY:

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2. Synopsis

SPONSOR:	SyntheMed, Inc. (AKA: Life Medical Sciences, Inc.) 200 Middlesex Essex Turnpike Suite 210 Iselin, NJ 08830 Phone: 732-404-1117 Fax: 732-404-1118
PRODUCT:	REPEL-CV™
PROTOCOL TITLE:	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 NUMBER:	LMS0103RCV
U.S. IDE NO:	G980030
INVESTIGATORS AND STUDY CENTER:	See cover page
STUDY PERIOD:	March 2004 - August 2006
STUDY OBJECTIVES:	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.
STUDY DESIGN AND DURATION OF TREATMENT:	This was a multi-center, randomized, evaluator-masked, parallel comparative study. One group received REPEL-CV and the second was the untreated control group. Patients were randomized to treatment at the initial surgery's time of chest closure. Assessment of effectiveness was made at the time of second sternotomy procedure. The anticipated duration of patient participation, from the time of initial sternotomy to the second sternotomy procedure, was between 2 to 8 months.
NUMBER OF PATIENTS:	One hundred forty four (144) patients (REPEL-CV, 73; control 71) were randomized into the study. The Per-Protocol population comprised fifty four (54) REPEL-CV treated and forty nine (49) control patients. The Intent-to-Treat population comprised fifty six (56) REPEL-CV treated patients and fifty four (54) control patients.
DIAGNOSIS AND MAIN INCLUSION CRITERIA:	Pediatric patients requiring staged cardiovascular sternotomy procedures for cardiothoracic surgery.

EFFICACY MEASUREMENTS	At the time of the second sternotomy procedure, the primary clinical end-point was the patient specific percentage of the study defined surface area (the investigational site) with severe adhesions (Grade 3).
SAFETY MEASUREMENTS:	Safety parameters included monitoring of adverse events, physical examination, changes in clinical laboratory tests and mortality.
STATISTICAL METHODS:	Three patient populations were used:

- Intent-to-Treat (ITT)
- Per-Protocol (PP)
- Safety

Baseline values were defined as those values obtained just prior to randomization. Demographic and baseline characteristics were summarized for the intent-to-treat, per-protocol and safety populations to assess treatment group balance.

All effectiveness analyses were presented for both the intent-to-treat and per-protocol population.

The primary effectiveness endpoint was the mean percent of the study-defined surface area with severe (Grade 3) adhesions at the time of the second surgery in the ITT population. This endpoint was considered to be a continuous outcome and should not be confused with the percentage of patients with any severe adhesions. Descriptive statistics (N, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum) were presented for each treatment group and treatment specific means compared using a two-sided t-test. A Wilcoxon rank sum test was presented as a confirmatory analysis.

The analysis approach for the primary study endpoint was to perform an analysis of variance (ANOVA) to test for treatment differences while controlling for study site. Those sites with 3 or fewer patients were grouped together as one site in this analysis. In the event that there was a significant (p-value<0.05) site by treatment interaction effect, results were displayed separately by study site. If the site by treatment interaction effect was non-significant it was removed from the ANOVA model.

For confirmation purposes, an analysis of covariance (ANCOVA) model was run for the ITT population where the mean percent of the study-defined surface area with severe adhesions at the time of the second surgery was the dependent variable. The model included study site (as defined above), age, gender, as well as any other baseline covariates found to be imbalanced between treatment groups. The significance level was 0.10 for a baseline covariate to be included.

A parallel analysis of the primary effectiveness endpoint was conducted

for each subgroup by gender, procedure type, use of heart-lung bypass during surgery, evaluation type and chest closure delay.

The secondary effectiveness endpoints:

1. The percentage of patients with Grade 0, 1, or 2 adhesions as worst degree (i.e., patients without severe adhesions). (Note: This endpoint is the complement of the percentage of patients with severe adhesions and will be referred as such for simplicity.) The frequency and percentage of patients with severe adhesions were displayed by treatment group and compared using Fisher's exact test.
2. Patient specific percentage of the study-defined surface area (the investigational surgical site) with Grade 0, 1, and 2 adhesions. (Note: This endpoint was meant to compare the patient specific percentage of the study-defined surface area within each grade.) The patient specific percentage of the study-defined surface area was categorized by adhesion grade. Descriptive statistics (N, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum) were presented for each treatment group within adhesion grade and treatment specific means compared within each adhesion grade using a two-sided t-test. A Wilcoxon rank sum test was presented as a confirmatory analysis.
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) Descriptive statistics (N, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum) for the dissection time of adhesions at the investigational surgical site was presented for each treatment group and treatment specific means compared using a two-sided t-test. A Wilcoxon rank sum test was presented as a confirmatory analysis.
4. The percentage of patients by worst degree of adhesions. Patients were divided into four subgroups: patients without any adhesions (Grade 0), patients with mild adhesions (Grade 1 as worst degree), patients with moderate adhesions (Grade 2 as worst degree), and patients with severe adhesions (Grade 3 as worst degree). The frequency and percentage of patients falling into each category were displayed by treatment group and treatment distributions compared using a Wilcoxon rank sum test.

All safety analyses were presented for the safety population. The safety parameters included: common medical events, adverse events, serious adverse events, clinical laboratory values, and observations at the second sternotomy and wound healing assessments at one month post second sternotomy. Frequency and percentage of the assessments were summarized by treatment group and compared using a Fisher's exact test.

Differences between treatment groups were considered statistically significant if the two-sided p-value was <0.05.

SUMMARY OF EFFECTIVENESS AND SAFETY RESULTS:

The study results for the ITT population demonstrated a statistically significant reduction (26.0%) in the mean percentage (patient specific) of the study defined surface area with severe (Grade 3) adhesions favoring the REPEL-CV treatment (21.3% vs. 47.3%, p=0.0008). The primary effectiveness endpoint was also confirmed in the following subgroups: males (p=0.0021), females (p=0.0454), Norwood procedure (p=0.0106), on Heart-Lung bypass machine (p=0.0050), masked evaluators (p=0.0045), and chest closure delays (p=0.0121). In addition, the percentage of patients with Grade 3 adhesions at the investigational site as 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. Similar statistically significant results favoring the REPEL-CV treatment were also demonstrated for the PP population.

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).

CONCLUSIONS:

The study has met the desired study objectives for the primary effectiveness measure. Results were established in the ITT and PP populations and confirmed for masked evaluators and key subgroups including Norwood, on bypass, and chest closure delays. Multiple prospectively defined statistical analyses were all confirmatory of significance for the ITT and PP populations. Although the standard deviation was somewhat higher than expected (leading to 74% power as opposed to the desired 80% power), the magnitude of the differences detected always exceeded the pre-defined 20% clinically meaningful difference used to plan the study as well as the 21.7% difference required to achieve 80% power. In addition, many secondary effectiveness outcomes are also significant. The potential for bias from withdrawals, time to withdrawal, and times to second sternotomy have been ruled out as have site and site-treatment interactions.

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

REPEL-CV, a bioresorbable barrier, has been shown to safely reduce the formation of post-operative cardiovascular adhesions.

3. Table of Contents of Study Report

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List of Abbreviations and Definition of Terms

CRF	Case Report Forms
CVP	Central venous pressure
DSMB	Data Safety Monitoring Board
ECMO	Extra Corporeal Membrane Oxygenation
FFP	Fresh frozen plasma
GCP	Good Clinical Practice
HLHS	Hypoplastic Left Heart Syndrome
IRB	Institutional Review Board
ISS	Investigational surgical site
KUB	Kidney, ureter, bladder
MVO_2	Myocardial oxygen consumption
NPO	Nothing by mouth
POD	Post-operative day
PT	Preferred Term
SOC	System organ class
TPN	Total parenteral nutrition

4. Ethics

4.1. Investigational Review Board

This protocol and its associated Informed Consent Agreement were reviewed and approved by the appropriate Institutional Review Board (IRB) associated with the respective study site. Protocol amendments were approved by the IRB prior to their implementation. A copy of the letter signed by the Chairman of the IRB to the Principal Investigator indicating IRB approval of the protocol was received by the sponsor and maintained in the study file prior to study initiation. Device supply was not shipped to the study site until the sponsor received this documentation.

4.2. Ethical Conduct of the Study

This study was conducted in accordance with Good Clinical Practice (GCP) requirements.

4.3. Patient Information and Consent

The risks and benefits of participating in this study were explained to the guardian of each potential patient prior to entering into the study. The informed consent was written in language readily understood by the guardian. The informed consent was approved by the IRB prior to study initiation, performance of any study procedure and dispensing of the study device. The Principal Investigator or his/her designee obtained a signed and witnessed Informed Consent Form for each patient. Receipt of the signed Informed Consent Form was documented in the Case Report Form and a copy retained by the Investigator. A copy of the signed Informed Consent Form was given to each guardian of the patient.

5. Investigators and Study Administrative Structure

5.1. Principal Investigator(s)

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5.2. Clinical Research Monitors

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5.3. Report Authors

Eli Pines, PhD, SyntheMed, Inc.

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6. Introduction

Adhesions are fibrous structures that connect tissues or organ surfaces that are not normally joined. They are an undesirable side effect of the body's normal healing process following damage to tissues. Adhesions can cause significant complications following surgery (e.g., infertility, bowel obstruction, pain, etc.). In cardiac surgery, adhesions can increase the complexity, duration and risk of subsequent surgery and sometimes can cause catastrophic sequelae. Several approaches have been advocated for the purpose of reducing post-operative adhesions, including: reduction in trauma, anti-inflammatory agents, anti-coagulants, thrombolytic agents and the use of barriers.[1]

SyntheMed, Inc. has developed REPEL-CV, a bioresorbable barrier, as a surgical adjuvant for reducing the formation of post-operative cardiothoracic adhesions. REPEL-CV is a sterile, bioresorbable polymeric barrier-film composed of polyethylene glycol and poly L-lactic acid. REPEL-CV is absorbed from the site of implantation within 4 weeks of application. REPEL-CV provides a temporary barrier to mechanically separate potentially opposing surfaces from interconnecting with each other during the early phases of the healing process.

7. Study Objectives

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 (cardiovascular) surgery.

8. Investigational Plan

8.1. Overall Study Design and Plan

This was a multi-center, randomized, evaluator-masked, parallel comparative study to evaluate the safety and effectiveness of REPEL-CV for the purpose of reducing 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). A flow chart of the study is provided in Appendix 1 of the protocol. 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 (Visit 1), just prior to chest closure, the patient's history was reviewed to confirm there were no exclusion criteria associated with the first sternotomy procedure and/or time of chest closure. The patient was then randomized to receive one of the following two treatment regimens at the initial surgery's time of chest closure: (1) REPEL-CV or (2) untreated. A balanced block design was used to ensure treatment group balance within sites. 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 (see protocol Appendix 2 for details). 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.

At the time of the planned second sternotomy procedure (Visit 3), an evaluator, masked to the randomization code, assessed the severity and extent (%) of adhesions at the investigational surgical site (as defined in the Protocol Appendix 3). In addition, the time to take down the adhesions at the investigative surgical site (ISS) was recorded. Histo-pathological evaluations were performed if the implanted material or fibrous capsule was visible or any abnormal tissue was present.

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

8.1.1. Study Visits

8.1.1.1. Screening (Visit 0)

1. Obtain informed consent
2. Obtain medical history
3. Perform physical examination
4. Perform clinical laboratory tests
5. Evaluate inclusion/exclusion criteria
6. Determine primary diagnosis

8.1.1.2. Time of First Sternotomy Procedure and/or Time of Chest Closure (Visit 1)

1. Confirm inclusion/exclusion criteria
2. Perform the surgical procedure
3. Record current medications at time of chest closure
4. Just prior to chest closure, randomize to either treatment with REPEL-CV or no treatment
5. If randomized to the REPEL-CV group:
   - Apply one piece of REPEL-CV to the epicardium, and suture it to the pericardium (4-0 Vicryl with a tapered needle, 2 to 3 tack sutures per edge).

- Limit the application of REPEL-CV 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, so that the tack sutures could be properly placed.
- Ensure that the area between the epicardial edges is completely covered with one continuous piece of REPEL-CV (see Protocol Appendix 2 for details).

6. Record concomitant medications
7. Monitor and record adverse events

8.1.1.3. Post-Operative Period

1. Monitor and record adverse events
2. Perform clinical laboratory tests (Day 3 post chest closure or at time of discharge from hospital, whichever occurred sooner)
3. Record concomitant medications

8.1.1.4. Safety Follow-Up Evaluation, 3 – 8 Weeks Post Chest Closure (Visit 2)

1. Monitor and record adverse events
2. Perform clinical laboratory tests as clinically indicated
3. Record concomitant medications

8.1.1.5. Time of Second Sternotomy Procedure (Visit 3)

1. Determine the severity of the adhesion(s), if any, at the investigational surgical site. Severity was graded as follows:

    - 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)

2. Record the extent of adhesion(s), the percent of the investigational surgical site area involved with each adhesion severity grade (as defined in 1 above)
3. Record time to take down the adhesions at the ISS (placement of sternal retractor)
4. Record time to heparinization prior to cannulation
5. Monitor and record adverse events

8.1.1.6. One Month Post Second Sternotomy Procedure

At a minimum of 1 month after the second sternotomy the patients were evaluated to assure that

their wound healed and that there were no infections.

8.2. Selection of Study Population

8.2.1. 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

8.2.2. Exclusion Criteria - First Sternotomy Procedure and/or Time of Chest Closure

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

8.2.3. Removal of Patients from Therapy or Assessment

Patients were discontinued from the study at the patient’s legal representative’s request, or if the investigator felt that it was not in the best interest of the patient to continue in the study. A final evaluation was done within 7 days of all premature discontinuations from the study.

8.3. Treatments

8.3.1. Treatments Administered

Patients were randomized to receive either REPEL-CV or no-treatment (Control)

Prior to applying REPEL-CV, all irrigation fluids and instillates were removed from the pericardial cavity. REPEL-CV was soaked in Ringer's lactate buffer or saline solution for approximately two minutes (no longer than 5 minutes).

Just prior to chest closure, REPEL-CV was applied to the epicardium and sutured to the pericardium (4-0 Vicryl with a tapered needle, 2 to 3 tack sutures per edge). The piece of REPEL-CV was applied to the area directly below the sternotomy site, between the epicardium and the sternum and 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.

8.3.2. Identity of Investigational Product

REPEL-CV is a sterile, bioresorbable polymeric anti-adhesion barrier-film composed of polyethylene glycol and poly L-lactic acid. It is stored in a sealed foil pack at a temperature between 4^{o}C and 8^{o}C, and provided sterile. Synthemed, Inc. provided all REPEL-CV.

8.3.3. Method of Assigning Patients to Treatment Group

Patients were randomly assigned to one of two treatment groups at the initial surgery's time of chest closure. One group received REPEL-CV and the second group was untreated. Patients were enrolled from 15 clinical sites; a balanced block design was used to ensure treatment group balance within sites.

8.3.4. Blinding

Evaluator-masked

8.3.5. Prior and Concomitant Therapy

Medications were recorded in the Case Report Form by class of medication common for this patient population (Protocol Appendix 7) and/or concomitant medication.

8.3.6. Treatment Compliance

Test materials were appropriately labeled (e.g., lot #, expiration dates). The lot numbers of the test materials were noted on the appropriate Case Report Form. Prior to dispensing and use, all test materials were accessible only to the appropriate study personnel. Device accountability was

recorded on the Device Accountability Log upon receipt and disposition of the test materials.

8.4. Effectiveness and Safety Variables

8.4.1. Effectiveness

8.4.1.1. Primary

The primary effectiveness endpoint was the patient specific percentage of the study-defined surface area, the investigational surgical site (ISS), with severe adhesions (Grade 3) at the second sternotomy procedure (Visit 3). This endpoint was considered to be a continuous outcome and should not be confused with the percentage of patients with any severe adhesions.

8.4.1.2. Secondary

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.

8.4.2. Safety

Safety was assessed by comparing common event rates, adverse event rates, serious adverse event rates, hematology and blood chemistry values, and mortality rates for each treatment group.

8.4.2.1. Patient Monitoring

At all visits, patients were monitored to determine whether or not any adverse events had occurred. A physical examination was performed at the screening visit. Interim physical examinations were performed as clinically indicated.

8.4.2.2. Laboratory Safety Studies

Hematology and blood chemistry tests were performed at screening, Day 3 post chest closure or at time of discharge (Protocol Appendix 1). Laboratory tests were also performed as clinically indicated at the safety follow-up visit, Weeks 3 - 8 post chest closure (Visit 2).

8.4.2.3. Adverse Events

An adverse event is any undesirable, unintentional or unexpected (unanticipated) event that occurs throughout the study, whether or not considered related to the device. Adverse events were monitored throughout the study, and such events were recorded at each examination on the Adverse Event page of the Case Report Form.

Events Common to this Patient Population are provided in the CRF and listed in Protocol Appendix 6. The occurrence of these Events Common was documented in the CRF on the pages titled Events Common to This Patient Population Prior to or Post Randomization. The expected (anticipated) adverse events associated with this patient population are provided in Protocol Appendix 5. The occurrence of these expected adverse events as well as the unexpected adverse events were documented in the CRF on the pages entitled Pre or Post Randomization Adverse Events. The Events Common were detailed on the pre or post-randomization Adverse Events Page of CRF only if their frequency and/or duration and/or severity were different than what was expected for this patient population. Adverse events resulting from concurrent illnesses, or reactions to concurrent medications were also recorded. In order to avoid vague expressions, the adverse event was recorded in standard medical terminology.

Each adverse event was evaluated for duration and intensity (see table below).

Degree of Intensity	Description
Mild	Awareness of signs and symptoms; easily tolerated
Moderate	Discomfort sufficient to interfere, but not prevent, daily activity
Severe	Unable to carry out usual activity

Events were also evaluated for:

Seriousness: See Section 8.4.2.4.

Action taken: whether or not the adverse event caused the patient/patient to be discontinued from the study.

Relationship to test product: whether or not the study device caused the adverse event (see table below).

Degree	Description
Definitely	There is evidence of exposure to the test product, for example, reliable history or acceptable compliance assessment; the temporal sequence of the AE onset relative to the device is reasonable; the AE is most likely to be explained by the device treatment than by another cause; the challenge is positive; rechallenge (if feasible) is positive; the AE shows a pattern consistent with previous knowledge of the device treatment.
Probably	There is evidence of exposure to the test product; the temporal sequence of the AE onset relative to the device administration is reasonable; the AE is more likely explained by the device treatment than by another cause; the challenge (if performed) is positive.
Possibly	There is evidence of exposure to the test product; the temporal sequence of the AE relative to the device administration is reasonable; the AE could have been due to another equally likely cause; the challenge (if performed) is positive.
Probably not	There is evidence of exposure to the device; there is another more likely cause of the AE; the challenge (if performed) is negative or ambiguous; rechallenge (if performed) is negative or ambiguous.
Definitely not	The patient/patient did not receive the device treatment; or temporal sequence of the AE onset relative to administration of the device is not reasonable; or there is another obvious cause of the AE.

In the event of blood/chemistry laboratory abnormalities, the Principal Investigator was to take appropriate medical action including, but not limited to additional blood draws for hematology and blood chemistry, and proper patient follow-up was to occur.

8.4.2.4. Serious Adverse Events

A serious adverse experience is any event that was fatal or life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly, cancer or overdose. An unexpected adverse event is any adverse event that was not identified in nature, severity, or frequency in the current Investigator Brochure.

Within 24 hours of occurrence, the Investigator was to report to the Medical Monitor and/or the Clinical Research Associate, who was then to inform the Sponsor of any serious and unexpected adverse event.

The sponsor was to notify the appropriate regulatory authorities as required and all participating Investigators of any adverse event associated with use of the device that was both serious and unexpected. The Investigator was also to notify the Institutional Review Board.

8.5. Data Quality Assurance

All study records including electronic Case Report Forms, patient progress notes, original copies of test results, signed informed consent forms, enrollment log and device dispensation logs, Institutional Review Committee approval letters, and other documents pertaining to the conduct of the study were kept on file by the Investigator, and copies maintained by the Clinical Monitor.

Study records subject to sponsor inspection at any time.

Each site entered the source document information directly into an Internet-based data collection system. The monitor was responsible for performing on-site monitoring at regular intervals throughout the study to verify adherence to the protocol; adherence to local regulations on the conduct of clinical research; and ensure completeness, accuracy, and consistency of the data entered in the CRF. At each site, the monitor had access to subject medical records and other study-related records needed to verify the entries on the CRFs. Additionally, study data could be monitored using the management module of Target e*CRF™, which included edit check and query systems that seamlessly integrate with the data entry system. All modifications to the data in the CRF were tracked by an electronic audit trail (date and identity of the person making the change were instantaneously recorded).

Final CRFs in electronic format, including data, electronic signatures, audit trail of data changes and queries were provided by the Sponsor to the sites at the end of the study.

8.6. Statistical Methods Planned and Determination of Sample Size

8.6.1. Statistical and Analytical Plans

The Analysis Plan (Section 15.1.9.1) was finalized prior to unmasking the study.

8.6.1.1. Study Populations

Three patient populations were used:

- 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.
- Per-Protocol (PP) population consisted of all randomized patients who had the 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.
- Safety population consisted of all patients who were randomized and treated.

8.6.1.2. Comparability of Treatment Groups at Baseline

Baseline values were defined as those values obtained just prior to randomization.

Demographic and baseline characteristics were summarized for the intent-to-treat, per-protocol and safety populations to assess treatment group balance. The following factors were displayed by treatment group and assessed for comparability:

- Age
- Gender (Male, Female)
- Race (Caucasian, African-American, Asian, Hispanic, Other)
- Height and weight at the time of surgery
- Procedure type (Norwood, non-Norwood)
- Use of a heart-lung bypass machine during surgery (On, Off)
- Chest Closure delay (delay vs. no delay)

Categorical factors were described using frequencies and percentages, and compared between treatment groups using Fisher's exact test for categorical measures. Continuous variables were described using summary statistics (N, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum) and compared between treatment groups using a one-way ANOVA. Differences between treatment groups were considered statistically significant if the two-sided p-value was <0.05.

8.6.1.3. Discontinued Patients Analysis – Bias Assessments

The study was designed and approved by the FDA to only analyze efficacy among those patients undergoing second sternotomy. Accordingly, the ITT population was defined as those patients who had the planned second sternotomy surgery.

Discontinued patients and reason for discontinuations were assessed for bias by examining the withdrawal reasons and timing as well as the times to second sternotomy overall (all patients randomized) and among those not withdrawn (patients who underwent the planned staged second sternotomy).

An analysis of withdrawals focused on differences in overall dropout rates, dropout timing, and specific reasons for dropouts, e.g., surgeon discretion and adverse experiences including, surgical procedures requiring reopening of the chest to address clinical concerns (e.g. exploratory surgery for re-bleeding, hemodynamic instability, shunt thrombosis, etc.).

The analyses compared the differences between missing data across treatment groups including the following:

1. The number and percentage of patients who withdrew early were presented by treatment group and compared using a Fisher's exact test. Separate analyses were performed on the overall patient population as well as for the subset of patients who did not have a second sternotomy.

2. The distribution of reasons for early withdrawal was presented by treatment group and compared using a Fisher Exact test. Separate analyses were performed on the overall patient population as well as for the subset of patients who did not have a second sternotomy. This analysis was performed on the early withdrawal category response as indicated by the investigator on the CRF and for the specific reasons for withdrawal based on the text field on the CRF; due to inconsistencies between response categorizations, each specific text

response was reclassified into a revised withdrawal reason category to establish consistencies across responses.

3. Kaplan-Meier methods were employed to assess the time to withdrawal across treatment groups. The analysis was performed on the overall patient population as well as for the subset of patients who did not have a second sternotomy. The number of patients who withdrew, number of patients still at risk of withdrawing, withdrawal percentage estimate, and 95% confidence interval of the withdrawal percentage estimate were presented by 30 day intervals for each treatment group. Patients who withdrew were regarded as events; those patients who did not withdraw were censored at the time of sternotomy. Kaplan-Meier lifetables (and corresponding figures) were generated for the time to withdrawal. The median time to withdrawal was presented by treatment group and a two-sided Wilcoxon-Gehan test with a 5% Type I error was used as an assessment of time to withdrawal between treatment groups.

4. Kaplan-Meier methods were employed to assess the time to second sternotomy from chest closure of first sternotomy (i.e., from randomization). Separate analyses were performed overall as well as for the subset who did not withdraw. The number of patients who had a second sternotomy, number of patients who were still candidates for the second sternotomy, estimate of percentage of patients with second sternotomy, and 95% confidence interval of the percentage of patients with second sternotomy estimates were presented by 30 day intervals for each treatment group. Patients who had a second sternotomy were regarded as events; those patients who did not have a second sternotomy were censored at the time of withdrawal. Kaplan-Meier lifetables (and corresponding figures) were generated for the times to second sternotomy. The median time to second sternotomy was presented by treatment group and a two-sided Wilcoxon-Gehan test with a 5% Type I error was used as an assessment of time to second sternotomy between treatment groups.

   Since patients could not be evaluated for efficacy without undergoing a second sternotomy, the intention was to proceed with the planned analyses for just the second sternotomy group if the treatment groups did not differ significantly (p-value<0.05) with respect to: (1) the withdrawal percents, (2) the withdrawal reasons, (3) the time to withdrawal, and (4) the time to second sternotomy.

   In the event that treatment group comparability was not established, the deviation pattern would be assessed at the site-level; if sites could be identified as the explanatory reason, then site would be considered as a random effect in all efficacy modeling. If site variations could not explain the outcomes, then a worst-case analysis would be applied where any patients who withdrew prior to second sternotomy for reasons related to safety or efficacy would be classified as worst possible efficacy for each analysis.

8.6.1.4. Effectiveness Analysis

Effectiveness analysis was performed in both the ITT and PP populations (see Analysis Plan in Appendix 15.1.9.1).

8.6.1.4.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint was the mean percent of the study-defined surface area with severe (Grade 3) adhesions at the time of the second surgery in the intent-to-treat population.

Descriptive statistics (N, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum) were presented for each treatment group and treatment specific means compared using a two-sided t-test. A Wilcoxon rank sum test was presented as a confirmatory analysis.

The analysis approach for the primary study endpoint was to perform an analysis of variance (ANOVA) to test for treatment differences while controlling for study site. Those sites with 3 or fewer patients were grouped together as one site in this analysis. In the event that there was a significant (p-value<0.05) site by treatment interaction effect, results would be displayed separately by study site. If the site by treatment interaction effect was non-significant it was removed from the ANOVA model.

For confirmation purposes, an analysis of covariance (ANCOVA) model was run for the ITT population where the mean percent of the study-defined surface area with severe adhesions at the time of the second surgery was the dependent variable. The model included study site (as defined above), age, gender, as well as any other baseline covariates found to be imbalanced between treatment groups. The significance level was 0.10 for a baseline covariate to be included.

Descriptive subgroup analyses were performed using the primary effectiveness endpoint. The following key subgroups were examined to display the depth of effectiveness. The p-values are regarded as descriptive statistics given the nature of multiple subgroups. The focus in the subgroups analyses was on the magnitude and the consistency of the REPEL-CV advantage vs. control. The power of the study was not appropriate for inference-based subgroup analyses. These analyses were performed on both the intent-to-treat and per-protocol populations.

- Gender: male versus female,
- Procedure type: Norwood versus non-Norwood procedures, which included shunt or bands procedures,
- Use of a heart-lung bypass machine during surgery: on versus off,
- Evaluation type: In some instances, the same surgeon who was responsible for randomizing the patient was also responsible for assessing the adhesion severity and extent. These observations were classified as unmasked evaluations since performing both assessments could have biased the surgeon's assessment of adhesion severity and extent. The primary effectiveness endpoint was separately evaluated using patients undergoing unmasked and masked assessments,

- Chest closure delay: Patients were classified by whether or not their chest closure was delayed. The primary effectiveness endpoint was separately evaluated using patients with a delayed chest closure and without a delayed chest closure.

8.6.1.4.2. Secondary Effectiveness Endpoint

All effectiveness analyses were presented for both the intent-to-treat and per-protocol population.

1. The percentage of patients with Grade 0, 1, or 2 as worst degree (i.e., patients without severe adhesions). (Note: This endpoint is the complement of the percentage of patients with severe adhesions and will be referred as such for simplicity.) The frequency and percentage of patients with severe adhesions were displayed by treatment group and compared using Fisher's exact test.

2. Patient specific percentage of the study-defined surface area (the investigational surgical site) with Grade 0, 1, and 2 adhesions. (Note: This endpoint was meant to compare the patient specific percentage of the study-defined surface area within each grade.) The patient specific percentage of the study-defined surface area was categorized by adhesion grade. Descriptive statistics (N, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum) were presented for each treatment group within adhesion grade and treatment specific means compared within each adhesion grade using a two-sided t-test. A Wilcoxon rank sum test was presented as a confirmatory analysis.

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). Descriptive statistics (N, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum) for the dissection time of adhesions at the investigational surgical site were presented for each treatment group and treatment specific means compared using a two-sided t-test. A Wilcoxon rank sum test was presented as a confirmatory analysis.

4. The percentage of patients by worst degree of adhesions. Patients were divided into four subgroups: patients without any adhesions (Grade 0), patients with mild adhesions (Grade 1 as worst degree), patients with moderate adhesions (Grade 2 as worst degree), and patients with severe adhesions (Grade 3 as worst degree). The frequency and percentage of patients falling into each category were displayed by treatment group and treatment distributions compared using a Wilcoxon rank sum test.

8.6.1.5. Interim Analysis

A Data Safety Monitoring Board (DSMB) was established at the beginning of the study and met periodically to review the safety data from the study (Appendix 15.3).

An interim analysis was conducted after approximately 20 per-protocol patients per treatment group completed the second surgery. The analysis addressed both safety and effectiveness. The safety analysis evaluated the overall adverse experience rates as well as all serious adverse experiences

including deaths. The effectiveness analysis assessed the dropout percents, dropout reasons, dropout impact on projected sample size, and individual success rates for each treatment group.

The analysis was not used to stop the study for superiority, but was used to evaluate the sample size assumptions and/or to stop the study due to futility; thus no p-value adjustment was required.

8.6.1.6. Safety Analysis

All safety analyses were presented for the safety population (see Analysis Plan, Appendix 15.1.9.1). Safety was assessed by comparing common event rates, adverse event rates, serious adverse event rates, hematology and blood chemistry values, and mortality rates for each treatment group.

1. Common Medical Events: Common events among safety patient population were summarized by treatment group and visit. (Visit 1: Pre Randomization, Visit 1: Post Randomization, Visit 2, and Visit 3).

2. Adverse Events: Medical events not predefined as common events, or common events occurring with greater frequency or severity than is usual for this population (as determined by the investigator) were defined as adverse events. Adverse events were coded using MedDRA 9.0. Adverse events were summarized by body system organ class (SOC) and preferred term (PT) for each treatment group. The number of events and the number and percentage of patients with events were categorized by highest intensity and displayed by body system for each treatment group. Separate displays were presented for adverse events occurring prior to randomization and adverse events occurring after randomization. Adverse events occurring after randomization were classified by the investigator as definitely not, probably not, possibly, probably, or definitely related to the study treatment.

   For the adverse event tabulations, patients who have multiple occurrences of the same adverse event (preferred term) were counted once for the total number of patients with that specific adverse event. For the tabulations by highest intensity, patients who had multiple occurrences of the same adverse event (preferred term) were classified according to highest intensity reported for that adverse event.

3. Serious Adverse Events: Serious adverse events were summarized by body system and primary coded term for each treatment group. The number of events and the number and percentage of patients with events were displayed by body system for each treatment group. Separate displays were presented for serious adverse events occurring prior to randomization and after randomization. Serious Adverse Events occurring after randomization were classified by the investigator as definitely not, probably not, possibly, probably, or definitely related to the study treatment.

4. Deaths: The frequency and percentage of deaths were presented by treatment group and compared using a Fisher's exact test.

5. Clinical Laboratory Values: Laboratory values were summarized by visit and treatment group.

Descriptive statistics were displayed for the distributions of each laboratory measure (Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase, Lactic Dehydrogenase (LDH), Blood Urea Nitrogen (BUN), Creatinine, Calcium, Sodium, Potassium, Glucose, Hematocrit, Hemoglobin, Red Blood Cell Count (RBC), White Blood Cell Count (WBC), Platelet Count). Laboratory values were classified as normal or abnormal by the investigator. The frequency and percentage of normal and abnormal laboratory values were displayed by visit and treatment group.

6. Observations at the Second Sternotomy and Wound Healing Assessments at One Month Post Second Sternotomy: The frequency and percentage of patients with implanted material or fibrous capsule visible or abnormal tissue present at time of second sternotomy were summarized by treatment group and compared using a Fisher's exact test. The frequency and percentage of the wound healing assessment results (abnormality of sternotomy site, presence of infection) at one month post second sternotomy were also summarized by treatment group and compared using a Fisher's exact test.

8.6.2. Determination of Sample Size

Sample size rationale was based on the current projection for the mean percentage of the surface area with severe adhesions. It was projected that the mean percent of the study-defined surface area with severe adhesions ranged between 50% and 80% without treatment; an absolute 20% improvement was considered to be clinically meaningful.

The null hypothesis was that there was no treatment difference in the success rates between treatments, while the alternative hypothesis was that there was 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) was required for 80% power and overall 5% Type I error for a two-sided hypothesis test. Because of the high anticipated dropout rate of 35%, including mortality, associated with this patient population, the study randomized up to 78 patients per group to allow for a loss of 28 patients/group.

8.6.3. Changes in Conduct of the Study or Planned Analyses

There was a protocol amendment issued during the study (26Jan2004) and the Statistical Analysis Plan (SAP) (Appendix 15.1.9.1) was finalized prior to unmasking the study.

The main changes to the protocol are listed below:

1. Patients were enrolled from up to 15 sites amended to 20 sites.
2. Inclusion criteria # 4 "Patient will be on Heart-Lung Bypass Machine during the first procedure" was deleted.

9. Study Patients

9.1. Disposition of Patients

Patients were randomized at 17 study sites. Table 1 lists the number of patients enrolled at each study site.

Table 1. Numbers of Patients Randomized at each Study Site

Centers	Principal Investigator	Number of Randomized Patients
01	Erle Austin, MD	10
02	Robert Jaquiss / James Tweddell MD*	6
03	Carl Backer, MD	14
05	Andrew Lodge, MD	19
06	Charles Huddleston, MD	7
07	Winfield Wells, MD	14
08	Richard G. Ohye, MD	9
09	Joanne Starr, MD**	4
10	Michel Ilbawi, MD	11
11	Michael Teodori, MD	10
12	Thomas Yeh, MD	1
13	James E. O'Brien, MD	14
15	Ralph Delius MD	9
16	William DeCampli, MD	9
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The following information is presented in the Effectiveness Analysis Summary in Appendix 15.1.9.2. Patient disposition was summarized by treatment group and included the reasons for withdrawal (Statistical Table 1.1A for investigator reasons, and Statistical Table 1.1B and Table 2 below for standardized reasons). Standardized reasons for withdrawal were used to impose consistency across investigator sites. A total of 144 patients (REPEL-CV, 73; Control, 71) were randomized across the 15 study sites. No study site randomized more than 19 patients. There were 20 (27.4%) REPEL-CV patients and 18 (25.4%) Control patients withdrawn from the study; this difference was not significant ($p = 0.8510$). Regarding the reasons for withdrawal (standardized), the major reason for withdrawal was adverse events for both treatment groups (REPEL-CV, 19; Control, 16); this difference was not significant ($p = 0.4733$).

Table 2. Patient Disposition (reclassified to establish consistency across responses) - All Randomized Patients

	REPEL-CV (N=73)	Control (N=71)	p-value*
Randomized	73	71	0.8510
Withdrew from Study	20 (27.4%)	18 (25.4%)	
Completed Study (% of patients randomized)	53 (72.6%)	53 (74.6%)	
Reasons for Early Study Withdrawal**:			0.4733
Adverse event	19	16	
Lost to follow-up	0	0	
Protocol violation	0	2	
Withdrew consent	1	1	
Non-compliance	0	0	
Other	0	0	

* Fisher's exact test
** Investigator reasons for early study withdrawa---------- lassified to establish consistency across responses.
Note: The study investigator indicated that Patien---------- ho received study control, completed the study because the second sternotomy was performed and efficac---------- ons were completed. The investigator also indicated a reason for early withdrawal (adverse event) due to the patient's death following the procedure

Ref.: Statistical Table 1.1B, Section 13.1

Patients withdrawn from the study prior to the second sternotomy procedure were summarized by treatment group and investigator reasons for withdrawal (Statistical Table 1.2A). Standardized reasons for withdrawal were used to impose consistency across investigator sites (Statistical Table 1.2B and Table 3 below). A total of 34 patients (REPEL-CV=17 and Control=17) were withdrawn prior to the second sternotomy. The primary reason (standardized) for withdrawal for both treatment groups was adverse events (REPEL-CV=16, Control=14); this difference was not significant (p=0.7341).

Table 3. Patient Disposition (reclassified to establish consistency across responses). Patients Without a Second Sternotomy

	REPEL-CV (N=17)	Control (N=17)	p-value*
Randomized	17	17	
Withdrew from Study	17 (100.0%)	17 (100.0%)	
Completed Study (% of patients randomized)	0 (0.0%)	0 (0.0%)	
Reasons for Early Study Withdrawal**:			0.7341
Adverse event	16	14	
Lost to follow-up	0	0	
Protocol violation	0	2	
Withdrew consent	1	1	
Non-compliance	0	0	
Other	0	0	

* Fisher's exact test
** Investigator reasons for early study withdrawal were reclassified to establish consistency across responses.

Ref.: Statistical Table 1.2B, Section 13.1

Patient disposition and the number of patients in each of the study populations (Randomized, Safety, Intent-to-Treat and Per-Protocol) are displayed in Table 4. For the REPEL-CV patients, there were 73 patients randomized and in the safety population, 56 patients in the Intent-to-Treat population (17 patients withdrew prior to the second sternotomy), and 54 patients in the Per-Protocol population (two patients had the second sternotomy within two months of randomization); for the Control patients, there were 71 patients randomized, 69 patients in the safety population (two patients did not receive study treatment), 54 patients in the Intent-to-Treat population (17 patients withdrew prior to the second sternotomy), and 49 patients in the Per-Protocol population (five patients had the second sternotomy within two months of randomization). These differences between treatment groups were unremarkable and were consistent with study planning expectations. Data Listing 9 provides information on the surgical procedure performed on individual patients and Data Listing 23 (clinical summary) displays individual patient status, including reasons for discontinuation from the study (see Appendix 15.2).

Table 4. Patient Disposition

	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 r----------d to establish consistency across responses. The study investigator indicated that Patient---------- ho received study control, completed the study because the second sternotomy was performed an---------- y 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

9.1.1. Bias Assessments

Bias was evaluated by examining proportions withdrawn, reasons for withdrawal, and time to withdrawal. As demonstrated in Table 2 (Statistical Tables 1.1A-B), the percents withdrawn were comparable across treatment groups (p=0.8510) as were withdrawal reasons (Statistical Table 1.1B: p=0.4733).

The time to withdrawal was comparable (Statistical Table 8.1, Figure 1.1) across treatment groups for the overall study population (N=144; 73 REPEL CV, 71 Control) using a Kaplan-Meier lifetable and a Wilcoxon-Gehan test (p=0.4838).

The time to withdrawal for the subset of patients without a second sternotomy (StatisticalTable 8.2, Figure 1.2) was longer in the REPEL CV group, where the median time to study withdrawal was 33.0 days, as compared to the Control group, where the median time to study withdrawal was 2.0 days (N=34; 17 REPEL CV, 17 Control; p=0.0267). A close inspection of the individual reasons for withdrawal diffused any safety concerns when considering the expected events and relationship of the events to the study treatments (Table 5 below). Although there was a significant difference in this subset, there was no significant difference among all randomized patients. In this regard, the

number of patients withdrawn from the study prior to the second planned sternotomy from the Control and REPEL-CV groups was the same (17 per treatment group). Further; the severity of the complications, morbidities and mortalities were comparable among these 34 withdrawals with no apparent differences in the specific reasons: deaths (6 Controls, 8 REPEL-CV), emergent chest re-opening (8 Controls, 8 REPEL-CV), and aborted study procedures following the initial surgery (3 Controls, 1 REPEL-CV). No events leading to withdrawal were unexpected for this patient population. The median time to withdrawal was higher in the REPEL-CV group; the Control group had earlier times to withdrawal due to earlier deaths, earlier times to emergent chest opening, and had earlier and more of the aborted study procedures after the initial surgery (protocol violations and off life support). No site-specific patterns were evident either. Given that the reasons for withdrawal were generally not related to study treatment, this does not suggest any safety concern as the REPEL-CV patients were more stable earlier in their post-operative course and came to withdrawal from the study protocol later than the Control patients.

The time to second sternotomy was comparable (Statistical Table 9.1, Figure 2.1) across treatment groups for the overall study population (N=144; 73 REPEL-CV, 71 Control) using a Kaplan-Meier lifetable and a Wilcoxon-Gehan test (p=0.3143). The time to second sternotomy was also comparable (Statistical Table 9.2, Figure 2.2) across treatment groups for the second sternotomy patients (N=110; 56 REPEL CV, 54 Control) using a Kaplan-Meier lifetable and a Wilcoxon-Gehan test (p=0.4213).

As stated earlier, the time to withdrawal analysis on the subset of patients without a second sternotomy was significant (p=0.0267) with longer times to withdrawal for the REPEL-CV group. The numbers of withdrawals were comparable and there was no evidence of any unexpected adverse events or clustering indicative of a safety concern. Thus bias was ruled out since there were no overall differences or clinical relevance to the difference between treatment groups with respect to: (1) the withdrawal percents, (2) reasons for withdrawal, (3) the time to withdrawal and (4) the time to second sternotomy. Overall treatment groups did not significantly differ with respect to withdrawal percents or withdrawal reasons and, treatment groups overall also did not significantly differ with respect to time to withdrawal or time to second sternotomy using the Kaplan-Meier methods as previously described for all randomized patients. Table 5 below presents a listing of reasons for patient withdrawal prior to second sternotomy and time to withdrawal post randomization.

Table 5. Patient Withdrawal Prior to Second Sternotomy

Patient Number	Reason for Withdrawal	Time to withdrawal (days post randomization)
CONTROL	**EMERGENT CHEST OPENING**	
-------	Chest reopened due to desaturation	0
-------	Chest reopened due to bleeding	0
-------	Chest reopened in O.R. due to fibrillatory arrest	0
-------	Re-exploration of chest on same day as first chest closure for valve annuloplasty	0
-------	Shunt thrombosis resulting in re-exploration of investigation site	2
-------	Patient randomized & treated during attempted chest closure patient had increased CVO & chest left open	0

Patient ----------	Reason for Withdrawal	Time to withdrawal (days post randomization)
-------	Chest was re-opened due to decreased oxygen saturations and pulmonary hypertension	2
-------	Patient coded; chest re-opened and site disturbed, placed on ECMO	13
----------	**DEATH**	
-------	Hypoxia and bradycardia	16
-------	Necrotizing enterocolitis	19
-------	Cardiopulmonary arrest	25
-------	Cardiac arrest	27
-------	Cardiac arrest	100
-------	Unknown illness leading to death	180
----------	**PROTOCOL VIOLATION/OFF LIFE SUPPORT**	
-------	Surgeon elected to place Goretex membrane at investigational site, pt not treated per randomization	0
-------	PI decided to not treat at the time of chest closure D/T conduit location. Randomization envelope already opened	0
-------	Withdrew consent. Due to prognosis parents requested withdrawal of life support	25
REPEL-CV	**EMERGENT CHEST OPENING**	
-------	Hemodynamic instability required re-opening chest	0
-------	Low cardiac output resulting in re-exploration of investigational site	0
-------	Surgical site disrupted due to PDA ligation	1
-------	Hemodynamic instability requiring re-exploration of chest	0
-------	Cardiopulmonary arrest required emergent opening of the chest. Surgical site disturbed	1
-------	Mediastinitis and chest was re-opened	11
-------	Mediastinitis resulting in re-exploration and disturbance of investigation site	110
-------	Patient had thoracotomy prior to sternotomy which may effect evaluation of surgical site	210
	DEATH	
----------	Cardiac arrest	27
-------	Respiratory and cardiac arrest	28
----------	Cardiac ischemia	32
----------	Cardiopulmonary arrest	90
-------	Coarcation of the aorta	99
-------	Sudden cardiac arrest	105
-------	Cardiopulmonary arrest at home	129
----------	Cardiopulmonary arrest	150
	OFF LIFE SUPPORT	
-------	Withdrew consent due to grave prognosis. Parents agreed to medical recommendation of withdrawal of life support	99
Ref: Data Listing 10, 20.2, 23, Appendix 15.2		

9.2. Protocol Violations

The control treatment group had two protocol violations (Randomization ----------and were discontinued from the study. These two patients were randomized----------

- 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. Rando-------- n envelope already opened

10. Effectiveness Evaluation

The following information is presented in the Effectiveness Analysis Summary in Appendix 15.1.9.2.

10.1. Data Sets Analyzed

The primary effectiveness endpoint was the patient specific percentage of the study-defined surface area with severe adhesions (Grade 3) at the time of the second sternotomy procedure. The study-defined surface area was the investigational surgical site located directly below the sternotomy site between the epicardium and the sternum (mediastinal space) and extending laterally to the pericardial edges. Effectiveness was analyzed in the ITT and PP populations.

In the ITT population, 56 randomized patients in the REPEL-CV treatment group and 54 in the control group had adhesion evaluations at the time of the planned second sternotomy and were eligible for endpoint effectiveness analysis.

In the PP population, 54 patients in the REPEL-CV treatment group and 49 in the control group had the 2nd sternotomy at least 2 months after randomization, provided adhesion evaluations, and had no major protocol violations.

10.2. Demographic and Other Baseline Characteristics

10.2.1. Demographics

Demographic variables are summarized in Table 6 below. 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 6. Demographics (ITT)

	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%)	
Ref.: Statistical Table 3.1, Section 13.1			

10.2.2. Other Baseline Characteristics

Medical histories are summarized in Statistical Table 5 (Section 13.1), and individual patient data can be found in Data Listing 5 (Appendix 15.2). There were no relevant differences between treatment groups.

Physical examinations are summarized in Statistical Table 6 (Section 13.1), and individual patient

data can be found in Data Listing 7 (Appendix 15.2). There were no relevant differences between treatment groups.

10.2.2.1. Events Common - Prior to Randomization

The Events Common that occurred prior to randomization are presented in Statistical Table 20 (Visit 1 = pre-randomization). The most frequent Events Common that occurred prior to randomization were: hemodynamic instability requiring inotropic support (REPEL-CV, 75.3% patients; Control, 68.1% patients), pain (REPEL-CV, 71.2% patients; Control, 69.6% patients), and electrolyte disturbances (REPEL-CV, 69.9% patients; Control, 71.0% patients). There were no relevant differences between treatment groups.

10.3. Measurements of Treatment Compliance

REPEL-CV was placed at the time of chest closure (Visit 1) for patients who were randomized to the REPEL-CV treatment (Data listings 9 and 10, Appendix 15.2).

10.4. Effectiveness Results and Tabulations of Individual Patient Data

10.4.1. Primary Effectiveness Results

The REPEL-CV group achieved the clinically meaningful objectives sought for the primary endpoint. The differences consistently achieved statistical significance in the ITT and PP populations. Results are presented for Grade 3 severity percents (Statistical Tables 10.1 and 10.2, Section 13.1) and Table 7 below for the ITT population.

Table 7. 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	35.6 ± 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				

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) for the ITT population, and 21.1% for REPEL-CV (N=54) and 49.5% for Control (N= 49) (p=0.0005 for the mean and p=0.0001 for the median) for the PP population. A t-test was used to compare treatment means and the Wilcoxon rank sum test for the medians was presented as a confirmatory analysis. The 26.0% and 28.4% mean differences for

the ITT and PP populations, respectively, exceeded the 20% criteria for being clinically meaningful and the 21.7% difference for 80% power.

Analysis of variance (ANOVA) models were used to test for treatment differences while controlling for study site. Site effect was ruled out (Statistical Tables 11.1, 11.2) for the primary effectiveness endpoint for the ITT population and the PP population. Site (p=0.6335 for ITT and p=0.5108 for PP) and site-treatment interactions (p=0.9129 for ITT and p=0.9003 for PP) were not significant in the ANOVA model. Since there was no significant site-treatment interaction, the interaction term was removed from the ANOVA model. Treatment was significant (p=0.0023 for ITT population and p=0.0014 for PP population), favoring REPEL-CV.

For confirmation purposes, an analysis of covariance (ANCOVA) model was run to include study site (as defined above), age, gender, weight and on/off heart-lung bypass machine (Statistical Tables 12.1 and 12.2 and Table 8 below). The significance level was 0.10 for a baseline covariate to be included. Treatment remained highly significant for both the ITT and PP populations (Full Model p=0.0014 and p=0.0031, Reduced Model p=0.0009 and p=0.0008 for ITT and PP, respectively).

Table 8. Analysis of Covariance Model of Percentage of the Investigational Surgical Site with Grade 3 Adhesions. Intent-to-Treat Population

Effect	Estimate	Standard Error	df* Num, Den	Test Statistic**	p-value
Reduced Model:					
Treatment					
REPEL-CV	-26.58	7.727	94	-3.44	0.0009
Control	-	-	-	-	-
Site			13, 94	0.85	0.6096
Gender					
Male	-15.80	8.232	94	-1.92	0.0580
Female	-	-	-	-	-

* Both the numerator and denominator degrees of freedom (df) are displayed for the F-distribution.
** The sampling distribution under the null hypothesis is a t-distribution when examining two-level factor or continuous effects and F-distribution when testing factor effects with more than two levels.

Note: The full model includes the main effects (treatment and site), a treatment by site interaction effect, and baseline covariates. Age and gender are forced as covariates of interest; weight and use of a heart lung bypass machine are included due to baseline treatment group imbalance. The reduced model removes the treatment by site interaction effect(p>.05) as well as the effects for age, weight, and heart lung bypass machine use(p>.10). The ITT modeling results are replicated for the PP population.

Note: Individual site estimates and standard errors are not displayed per the analysis plan.

Ref: Statistical Table 12.1, Section 13.1

An ad hoc analysis was performed to examine the correlation between the surface area of grade 3 severe adhesions and the time to second sternotomy in each treatment group (Ad hoc Figures 1.1 and 1.2). No correlation was found in either treatment group [REPEL-CV: (r=0.0354, p=0.7958) for ITT and (r=0.0382, p=0.7837) for PP and Control: (r=-0.0223, p=0.8728) for ITT and (r=-0.1469, p=0.3138) for PP]. Time to second sternotomy had no affect on extent of grade 3 severe adhesions.

10.4.2. Secondary Effectiveness Results

REPEL-CV advantages were also observed for secondary effectiveness endpoints, specifically:

1. REPEL-CV reduced the percentage of patients with Grade 3 adhesions as worst degree of adhesions (Statistical Tables 18.1 and 18.2 and Table 9 below). For REPEL-CV, 30.4% (17/56) of the ITT population and 29.6% (16/54) of the PP population had Grade 3 adhesions. In comparison, 72.2% (39/54) and 71.4% (35/49) of the Control group for the ITT and the PP populations, respectively, had Grade 3 adhesions ($p<0.0001$ for both populations).

Table 9. Worst Degree of Adhesions within the Investigational Surgical Site. Intent-to-Treat Population

	REPEL-CV (N=56)	Control (N=54)	p-value
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			
Ref: Statistical Table 18.1, Section 13.1			

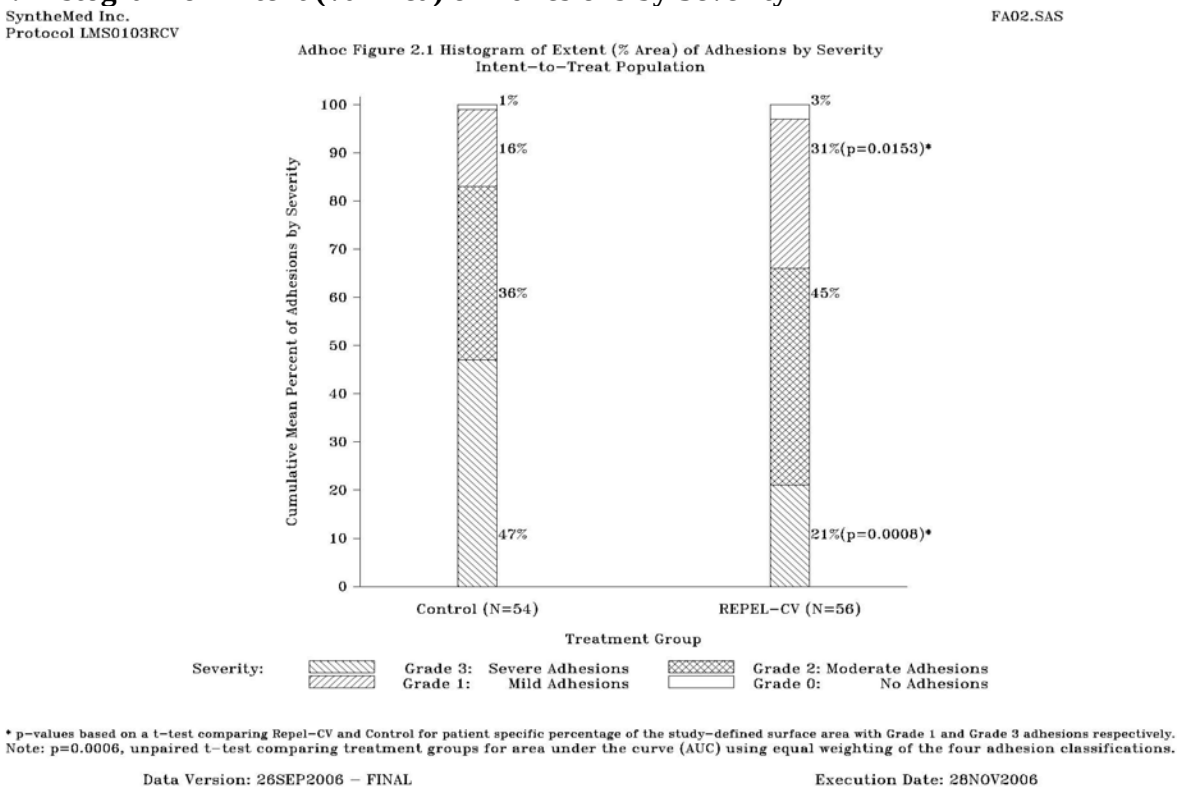
2. As described above (Section 10.4.1.), the mean percent of the study-defined surface area with severe (Grade 3) adhesions at the time of the second surgery was significantly lower for REPEL-CV as compared to Control. In addition, the mean percent of the study-defined surface area with mild (Grade 1) 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) for the ITT population (Table 7 and Statistical Table 10.1), and 32.2% for REPEL-CV (N=54) and 15.0% for Control (N= 49) ($p=0.0065$ for the mean and $p=0.0115$ for the median) for the PP population (Statistical Table 10.2).

   Furthermore, there were no statistical differences between REPEL-CV and Control for the mean percent of the study-defined surface areas with moderate (Grade 2) adhesions, where the mean was 44.8% for REPEL-CV (N= 56) and 35.6% for Control (N= 54) ($p=0.1778$ for the mean and $p=0.1650$ for the median) for the ITT population, and 45.6% for REPEL-CV (N=54) and 34.5% for Control (N= 49) ($p=0.1228$ for the mean and $p=0.1080$ for the median) for the PP population. Likewise, there were no statistical differences between REPEL-CV and Control for the mean percent of the study-defined surface areas with no (Grade 0) adhesions, where the mean was 2.9% for REPEL-CV (N= 56) and 0.9% for Control (N= 54) ($p=0.3217$ for the mean and $p=0.3296$ for the median) for the ITT

population, and 1.1% for REPEL-CV (N=54) and 1.0% for Control (N= 49) (p=0.9143 for the mean and p=0.5740 for the median) for the PP population.

The histogram below (Ad hoc Statistical Figure 2.1 and 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) for the ITT population. Similar results occurred in the PP population (Ad hoc Statistical Figure 2.2), where the area under the curve was significantly lower for the REPEL-CV group with an AUC of 186.7 units as compared to the Control group with an AUC of 232.4 units (N=103; 54 REPEL-CV, 49 Control; p=0.0005).

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



3. Adhesion dissection time was not influenced by REPEL-CV (Statistical Tables 19.1 and 19.2). For both the ITT and 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 for the mean and p=0.9559 for the median; PP: REPEL-CV=26.6 minutes (N=53), Control=25.7 minutes (N=48), p=0.8414 for the mean and p=0.9214 for the median).

An ad hoc analysis was performed to examine the relationship between dissection time of adhesions with severe adhesion status (Table 10 below and Ad Hoc Statistical Tables 19.3 and 19.4). For both the ITT and PP populations for 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. Similarly, in the PP population, mean dissection time was reduced for those without severe adhesions by 11.2 minutes (corresponding to a 48% relative reduction) for REPEL-CV and 11.2 minutes (corresponding to a 63% relative reduction) for Control. Statistical significance is borderline in each treatment group (Table 10), suggesting that dissection time is greater when severe adhesions are present.

The impact of the presence vs. absence of severe adhesions was also assessed in the overall ITT and PP populations. 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 without vs. with 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 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. Similar results occurred in the overall PP population, where dissection time was significantly reduced from 30.7 to 21.7 minutes (a 9.0 minute difference corresponding to a 41% relative reduction) for those without severe adhesions ($p=0.0368$ for the mean and $p=0.0131$ for the median).

Table 10. Dissection Time of Adhesions by Severe Adhesion Status

	ITT Population			PP Population		
	Overall	REPEL-CV	Control	Overall	REPEL-CV	Control
Severe Adhesions Present						
N	55	17	38	50	16	34
Mean ± SD	29.6 ± 21.8	33.1 ± 19.1	28.0 ± 23.0	30.7 ± 22.4	34.4 ± 18.8	29.0 ± 24.0
Median	27.0	38.0	23.0	27.5	39.5	26.0
No Severe Adhesions Present						
N	53	38	15	51	37	14
Mean ± SD	21.2 ± 20.1	22.7 ± 21.4	17.5 ± 16.9	21.7 ± 20.4	23.2 ± 21.4	17.8 ± 17.5
Median	14.0	13.0	14.0	14.0	13.0	14.5
Differences in Means**	8.4	10.4	10.5	9.0	11.2	11.2
p-value*: t-test	0.0408	0.0918	0.1127	0.0368	0.0757	0.1204
p-value*: Wilcoxon rank sum	0.0114	0.0556	0.0504	0.0131	0.0469	0.0693

*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

4. The distribution of the worst degree of adhesions also favored REPEL-CV (Statistical Tables 18.1 and 18.2). For both the ITT and PP populations, there was a one grade shift downwards favoring REPEL-CV ($p<0.0001$ for both populations).

10.4.3. Subgroup Effectiveness

Subgroup analyses were performed using the primary effectiveness endpoint for the ITT and PP populations (Table 11 below). The following p-values are descriptive statistics; this is appropriate given the nature of multiple subgroups. The focus below in the subgroups should be on the magnitude and the consistency of the REPEL-CV advantage vs. Control. There was a consistent general trend for reduction in Grade 3 adhesions for the REPEL-CV group, which was apparent in all subgroups. Furthermore, these subgroups are not independent. Specifically, there were 96 patients who were on a heart lung bypass machine, of which 78 (81.3%) were part of the Norwood population and had a chest closure delay. Of the 81 Norwood patients, 78 (96.3%) had delayed chest closure. Again, the study was not designed to assess effectiveness within subgroups.

Table 11. Subgroup Effectiveness (ITT)

Area (%) with Grade 3 severe Adhesion	REPEL-CV	Control	p-value
Gender			
Male (N=69)	31	38	
Mean ± SD	13.5 ± 30.47	42.5 ± 42.36	0.0021
Median	0.0	25.0	0.0002
Female (N=41)	25	16	
Mean ± SD	31.0 ± 41.41	58.8 ± 42.76	0.0454
Median	0	82.5	0.0295
Procedure Type			
Norwood Procedure (N=81)	38	43	
Mean ± SD	25.8 ± 39.85	49.7 ± 41.71	0.0106
Median	0.0	40.0	0.0017
Non-Norwood Procedure (N=29)	18	11	
Mean ± SD	11.7 ± 26.62	38.2 ± 47.50	0.1122
Median	0.0	10.0	0.0753
Use of Heart-Lung Bypass Machine During Surgery			
On Heart-Lung Bypass Machine (N=96)	45	51	
Mean ± SD	24.0 ± 39.35	48.1 ± 42.31	0.0050
Median	0.0	40.0	0.0005
Off Heart-Lung Bypass Machine (N=14)	11	3	
Mean ± SD	10.0 ± 18.44	33.3 ± 57.74	0.5579
Median	0.0	0.0	0.6965
Evaluation Type			
Masked Evaluation (N=84)	43	41	
Mean ± SD	24.0 ± 38.60	50.4 ± 44.09	0.0045
Median	0.0	40.0	0.0010
Unmasked Evaluation (N=26)	13	13	
Mean ± SD	12.5 ± 27.95	37.7 ± 38.11	0.0662
Median	0.0	15.0	0.0294
Chest Closure Delay			
Chest Closure Delay (N=83)	40	43	
Mean ± SD	27.1 ± 40.79	50.3 ± 41.80	0.0121
Median	0.0	40.0	0.0015
No Chest Closure Delay (N=27)	16	11	
Mean ± SD	6.9 ± 15.80	35.5 ± 46.34	0.0734
Median	0.0	0.0	0.0867
Ref.: Statistical Tables 13.1-17.1, Section 13.1			

10.4.3.1. Gender

For the males (N=69; 31 REPEL-CV, 38 Control) in the ITT population (Statistical Table 13.1 and Table 11 above), the 29.0% reduction in Grade 3 adhesions (REPEL-CV=13.5%, Control=42.5%) was significant (p=0.0021 for the mean and p=0.0002 for the median); for the females in the ITT population (N=41; 25 REPEL-CV, 16 Control), the 27.8% reduction in Grade 3 adhesions (REPEL-CV=31.0%, Control=58.8%) was significant (p=0.0454 for the mean and p=0.0295 for the median).

Similar reductions in severe adhesions occurred in the PP population. Males (N=63; 29 REPEL-CV, 34 Control) in the PP population (Statistical Table 13.2) had a 33.9% reduction in Grade 3 adhesions

(REPEL-CV=12.7%, Control=46.6%). This reduction was significant (p=0.0007 for mean, p=0.0002 for median). Females in the PP population (N=40; 25 REPEL-CV, 15 Control) had a 25.0% reduction in Grade 3 adhesions (REPEL-CV=31.0%, Control=56.0%). Although the difference in the mean percentage of Grade 3 adhesions was not significant (p=0.0757), whereas the difference in the median percentage of Grade 3 adhesions was significant (p=0.0486), the reduction of 25.0% is favorable and consistent with the overall study results.

It should again be emphasized that the study was not designed to assess effectiveness within gender, although significant reductions in Grade 3 adhesions for the REPEL-CV group occurred for both males and females despite the limited sample size.

10.4.3.2. Procedure Type

For the ITT population (Statistical Table 14.1 and Table 11 above), the Norwood procedure (N=81; 38 REPEL-CV, 43 Control) had a 23.9% reduction (REPEL-CV=25.8%, Control=49.7%), which was significant (p=0.0106 for the mean and p=0.0017 for the median). Other procedures (N=29; 18 REPEL-CV, 11 Control) had a favorable 26.5% reduction (REPEL-CV=11.7%, Control=38.2%), which was not significant (p=0.1122 for the mean and p=0.0753 for the median) due to a decreased sample size, but was consistent with the overall study results.

For the PP population (Statistical Table 14.2), the Norwood procedure (N=77; 37 REPEL-CV, 40 Control) had a 27.4% reduction (REPEL-CV=25.2%, Control=52.6%), which was significant (p=0.0045 for the mean and p=0.0013 for the median). Other procedures (N=26; 17 REPEL-CV, 9 Control) had a favorable 23.2% reduction (REPEL-CV=12.4%, Control=35.6%), which was not significant (p=0.1192 for the mean and p=0.1195 for the median) due to the decreased sample size, but was consistent with the overall study results.

It should again be emphasized that the study was not designed to assess effectiveness within procedure type, although a general trend for a reduction in Grade 3 adhesions for the REPEL-CV group occurred for both Norwood and Non-Norwood procedures.

10.4.3.3. Use of Heart-Lung Bypass During Surgery

Surgeries were classified as occurring on or off the heart-lung (HL) bypass machine as indicated on the CRF. For the patients in the ITT population (Surgeries were classified as occurring on or off the heart-lung (HL) bypass machine as indicated on the CRF. For the patients in the ITT population (Statistical Table 15.1 and Table 11 above) on HL bypass (N=96; 45 REPEL-CV, 51 Control), the 24.1% reduction (REPEL-CV=24.0%, Control=48.1%) was significant (p=0.0050 for the mean and p=0.0005 for the median). For the off HL bypass subgroup (N=14; 11 REPEL-CV, 3 Control), there was an insufficient number of patients to make a comparison.

For the patients in the PP population (Statistical Table 15.2) on HL bypass (N=90; 43 REPEL-CV, 47 Control), the 27.6% reduction (REPEL-CV=24%, Control=51.6%) was significant (p=0.0021 for the mean and p=0.0004). For the off HL bypass subgroup (N=13; 11 REPEL-CV, 2 Control), there was an insufficient number of patients to make a comparison.

It should again be emphasized that the study was not designed to assess effectiveness within on and off bypass procedures, although a general trend for a reduction in Grade 3 adhesions for the REPEL-CV group occurred for both on and off bypass procedures.

10.4.3.4. Evaluation Type

In some instances, the same surgeon who was responsible for randomizing the patient was also responsible for assessing the adhesion severity and extent. These observations were classified as unmasked evaluations since performing both assessments could have biased the surgeon's assessment of adhesion severity and extent. The primary effectiveness endpoint was separately evaluated for patients undergoing unmasked and masked assessments.

The masked evaluations were the majority and attained clinically meaningful and statistically significant differences. For the masked evaluations in the ITT population (Statistical Table 16.1 and Table 11 above, N=84; 43 REPEL-CV, 41 Control), a 26.4% reduction (REPEL-CV=24.0%, Control=50.4%) was observed (p=0.0045 for the mean and p=0.0010 for the median); for the unmasked evaluations (N=26; 13 REPEL-CV, 13 Control), a 25.2% reduction (REPEL-CV=12.5%, Control=37.7%) was observed (p=0.0662 for the mean and p=0.0294 for the median).

For the masked evaluations in the PP population (Statistical Table 16.2, N=79; 41 REPEL-CV, 38 Control), the 27.3% reduction (REPEL-CV=23.9%, Control=51.2%) was significant (p=0.0047 for the mean and p=0.0016 for the median). For the unmasked evaluations in this population (N=24; 13 REPEL-CV, 11 Control) the 31.1% reduction (REPEL-CV=12.5, Control=43.6) was significant (p=0.0318 for the mean and p=0.0193 for the median).

Again, it should again be emphasized that the study was not designed to assess effectiveness within evaluation type, although a general trend for a reduction in Grade 3 adhesions for the REPEL-CV group occurred for both masked and unmasked evaluation types. Statistical significance was in fact achieved for the critical masked evaluations where the evaluator did not know the original treatment group assignment.

10.4.3.5. Chest Closure Delay

Patients were classified by whether or not their chest closure was delayed. The primary effectiveness endpoint was separately evaluated using patients with a delayed chest closure and without a delayed chest closure. For the delayed subgroup in the ITT population (Statistical Table 17.1 and Table 11 above, N=83; 40 REPEL-CV, 43 Control), the 23.2% reduction (REPEL-CV=27.1%, Control=50.3%) was significant (p=0.0121 for the mean and p=0.0015 for the median); for those without delays (N=27; 16 REPEL-CV, 11 Control), the 28.6% reduction (REPEL-CV=6.9%, Control=35.5%) was not significant (p=0.0734 for the mean and p=0.0867 for the median), consistent with the overall study results.

For the delayed subgroup in the PP population (Statistical Table 17.2, N=78; 38 REPEL-CV, 40 Control), the 26.2% reduction (REPEL-CV=27.2%, Control=53.4) was significant (p=0.0069 for the

mean and p=0.0016 for the median); for those without delays (N=25; 16 REPEL-CV, 9 Control), the 25.3% reduction (REPEL-CV=6.9%, Control=32.2%) was not significant (p=0.1337 for the mean and p=0.1241 for the median), with the magnitude of the reductions consistent with the overall study results.

It should again be emphasized that the study was not designed to assess effectiveness by chest closure delay, although a general trend for a reduction in Grade 3 adhesions for the REPEL-CV group occurred for both chest closure delay and no chest closure delay.

10.4.4. Statistical/Analytical Issues

10.4.4.1. Multiple Comparisons

Not applicable.

10.4.4.2. Use of an "Efficacy Subset" of Patients

Subgroup analyses were performed for the primary effectiveness endpoint.

10.4.4.3. Active-Control Studies Intended to Show Equivalence

Not applicable.

10.4.4.4. Examination of Subgroups

Statistical Tables 13-17 present the primary efficacy results using the analysis of covariance model. Subgroups were examined by the following variables: gender, procedure type, use of Heart-Lung Bypass during Surgery, evaluation type, and chest closure delay (see Section 10.4.3.).

10.4.5. Tabulation of Individual Response Data

See Data Listings 14 and 15 (Appendix 15.2).

10.4.6. By-Patient Displays

Individual patient listings were displayed in Appendix 15.2.

10.4.7. Effectiveness Conclusions

The study results for the ITT population demonstrated a statistically significant reduction (26.0%) in the mean percentage (patient specific) of the study defined surface area with severe (Grade 3) adhesions favoring the REPEL-CV treatment (21.3% vs. 47.3%, p=0.0008). The primary effectiveness endpoint was also confirmed in the following subgroups: males (p=0.0021), females (p=0.0454), Norwood procedure (p=0.0106), on Heart-Lung bypass machine (p=0.0050), masked evaluators (p=0.0045), and chest closure delays (p=0.0121). In addition, the percentage of patients with Grade 3 adhesions at the investigational site as 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 has met the desired study objectives for the primary effectiveness measure. Results were established in the ITT and PP populations and confirmed for masked evaluators and key subgroups including Norwood, on bypass, and chest closure delays. Multiple prospectively defined statistical analyses were all confirmatory of significance for the ITT and PP populations. Although the standard deviation was somewhat higher than expected (leading to 74% power as opposed to the desired 80% power), the magnitude of the differences detected always exceeded the pre-defined 20% clinically meaningful difference used to plan the study as well as the 21.7% difference required to achieve 80% power. In addition, many secondary effectiveness outcomes are also significant. The potential for bias from withdrawals, time to withdrawal, and times to second sternotomy have been ruled out as have site and site-treatment interactions.

11. Safety Evaluations

11.1. Extent of Exposure

Seventy three (73) patients received REPEL-CV treatment. At the first surgery, one continuous piece of the REPEL-CV was 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.

11.2. Adverse Events

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% were patients with a single ventricle. In addition, greater than 85% of patients had their sternum left open for several days as a routine prior to closure. The adverse event terms summarized below reflect the events captured in the case report form as reported by the investigator.

11.2.1. Brief Summary of Events Common

The Events Common to this study population that occurred post-randomization are presented in Statistical Table 20. 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 were similar to the Events Common that occurred prior to randomization (Section 10.2.2.1.)

11.2.2. Brief Summary of Adverse Events

Medical events not predefined as Events Common, or Events Common occurring with greater frequency or duration or severity than is usual for this study population (as determined by the investigator) were defined as adverse events. There were no differences in adverse events occurring post-randomization between the REPEL-CV and the non-treatment control group (p=1.000) (Table 12 below). In the REPEL-CV treatment group, 51 patients experienced 135 AEs post-randomization, of which 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, of which only one patient experienced one AE that was possibly, probably or definitely treatment related AEs. Thirty-two (32) patients experienced 53 SAEs, none of these SAEs was considered possibly, probably or definitely treatment related AE (Table 12).

Table 12. Summary of Adverse Events and Death – 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					

11.2.3. Analysis of Adverse Events

A summary of overall AEs (pre- and post-randomization) by System Organ Class (SOC) and preferred term (PT) is presented in Statistical Table 22.

Prior to randomization (Statistical Table 21), 21 patients in the REPEL-CV treatment group experienced 29 AEs and the most frequent AEs by SOC and PT were (Statistical Table 23.1): Cardiac Disorders (8.2% patients), Vascular Disorders (6.8%), and Respiratory, Thoracic and Mediastinal Disorders (5.5% patients) (Statistical Table 23.1). Seventeen (17) patients in the control treatment group experienced 21 AEs, the most frequent AEs were Injury, Poisoning and Procedural Complications (7.2%) and Congenital, Familial and Genetic Disorders (5.8%).

The post-randomization AEs by SOC and PT are displayed in Statistical Table 23.2. In the REPEL-CV treated group, the most frequently observed post-randomization adverse events were: Infections and Infestations (26.0% patients), Cardiac Disorders (24.7% patients), Respiratory, Thoracic and

Mediastinal Disorders (23.3% patients), 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% patients), Respiratory, Thoracic and Mediastinal Disorders (18.8% patients), 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 is too infrequent to draw meaningful conclusion. It should be noted: (i) that the above adverse events include adverse events associated with the patient's surgical procedure and the patient's medical condition, and (ii) The adverse event profile in both treatment groups was expected and consistent with the clinical experience for this study population.

Some AEs were reported between the second sternotomy procedure and the one-month follow-up visit to evaluate wound healing. These AEs are identified in Listing 20.0, Appendix 15.2.7.

11.2.4. Display of Adverse Events that Occurred Post-Randomization

Table 13 displays a summary of the adverse events with an incidence of ≥ 2%. There were few events in each category and no pattern of events indicating a safety signal when comparing REPEL-CV treatment against control.

Table 13. Incidence of Adverse Events ≥ 2% by Treatment Group, System Organ Class, Preferred Term

MedDRA		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%)	0
	Respiratory Syncytial Virus Infection	2 (2.7%)	0

MedDRA		REPEL-CV (n=73)	Control (n=69)
System Organ Class and Preferred Term		N (%)	N (%)
	Sepsis	0	2 (2.9%)
	Viral Infection	0	2 (2.9%)
	Wound Infection	4 (5.5%)	3 (4.3%)
Injury, Poisoning and Procedural Complications			
	Postoperative Thoracic Procedure Complication	2 (2.7%)	4 (5.8%)
	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
	Hypotension	2 (2.7%)	0
Ref: Statistical Table 23.2			

A summary of the possibly, probably or definitely treatment-related adverse events by SOC and PT is presented below (Table 14). None of the events were considered definitely treatment-related. While more events occurred in the REPEL-CV treatment group, the numbers are small. Furthermore, several events occurred after the second sternotomy, at a time when REPEL-CV would not be expected to be present at the site of implantation and may not reflect a relationship with REPEL-CV (Listing 20.0) (See also Section 11.3.2).

Table 14. Summary of the Possibly, Probably or Definitely Treatment-related Adverse Events

MedDRA		REPEL-CV (n=73)	Control (n=69)
System Organ Class and Preferred Term		N (%)	N (%)
Infections and Infestations			
	Mediastinitis	2 (2.7%)	0
	Wound Infection	2 (2.7%)	1 (1.4%)
Injury, Poisoning and Procedural Complications			
	Postoperative Thoracic Procedure Complication	1 (1.4%)	0
Investigations			
	Cardiac Output Decreased	1 (1.4%)	0
Ref: Statistical Table 23.3, Section 13.1			

A summary of adverse events by SOC, PT and severity is provided in Statistical Table 24 (Section 13.1).

11.2.5. Listing of Adverse Events by Patient

See Data Listing 20.

11.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Event

11.3.1. Listings of Deaths and Other Serious Adverse Events

As per Table 12, 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) and mortality (16.4% vs. 13.0% of patients, p=0.6405). Death occurred as an outcome in 12 patients treated with REPEL-CV and 9 control patients.

Table 15 below lists the AEs which were associated with death. The distribution of events between the REPEL-CV and control groups is similar. The adverse event profiles in both treatment groups were expected and consistent with the surgical procedures and clinical condition of this study population.

Table 15. AEs Associated with Death

PID	AEs	Date of Randomization	Date of Death	Surgical Procedure
		REPEL-CV		
----------	Sclerosing Venitis	9Feb2004	19May2004	Non-Norwood
----------	Cardiac Arrest	4Oct2005	31Oct2005	Norwood
----------	Aortic Coarctation	20Mar2004	29Jun2004	Norwood
----------	Cardiorespiratory Arrest	23Feb2005	22May2005	Norwood
-------	Low Cardiac Output	2Aug2004	14Jan2005	Norwood
-------	Low Cardiac Output	17Nov2004	8Apr2005	Non-Norwood
-------	Sudden Cardiac Arrest	30Jun2004	17Oct2004	Norwood
----------	Cardiac Failure	4Oct2004	20Mar2005	Non-Norwood
----------	Cardiac Ischemia	18Jan2005	20Feb2005	Non-Norwood
----------	Cardiopulmonary Arrest	25Aug2005	25Jan2006	Norwood
----------	Cardiopulmonary Arrest	18Nov2005	27Mar2006	Non-Norwood
----------	Respiratory Failure	17Jan2006	15Feb2006	Norwood
		Control		
----------	Shunt Insufficiency	1Apr2004	15May2004	Norwood
----------	Cardiopulmonary Arrest	4Dec2003	29Dec2003	Non-Norwood
-------	Low Cardiac Output	7May2004	5Nov2004	Norwood
----------	Cardiac Arrest	10Nov2004	7Dec2004	Non-Norwood
-------	Removal of life support	11Feb2004	7Mar2004	Norwood
----------	Severe Illness	14Sep2004	18Mar2005	Non-Norwood
----------	Necrotizing enterocolitis	6Mar2005	25Mar2005	Norwood
----------	Cardiopulmonary Arrest	21Apr2004	28Jul2004	Non-Norwood
-------	Hypoxia, Bradycardic Arrest	12Jan2006	28Jan2006	Norwood

Ref: Data Listings 9, 10, 20.1

SAE(s) information for individual patient is provided in Data Listing 20.1. The most frequently occurring SAEs post-randomization (Statistical Table 26.2, Section 13.1) were Infection and Infestations (REPEL-CV 13.7%; control 13.0%), Cardiac Disorders (REPEL-CV 15.1%; control 13.0%), and Respiratory, Thoracic and Mediastinal Disorders (REPEL-CV 12.3%; control 7.2%). Four patients in the REPEL-CV treatment group experienced 4 SAEs (2 with mediastinitis, wound infection, and cardiac output decreased), which were considered related to REPEL-CV treatment (Statistical Table 26.3, Section 13.1). None of the SAEs were rated by the respective investigator as "definitely related" to the study device (See also Section 11.3.2).

A summary of serious adverse events (SAEs) by MedDRA SOC and PT with an incidence of ≥2% is presented in Table 16. The numbers of events do not indicate a safety signal for individual events or categories of events by SOC.

Table 16. Incidence of Serious Adverse Events ≥ 2% by Treatment Group, System Organ Class, Preferred Term

MedDRA	REPEL-CV (n=73)	Control (n=69)
System Organ Class and Preferred Term	N (%)	N (%)
Cardiac Disorders		
Cardiac Arrest	3 (4.1%)	4 (5.8%)
Cardio-Respiratory Arrest	4 (5.5%)	2 (2.9%)
General Disorders		
Death	0	2 (2.9%)
Infections and Infestations		
Bronchiolitis	3 (4.1%)	0
Gastroenteritis	0	2 (2.9%)
Mediastinitis	2 (2.7%)	0
Sepsis	0	2 (2.9%)
Wound Infection	1 (1.4%)	2 (2.9%)
Investigations		
Cardiac Output Decreased	3 (4.1%)	1 (1.4%)
Oxygen Saturation Decreased	1 (1.4%)	4 (5.8%)
Nervous System Disorders		
Convulsion	0	2 (2.9%)
Respiratory, Thoracic and Mediastinal Disorders		
Hypoxia	3 (4.1%)	1 (1.4%)
Pleural Effusion	0	2 (2.9%)
Respiratory Distress	2 (2.7%)	3 (4.3%)
Vascular Disorders		
Haemodynamic Instability	2 (2.7%)	0
Ref: Statistical Table 26.2, Section 13.1		

11.3.2. 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. AEs and SAEs of this special interest are presented in Table 17 below. 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.

Table 17. Adverse Events of Special Interest

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					

Mediastinitis was of specific interest because it was only reported in the REPEL-CV group. The adverse event terms reflected the events captured in the case report form as reported by the investigator. In order to impose consistency across investigator sites, events that could be classified as mediastinitis (coded as MEDIASTINAL INFECTION, MEDIASTINITIS, and WOUND INFECTION) 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% were patients with a single ventricle. In addition, greater than 85% 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).[2] 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.[2,3,4,5] 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).[2] 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 developed mediastinitis. 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%).

Mediastinitis following the first operation:

1. Patient---------- developed mediastinitis (reported AE description = Wound infection) in a time frame remote from randomization (~ 4 months subsequent to randomization, the first operation), following a catheterization procedure in preparation for the second operation, the Glenn Shunt. "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 (23Mar2005). Two days later at the time of chest closure the patient was randomized to the REPEL-CV group (25Mar2005). The patient was readmitted with mediastinitis (reported AE description = Mediastinitis – bacteria culture found staph aureus) on 6Apr2005 (14 days from 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.

Mediastinitis following the second operation:

1. Patient--------- underwent a Norwood operation (2Feb2004) with delayed sternal closure (4Feb2004). This patient required an additional sternotomy to create a new source of pulmonary blood flow with a Blalock-Taussig shunt on 24Mar2004 (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 (15Apr2004). 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 (23Apr2004) 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 30Dec2005 and delayed chest closure and randomization on 31Dec2005. On 10Jan2006 the patient underwent cardiac catheterization and stent placement in shunt narrowing. Six months later (15Jun2006), the patient underwent the second surgery (Glenn Shunt). On 19Jun2006 (4 days later), the patient developed serous drainage from the incision which grew staph. 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. This case of mediastinitis, as described in the clinical papers on the topic,[2,3,4,5] would be

considered related to the operation that proceeded it, the Glenn Shunt, and not the operation 6 months prior.

The overall incidence of mediastinitis following cardiac surgery in the pediatric population is well reported in the literature. The incidence of mediastinitis requiring open drainage and antibiotics in this study is similar to the incidence reported in the literature. The patient population in the REPEL-CV Study (neonates, cyanotic, delayed sternal closure) is predisposed to a higher infectious risk.

11.3.3. Narratives of Deaths and Other Serious Adverse Events

11.3.3.1. REPEL-CV

Patien----------	**Randomization----------**		
SAEs	**Hemodynamic Instability**	**3Oct2003 – 5Oct2003**	**Probably not related**

This male infant was born on ---------- with tricuspid atresia, transposition of the great vessels, and severe coarctation of the aorta. He underwent a modified Norwood procedure on 30Sep2003 and at that time was enrolled into this study following pediatric cardiothoracic surgery.

Shortly after chest closure (3Oct2003), his blood pressure and O_2 saturation dropped. He was treated with volume, inotropes, and ventilator changes without success. The patient's chest was reopened and the REPEL-CV™ was removed. Blood pressure slowly improved, and the chest was closed on 5Oct2003 without problem.

The patient was withdrawn from the study because chest reopening disqualified him from further evaluation. In the judgment of the investigator, the serious adverse event was probably not related to the study device.

Patien-----	**Randomization----------**		
SAEs	**Acute Viral Ga---------- itis**	**13Nov2003 – 15Nov2003**	**Definitely not related**
	Bronchiolitis	**10Dec2003 – 12Dec2003**	**Definitely not related**

This male infant was born on ---------- with single ventricle heart disease and underwent a Norwood procedure on 22Sep20---------- ime, he was enrolled into this study following pediatric cardiothoracic surgery.

Patient presented with a history of green loose stools and decreased oral intake over 12 hrs, which started on the morning of 13Nov2003. The patient's parents reported his temperature of 101.4°F at home. There was no vomiting or rash noted. The patient was admitted to the hospital and treated with IV fluids and monitoring. The patient did well during hospitalization, and the number of stools significantly decreased. Blood cultures were negative on day of discharge (15Nov2003).

On 10Dec2003 he presented to the ER with increased cyanosis, decreased peripheral oxygen

saturation and coughing. Patient was afebrile and his parents reported that he had a slightly decreased appetite. Patient had no vomiting or diarrhea. The principal diagnosis was primary bronchiolitis with decreasing O_2 saturation. During hospitalization, he had a chest x-ray and CBC test, and received O_2 via nasal cannula to maintain O_2 saturation >75%. The subject was in stable condition at discharge on 12Dec2003.

In the judgment of the investigator, the acute viral gastroenteritis and bronchiolitis were definitely not related to the study device.

Patient-------	**Randomization----------**		
SAEs	**Low Cardiac Output**	**27Oct2003 – 27Oct2003**	**Possibly related**

This male infant was born on ---------- with hypoplastic left heart syndrome and underwent Norwood and 3.5mm Blalock-T----------t procedure on 24Oct2003. At that time, he was enrolled into this study. The subject underwent sternal closure on 27Oct2003, and REPEL-CV was applied. The subject required initiation of epinephrine drip 0.01-0.03 mcg/kg/min during closure; CVP increased from 9 to 12; MVO2 decreased from 60 to 43%. Approximately 8 hours post-chest closure, the subject required increased inotropic support (epinephrine up to 0.14 mcg/kg/min and milrinone up to 1 mcg/kg/min with evidence of decreasing cardiac output (falling MVO2) and decreased urine output.

The sternum was re-opened and the findings included: tense ascites and a small amount of pericardial and pleural effusion. The adhesion barrier fractured in multiple pieces ranging in size from 3x5 mm to 2x2 cm, capable of being removed with forceps. The usual amount of clotted blood was observed in the mediastinum and chest tubes with no active bleeding or collection of blood. The CVP decreased when the chest was opened, and the pericardial and ascitic fluid was drained. The subject's mediastinum was closed with silastic sheeting and the sternum was left open.

The investigator stated that it is unusual (<5%) for a subject with a single ventricle to require re-sternotomy after successful closure. The patient was withdrawn from the study because chest reopening disqualified him from further evaluation. In the judgment of the investigator, due to the temporal relationship of REPEL-CV placement, the serious adverse event was possibly related to the study device.

Patien-----	**Randomization----------**		
SAEs	**Hypoxia**	**18Dec2003 – 23Dec2003**	**Definitely not related**

This male infant was born on ----------with hypoplastic left heart syndrome and underwent a Norwood Stage I procedure on 30Oct2003 using the Sano Modification. At that time he was enrolled into this study. The patient experienced an uneventful postoperative course and was discharged on post operation day (POD) 14.

The patient was seen at follow-up visit on 18Dec2003 and his O_2 saturations were at 60%. An echocardiogram was performed which revealed narrowing at the distal end of the RV-PA conduit. The patient was admitted and scheduled for immediate cardiac catheterization. Balloon angioplasty

of the conduit with a 3.5mm and 4mm balloon resulted in an immediate increase in the oxygen saturations. The patient had been intubated prior to the procedure and received a blood transfusion following the procedure. He returned to the PICU following the procedure for observation.

Post-procedure complications included hyperkalemia requiring kayexalate, sodium bicarbonate for metabolic acidosis, and a LLL (left lower lobe) infiltrate with sputum positive for *Enterobacter cloacae*. The patient was extubated on 23Dec2003 and transferred to the ward the following day. He was discharged home on 26Dec2003.

In the judgment of the investigator, the hypoxia was definitely not related to the study device.

Patient-------	**Randomization---------**		
SAEs	**Renal Dysfunction**	**29Dec2003 – 12Jan2004**	**Definitely not related**
	Cardiac Arrest	**7Jan2004 – 20Jan2004**	**Definitely not related**
	Intraventricular Hemorrhage	**7Jan2004 – 27May2004**	**Definitely not related**
	Endocarditis	**24Apr2004 – 28Jun2004**	**Probably not related**
	Embolic Event	**21Apr2004 - 22Apr2004**	**Definitely not related**
	Psoas Muscle Abscess	**22Apr2004 - 7May2004**	**Probably not related**
	Wound Infection	**25Apr2004 – 18May2004**	**Possibly related**

This male infant was born on ----------with a diagnosis of critical pulmonary stenosis vs. pulmonary atresia and hypopla----------ntricle and underwent a balloon angioplasty of the pulmonary valve on day one of life. The dye required for the procedure exacerbated his condition. Following surgery the patient's renal function steadily worsened due to the use of CPB (cardiopulmonary bypass), nephrotoxic drugs and diuretics. Patient had elevated BUN and creatinine due to decreased pre-operative cardiac output. Cardiac output was supported with inotropes and diuretics and volume were given as needed. Renal function slowly improved with return to normal BUN and creatinine levels on 12Jan2004.

On 2Jan2004, this patient underwent placement of a Blalock-Taussig shunt and a partial atrial septectomy. He was enrolled into this study on 31Dec2003. The postoperative course was complicated by a cardiac arrest on 7Jan2004, when the patient suddenly developed hypoxia, bradycardia and hypotension. He was emergently reintubated and received chest compressions, volume, atropine, several doses of epinephrine, calcium, and sodium bicarbonate. A heparin bolus was also given due to an inaudible shunt murmur. He was started on an epinephrine drip and the inotropic support was increased. He required an insulin drip. An echocardiogram was obtained which revealed shunt patency. By POD#7, the epinephrine drip was weaned off and the inotropic support was back down to pre-arrest levels. Blood culture was positive for *Staphylococcus epidermidis*, and the patient started on 7-day course of vancomycin. By POD#11, he was weaned off all inotropic support and was extubated on POD#18.

A head ultrasound was obtained due to an acute drop in the HCT and revealed a parenchymal bleed in the left frontal lobe. He also received FFP (fresh frozen plasma), vitamin K and platelets due to coagulopathy. Head CT revealed frontal lobe bleed, small bilateral intraventricular hemorrhage (IVH), and blood in the basal ganglia. On 12Jan2004, ultrasound of the head revealed resolving

IVH.

On 21Apr2004, the patient was admitted for hemodynamic cardiac catheterization. Following the procedure, he developed decreased pulses in the right lower extremity (RLE) and an area of suspected necrosis in the right fourth toe, which was treated with heparin drip. The subject improved and was discharged the following day.

The parents brought the infant to the emergency room one day later (22Apr2004) after noting a peticheal rash on the right lower extremity (RLE) and decreased movement of the right leg. The patient was admitted to the hospital and underwent a work-up which included blood cultures, an ultrasound of the right hip to rule out fluid, and a cardiac echocardiogram. On 27Apr2004, it was noted that the patient continued to exhibit decreased movement of the RLE. MRI was obtained on 29Apr2004 and revealed a large fluid collection near the right psoas muscle. On 1May2004, incision and drainage of the psoas abscess was performed, and a Penrose drain left in place. This was advanced progressively and removed on 7May2004. The patient was treated with 6 weeks of antibiotic therapy. Blood cultures obtained on 28Apr2004 were negative, and this SAE was deemed resolved.

On 25Apr2004 (~4 months after initial Sternotomy), the subject developed a small pustule on the median sternotomy incision. The median sternotomy site had increased to a 2x2cm erythematous, fluctuant area and was debrided surgically on 26Apr2004. The subject had elevated white blood cell count with a shift in the differential and continued fever. Echocardiogram revealed moderate mitral regurgitation. The patient was treated initially with Vancomycin IV (04.25/2004) with Oxacillin IV added (04/26/04-06/14/04) and Rifampin IV (05/18/04-06/12/04) for synergy. Blood cultures obtained on 28Apr2004 were negative. The VAC drain was removed on 18May2004. A repeat culture was done at that time which was positive for a few coagulase negative Staphylococcus species.

The patient was withdrawn from the study because chest reopening disqualified him from further evaluation (surgical site disturbed). In the judgment of the investigator, cardiac arrest, IVH, embolic event and renal dysfunction were definitely not related to the device; endocarditis and psoas muscle abscess probably not device related; only the wound infection was possibly related to the study device. The investigator felt that the mediastinitis was 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.

Patien-------- Randomization---------
SAEs Sclerosing Venitis 22Feb2004 – 19May2004 Definitely not related

This female infant was born on ---------- ith complex cyanotic heart disease (situs inversus, dextrocardia, supracardiac total anomalous pulmonary venous return, pulmonary atresia, discontinuous branch pulmonary arteries, bilateral ducti, criss-cross oriented ventricles, a large ventricular septal defect, and a moderate atrial septal defect). On 5Feb2004, the patient underwent a staged palliation, which included reconnection of the branch pulmonary arteries, ligation of bilateral

ducti and placement of a Blalock-Taussig shunt, atrial septectomy and repair of total anomalous pulmonary venous return. At that time she was enrolled into this study.

The post-operative course was extremely complicated. On 17May2004, she suffered a tracheal hemorrhage, and her condition deteriorated. Her parents requested a do not resuscitate status and on 19May2004, requested that support be withdrawn. She was removed from the ventilator and expired immediately. The cause of death was inoperable sclerosing venitis with hemorrhage.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patient ----	**Randomization----------**		
SAEs	**Desaturation**	**7Aug2006 – 7Aug2006**	**Definitely not related**

This male infant was born on---------- with a diagnosis of hypoplastic left heart syndrome. On 26Sep2005 the patient was c---------- entered into the study.

On 7Aug2006, the patient had extreme cyanosis and hemodynamic instability and was taken immediately to the operation room for pericardial patch augmentation of bi-directional Glenn shunt with bilateral pulmonary embolectomy. In the opinion of the investigator, this desaturation was definitely not related to the study device.

Patien------	**Randomization----------**		
SAEs	**Cardiac Arrest**	**31Oct2005 – 31Oct2005**	**Definitely not related**

This male infant was born on---------- with congenital heart disease. He underwent a stage 1 Norwood procedure with a Blalock-Taussig shunt on 28Sep2005. At that time he was enrolled into the study. On 31Oct2005, he was transferred to a wardroom where he vomited, experienced desaturation and cardiac arrest, and could not be resuscitated.

In the opinion of the Investigator, this event was definitely not related to the study device.

Patien-----	**Randomization----------**		
SAEs	**Acute Cardiop----------**	**~~21Jan~~2004 – 26Jan2004**	**Definitely not related**
	Failure		
	Prolonged Mechanical Ventilation	**2Jun2004 - 10Jun2004**	**Definitely not related**

This male infant was born on---------- with hypoplastic left heart syndrome. He underwent a Norwood procedure on 6Jan2004. At that time he was enrolled into this study. On 21Jan2004, he experienced oxygen desaturation to below 50%, which was treated by manual bag ventilation and suctioning without improvement. Shortly thereafter, he experienced an acute decompensation with desaturation into the 30% range followed by a left bundle branch block pattern down to a junctional bradycardia. At this point, a code was called and full resuscitation initiated.

He was resuscitated with chest compressions, inotropic medications, vasoconstrictors and bicarbonate buffer. His arterial blood gas was obtained and showed combined respiratory and metabolic acidosis. He also suffered from hyperkalemia associated with systemic acidosis, which was treated with calcium, bicarbonate, insulin, and glucose.

With initiation of vasopressor and epinephrine infusion approximately 45 minutes into the resuscitation, he experienced a sudden return of spontaneous circulation with a narrow complex conducted sinus rhythm at greater than 100 beats/minute and measurable pulse. He was observed for approximately one hour cannulated, but not flowing on ECMO while on high inotropic support. With gradual decreases in his inotropic support he experienced transient decrease in blood pressure, so the decision was made to initiate ECMO flow. With initiation of ECMO flow, there was gradual increase in oxygenation to 99-100%.

On 2Jun2004, he underwent creation of a Glenn shunt. Postoperatively he experienced persistent respiratory failure, which did not improve despite maximal medical and respiratory intervention. A bubble contrast study was performed on 4Jun2004, which suggested venovenous collateral blood flow. On 7Jun2004, a cardiac catheterization demonstrated two small venovenous collaterals which were coil embolized. His respiratory status slowly improved, and he was extubated on 10Jun2004.

In the judgment of the investigator, both the acute cardiopulmonary failure and prolonged mechanical ventilation were definitely not related to the study device.

Patient-------	**Randomization ----------**		
SAEs	**GI Bleed**	**25Dec2004 - 25Dec2004**	**Definitely not related**
	MRSA Bacteremia	**4May2005 – 13May2005**	**Definitely not related**

This female infant was born on----------with complex congenital heart disease, hypoplastic left heart syndrome, status post Norwood repair on 26Nov2004. On 25Dec2004, she suffered a life-threatening upper GI bleed following insertion of a nasogastric (NG) tube.

More than 400ml of blood was aspirated by NG tube. She received transfusions with multiple blood products, GI medications, and NG lavage. Following medical stabilization an upper endoscopy was performed. A duodenal ulcer was found with a large amount of blood remaining in the stomach. She was treated with GI agents and gastric decompression with steady improvement.

She subsequently was found also to have heterotaxia, polysplenia and chronic respiratory insufficiency. She was scheduled for a B-T shunt on 4May2004. The patient reportedly developed fever on 3May2005 and surgery was postponed pending culture results. Cultures indicated MRSA bacteremia; vancomycin and gentamicin were prescribed. The patient was afebrile since 7May2005.

In the judgment of the investigator, the GI bleed and the MRSA bacteremia were definitely not related to the study device.

Patient--------	**Randomization---------**		
SAEs	**Re-hospitalizat----------5May2005 – 6May2005**		**Definitely not related**
	Cardiac Catheterization		

A female infant was born on----------with hypoplastic left heart syndrome and systemic ejection murmur. On 20Jan2005 th---------- s enrolled into the study.

A Glenn shunt procedure was performed on 21Apr2005 and this four-month-old infant was discharged on 26Apr2005. She was re-admitted to the hospital on 5May2005. The patient had developed decreased PO_2 intake and increase work of breathing a couple days prior to admission.

Chest x-ray showed small right pleural effusion. Cardiac catheterization was done on 6May2005 to assess for Glenn shunt pressures and collateral circulation. The patient was discharged on 10May2005. The patient required left apical embolization coil times one (veno-venous coil).

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien-------	**Randomization---------**		
SAEs	**Right Ventricle----------nary**	**10Feb2004 – 19Feb2004**	**Definitely not related**
	Artery Conduit Narrowing		

This male infant was born on---------- with hypoplastic left heart syndrome. He underwent Sano Norwood repair on 20Nov2003. On 10Feb2004, he presented to the clinic with progressive cyanosis. Oxygen saturation was 70% on room air. He was admitted to the hospital and given oxygen to maintain saturations above 75%.

Cardiac catheterization on 14Feb2004 revealed a discrete narrowing of the right ventricle to pulmonary artery conduit at the proximal end. On19Feb2004, the patient underwent a bidirectional Glenn procedure. Adhesion evaluation was performed as per protocol. Postoperatively the patient had to be reintubated because of a paralyzed left hemidiaphragm secondary to phrenic nerve injury. On 23Feb2004, left hemidiaphragm plication was performed. On 29Feb2004, the patient was discharged.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien-----	**Randomization---------**		
SAEs	**Dynamic Muscular Narrowing**	**24Feb2004 – 25Mar2004**	**Definitely not related**
	at Proximal SANO		
	Mediastinal Infection	**24Apr2004 – 5Jun2004**	**Definitely not related**

This male infant was born on ---------- with hypoplastic left heart syndrome. He underwent a Sano Norwood procedure on 2---------- layed sternal closure on 4Feb2004 and was enrolled into this study.

On 24Feb2004, the patient experienced dynamic muscular narrowing at proximal Sano and a Blalock-Taussig shunt for increased pulmonary artery flow was performed on 25Mar2004 and PEG tube placement on 4Apr2004.

The patient had 2nd sternotomy on 25Mar2004. On 21Apr2004 (~4 weeks after 2nd sternotomy), he was admitted to the hospital in respiratory distress with elevated WBC and CRP levels. On 23Apr2004 the mediastinal wound was erythematous and fluctuant. Debridement was performed the next day, and a wound swab was positive for methicillin resistant *Staphylococcus aureus*. He remained in the hospital for a 42 day course of IV antibiotic therapy and recovered well.

In the judgment of the investigator, the serious adverse events were definitely not related to the study device.

Patien----	**Randomization----------**		
SAEs	**Midsternal Wound Drainage**	**25Mar2004 – 14Apr2004**	**Definitely not related**
	Aortic Coarctation	**26Jun2004 – 29Jun2004**	**Definitely not related**

This male infant was born on---------- with hypoplastic left heart syndrome and underwent a Norwood procedure with a 3.5 BT shunt on 18Mar2004. The chest was closed on 20Mar2004.

On 25Mar2004, the 10-day-old infant had midsternal wound drainage performed for wound inflammation from which he recovered completely on 14Apr2004.

At 3 months of age, he was taken to the pediatrician for vomiting. The pediatrician thought it was viral and sent the patient home. On 26Jun2004, the patient was taken to the ER for continued vomiting. He was found to have coartation of the aorta and was admitted to ICU. On 28Jun2004, balloon angioplasty was attempted without success. The patient expired the next day despite resuscitative measures.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien----	**Randomization----------**		
SAEs	**Pulmonary Overcirculation**	**19Feb2005 – 19Feb2005**	**Definitely not related**
	Hypoxemia	**19Feb2005 – 19Feb2005**	**Definitely not related**

This male infant was born on---------- with total anonymous pulmonary venous return (TAPVR) unbalanced atrioventricular s---------- hypoplastic left ventricle, double outlet right ventricle, and transposed great vessels. He underwent repair of TAPVR on 8Feb2005, with pulmonary artery banding (PAB) to control pulmonary blood flow. Sternal closure was performed on 11Feb2005.

On 17Feb2005, the patient developed pulmonary overcirculation with hypoxemia, tachypnea and elevated saturations. He was reoperated on 19Feb2005 to revise and tighten the pulmonary artery banding (PAB). The revision was successful. The second sternotomy was performed less than two month after the first sternotomy.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien----	**Randomization----------**		
SAEs	**Bilateral Diffuse Atelectasis**	**28Feb2005 – 3Mar2005**	**Definitely not related**
	Apical Pericardial Effusion	**1May2005 – 8May2005**	**Definitely not related**
	Cardiorespiratory Arrest	**22May2005 – 22May2005**	**Definitely not related**

This male infant was born on----------with hypoplastic left heart syndrome, non-restrictive ductus arteriosus and restrictive atrial septal defect underwent Norwood and 3.5mm Gore-Tex Shunt procedure on 21Feb2005. Sternal closure was performed on 23Feb2005 and at that time he was enrolled into this study. On 28Feb2005, he experienced bilateral diffuse atelectasis from which he recovered completely on 3Mar2005.

On 1May2005, this infant experienced apical pericardial effusion from which he recovered completely on 8May2005.

On 22May2005, the patient collapsed at home and was taken to the hospital via the parent's car and no cardiopulmonary resuscitation was performed. Patient arrived in hospital in full cardiac arrest, cyanotic, apneic and pulseless. He was pronounced dead after several rounds of drug resuscitation.

In the judgment of the investigator, these three serious adverse events were definitely not related to the study device.

Patient-------	**Randomization----------**		
SAEs	**Respiratory Di-------**	**18May2004 - 19May2004**	**Definitely not related**

This male infant was born on ----------with hypoplastic left heart syndrome and underwent a Norwood procedure followed ---------- ure. On 21May2004, the patient was enrolled into this study.

He developed GERD, and was admitted on 18May2004 after an episode of emesis and a breath holding spell during which he turned blue/grey. At the local ER, his saturations were 74% on room air. In the hospital, RSV screen was negative, and the episode was thought to be reflux with choking. It was recommended that he remain on Prilosec.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

---	**Randomization** ---		

---	**Low Cardiac Output**	**14Jan2005 - 14Jan2005**	**Definitely not related**

This male infant was born on--- with hypoplastic left heart syndrome which was treated with a Norwood procedure. --- 4, the patient was enrolled into this study.

He returned to the ICU with low cardiac output experiencing brief runs of JET (Junctional Ectopic Tachycardia) and SVT (Supraventricular Tachyarrhythmia). After 2 hours, the blood pressure was stabilized. He next had ventricular fibrillation resistant to multiple attempts at defibrillation. The chest was opened and internal manual compression was performed for 25 minutes after which CPR was stopped. He expired on 14Jan2005, secondary to post operative complications.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patient---	**Randomization**---		
SAEs	**Hypernatremic Dehydration**	**5Feb2005 – 17Feb2005**	**Probably not related**
	Clostridium Difficile	**14Feb2005 – 28Feb2005**	**Probably not related**
	Low Cardiac Output	**30Mar2005 – 8Apr2005**	**Probably not related**

This female infant was born on--- with hypoplastic left heart syndrome as well as multiple other congenital abnormalities. She underwent first stage Hybrid procedure (PA bands and PDA stent) on 17Nov2004.

On 5Feb2005, the patient was admitted with hypernatremic dehydration. She was treated successfully and discharged home with no long-term sequela.

On 14Feb2005, the patient tested positive for clostridium difficile, which was successfully treated with antibiotic therapy.

On 30Mar2005, she underwent the second stage procedure, a bilateral Glenn, bilateral lobar branches PA plasties, aortic arch reconstruction, and ductal stent removal. Several hours post-operatively, she developed a low cardiac output state with decreasing oxygenation. The decision was made to place her on ECMO. Attempts were made to wean her from ECMO, including interventions in the catheterization lab, but weaning was unsuccessful. It was determined that no further treatment was available and she was removed from ECMO on 8Apr2005, at which time she

expired.

In the opinion of the Investigator, this event was probably not related to the study device.

Patien-------	**Randomization----------**		
SAEs	**Thrombus For----------Central Shunt Requiring Re-operation**	**21Apr2004 – 22Apr2004**	**Definitely not related**

This female infant was born on ----------with tricuspid atresia, ventricular septal defect, pulmonary stenosis, and dextrocardia. She underwent central shunt placement from the aorta to the pulmonary artery on 20Apr2004. The following day the shunt was found to be occluded by echocardiogram. She returned to surgery for a new shunt placement on post-operative day #2 (22Apr2004), from which she was recovering at the time of this report.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patient-------	**Randomization ----------**		
SAEs	**Malrotation of B------**	**3Jan2005 – 6Jan2005**	**Definitely not related**
	Respiratory Syncytial Virus Bronchiolitis	**31Jan2005 – 1Feb2005**	**Definitely not related**
		11Mar2005 – 14Mar2005	**Definitely not related**

This female infant was born on----------with heterotaxy syndrome, mitral atresia, ventricular septal defect, hypoplastic left ventricle, aortic calve, and aortic arch, double outlet right ventricle and subaortic stenosis. She underwent a Norwood procedure.

Although the patient was asymptomatic, due to various abnormalities noted at birth an upper GI study was ordered to rule out Malrotation. The study confirmed Malrotation and the patient underwent surgical repair on 6Jan2005 and was discharged home on 15Jan2004.

The medical record stated that the patient had a previously unreported hospitalization of one day for observation during an episode of RSV.

On 11Mar2005, during a routine clinic visit, the patient was noted to have respiratory distress and rhinorrhea. She was admitted for observation and treated for bronchiolitis with albuterol, prednisolone, and azithromycin. She recovered uneventfully and was discharged to home.

In the opinion of the investigator, all three events were definitely not related to the study device.

Patien--------	**Randomization----------**		
SAEs	**Surgery for Placement of Subclavian Pulmonary Shunt**	**22Dec2005 – 30Dec2005**	**Definitely not related**

A two-month-old male infant with congenital heart defect required a subclavian-pulmonary shunt to

increase pulmonary blood flow in order to prepare him for the next stage of a 3 stage surgical repair of hypoplastic left heart syndrome. The patient was enrolled into this study on 7Nov2005. The infant had a successful surgery with uneventful recovery. The thoracotomy procedure rendered the patient ineligible for continuation in the study. The procedure was considered not uncommon for this patient population.

In the opinion of the Investigator, the event was definitely not related to the study device.

Patient----- Randomization----------
SAEs Hemodynamic Instability 10May2004 – 10May 2004 Definitely not related

This male infant was born on----------with hypoplastic left heart syndrome, he was treated with a Norwood procedure Stage 1 palliation, atrial septectomy and 3.5 mm Gore-Tex shunt. Sternal closure was performed. On 10May2004, the patient was enrolled into this study.

On 10May2004, patient had hemodynamic instability with bleeding requiring reexploration of the chest for probable tamponade physiology and received inotropic support.

The patient was withdrawn from the study because chest reopening disqualified him from further evaluation. In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patient----- Randomization----------
SAEs Sudden Cardiac Arrest 17Oct2004 – 17Oct2004 Definitely not related

This male infant was born on----------with hypoplastic left heart syndrome, mitral atresia and aortic atresia, treated with a Norwood procedure using a 4.0 mm Gore-Tex shunt. The patient was enrolled into this study on 30Jun2004.

On 17Oct2004, the subject experienced sudden cardiac arrest and death.

In the opinion of the Investigator, the serious adverse event was definitely not related to the study device.

Patient------- Randomization----------
SAEs Mediastinitis 6Apr2005 – 20Apr2005 Possibly related

This female infant was born on----------with transposition of the great arteries with unbalanced ventricles, interrupted aortic ar---------- ight subclavian emerging from the descending thoracic aorta, and ventricular septal defect. She was treated surgically with a Norwood procedure, creation of a central shunt, ligation of patent ductus arteriosus, and atrial septectomy. The patient was enrolled into this study on 25Mar2005.

On 6Apr2005, patient returned with a sternal wound infection. She returned to the OR for exploration, evacuation of mediastinal fluid, irrigation, and repeat primary chest closure.

REPEL-CV remnants (small flakes of patch) were noted on the epicardial surface. No obvious source of infection was identified. The patient recovered well and was discharged home on antibiotics, in stable condition.

In the opinion of the Investigator, this event was possibly related to the study device.

Patien-------	**Randomization----------**		
SAEs	**Rotovirus / Gas----------tis /Bacteremia**	**6Feb2006 – 17Feb2006**	**Probably not related**

This two-month-old female infant had Shone's Complex consisting of Mitral valve, atresia, hypoplastic aortic arch with critical coarctation of the aorta, and was status post Norwood procedure and status post gastrostomy tube placement and Thal Fundoplication. On 22Dec2005 the patient was enrolled into this study.

This infant was admitted to hospital on 6Feb2006 with fever, jaundice and tachypnea. Cultures were positive initially for *Enterococcus faecium*, and later also positive for *C. difficle* and Rotavirus. The patient was treated with vancomycin, ampicillin, gentamycin and flagyl and fully recovered from the febrile illness and was discharged to home.

In the opinion of the Investigator, this event was probably not related to the study device.

Patient------	**Randomization----------**		
SAEs	**Rule Out Sepsis**	**15May2004 – 21May2004**	**Probably not related**
	Congestive Heart Failure	**7Jun2004 – 18Jun2004**	**Definitely not related**
	Oral Thrush	**2Jul2004 – 3Jul2004**	**Definitely not related**
	RSV-Bronchiolitis	**26Jan2005 – 1Feb2005**	**Definitely not related**

This male infant was born on---------- with a large ventricular septal defect (VSD), was treated with pulmonary artery bandi----------004. At that time he was enrolled into this study.

The infant was discharged on 14May2004 with history of VSD, S/P PA Banding. During hours at home, his mother noticed that he was not waking up to feed and was pale and cool. On 15May2004, the patient was admitted to the hospital, the patient was lethargic and cool to the touch. He was intubated and worked up for sepsis. He was placed on Vancomycin and Cefapime. All cultures were negative, and he was discharged on 21May2004.

The patient was admitted to the ER for increased sleepiness and tiredness while feeding, cough and runny nose. On 8Jun2004, he experienced two episodes of apnea with the heart rate decreasing to the 30s and oxygen saturation to 54%. He was given oxygen and Lasix and improved. His dosages of Lasix and Aldactone were increased and he was discharged on 18Jun2004.

On 2Jul2004, patient was noted to have intercostals and subcostal retractions with tachypnea, and oxygen saturation 94% during a routine visit. He was also noted with eye discharge bilaterally x 1 day and oral thrush x 2 days. Culture of eye drainage was negative; patient was admitted for

observation to rule out possible congestive heart failure. On 3Jul2004, the patient was discharged home on Nystatin, diuril, aldactone, lasix, zantac and reglan.

On 26Jan2005, this patient presented with chief complaint of fever and congestion, which started two days prior along with a non-productive cough. Patient was admitted to the hospital. Respiratory cultures found positive for RSV; blood cultures were negative. Patient was started on antibiotic therapy, chest x-ray, supplemental oxygen 1-liter nasal cannula, and albuterol treatments (every three hours). On 31Jan2005, patient was weaned from supplemental oxygen and discharged home on 1Feb2005 with a prescription for albuterol treatments as needed for difficulty in breathing.

In the judgment of the investigator, rule out sepsis was considered to be probably not device related, the CHF, oral thrush and RSV-bronchiolitis events were definitely not related to the study device.

Patien------	**Randomization---------**		
SAEs	**Cardiac Failure**	**9Mar2005 – 20Mar2005**	**Probably not related**

This male infant was born on---------- with complex congenital heart disease consisting of complete atrial ventricle canal w---------- ed ventricles. He underwent pulmonary artery banding. On 4Oct2004 he was enrolled into this study. He developed significant myocardial dysfunction and severe atrial ventricular regurgitation which responded to medical therapy.

On 9Mar2005, patient underwent removal of the pulmonary artery band and repair of atrial ventricular regurgitation with Hemi-Fontan procedure. This was complicated by thrombosis of the right femoral artery, treated by thrombectomy. Multiple desaturations were treated with oxygen and nitric oxide, fresh frozen plasma and packed red blood cells. He was placed on ECMO but continued to desaturate when weaned. He was returned to the OR for emergent BT shunt and Hemi-Fontan takedown. On 20Mar2005, five and half month post randomization, he was weaned off ECMO and Nipride® drip was discontinued. He expired shortly thereafter.

In the judgment of the investigator, the serious adverse event was probably not related to the study device.

Patien------	**Randomization---------**		
SAEs	**Stridor**	**10Feb2005 - 14Feb2005**	**Definitely not related**

This male infant was born on---------- with coarctation of the aorta, ventricular septal defect and patent ductus arteriosus which was treated by repairing the coarctation and banding the pulmonary artery. He also has a history of necrotizing enterocolitis. On30Dec2004 he was enrolled into this study.

He was brought to the ER with a history of stridor. X-ray showed severe patchy atelectasis, increased aeration in the right lung and subglottal narrowing. On 14Feb2005, a direct laryngobronchoscopy was performed which revealed left vocal cord paralysis and laryngomalacia with adequate airway. No interventions were necessary. It is anticipated that the stridor will decrease as the infant grows.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien---------	**Randomization ---------**		
SAEs	**Cardiac Ischem---**	**20Feb2005 - 20Feb2005**	**Definitely not related**

This male infant was born on----------with a history of right hypoplastic heart syndrome, pulmonary atresia, and tricusp----------underwent PDA ligation and modified BT shunt on 18Jan2005. At that time he was enrolled into this study. Postoperative complications included desaturations and metabolic acidosis.

On 20Feb2005 the patient was accidentally extubated. He was mottled and cold, with poor perfusion and heart rate in 110s. He was reintubated immediately with no change in color. Eventually CPR was initiated, but the parents requested its cessation, and the patient expired.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien-------	**Randomization---------**		
SAEs	**Cardiopulmona---------- t**	**31Aug2005 - 31Aug2005**	**Definitely not related**
	Cardiopulmonary Arrest	**25Jan2006 - 25Jan2006**	**Definitely not related**

This female infant was born on ---------- with hypoplastic left heart syndrome underwent Norwood Stage 1 procedure on 25Aug2005. At that time, she was enrolled into this study.

On 31Aug2005, the infant experienced sudden unexplained cardiac arrest requiring ECMO. Cauterization showed no anatomy inoculi nor evidence of thrombus.

On 29Sep2005 the patient was taken to the OR for placement of a percutaneous gastrostomy feeding tube for severe gastroesophgeal reflux and inability to nipple feed. The surgical procedure was aborted due to the patient having a near cardiopulmonary arrest. The feeding tube was eventually placed on 18Oct2005and the patient was discharged home on 27Oct2005 with the assistance of biweekly home health services.

The patient was readmitted to-------on 29Oct2005 for temperature instability and increased seizure activity. The seizure medicat ------ ere adjusted and the patient was discharged on 31Oct2005. She returned for a follow-up visit on 17Nov2005 and was noted to be tolerating feeds and had no increasing cyanosis. The patient's parents reported 2-3 seizures per day. On 25Jan2006, the patient was reported having fever and noted heavy breathing, CPR was begun and EMS activated. The patient was pronounced dead.

In the opinion of the Investigator, these two events were definitely not related to the study device.

Patien-------	**Randomization ----------**		
SAEs	**Coarctation of A------ Anastomosis**	**7Feb2006 - 7Feb2006**	**Definitely not related**

This male infant was born on----------ith hypoplastic left heart syndrome underwent a Norwood Stage 1 procedure on 13Oct2----------as enrolled into this study on 12Oct2005. Recovery from Stage I was unremarkable and patient was discharged 14 days post surgery. On 6Feb2006, he had upper airway congestion, cough and weight loss and was referred to APH Urgent Care. ECG demonstrated severely decreased LV function and distal aortic arch anastomosis obstruction. On 7Feb2006, balloon angioplasty was performed to dilate the aortic arch. Aortic arch gradient decreased from 70 to 10 mmHg. Patient recovery was good but supportive care and antibiotics were continued for cough with upper airway congestion and positive sputum cultures. The patient was discharged to home on 10Feb2006.

In the opinion of the Investigator, this event was definitely not related to the study device.

Patien-------	**Randomization ----------**		
SAEs	**Mild Respiratoo---------- ss with Oxygen desaturations**	**3Dec2005 – 17Dec2005**	**Definitely not related**
	Cardiopulmonary Arrest	**27Mar2006 – 27Mar2006**	**Definitely not related**

This male infant was born on ----------, with heterotaxy syndrome, complete AV canal, interrupted inferior vena cava, pulmonary atresia and complete heart block. He had a pace maker placed for his complete heart block on the date of birth and a modified B-T shunt performed on 18Nov2005. At that time he was enrolled into this study.

The patient was weaned from the ventilator and oxygen slowly since surgery and required reintubation on 24Nov2005. He was extubated on 26Nov2005. Since then he required frequent supplemental oxygen when agitated or feeding to maintain his oxygen saturation greater than 70%. On 9Dec2005, the patient was taken to the cath lab for a diagnostic catheterization to rule out cardiac reasons for his continued oxygen desaturations. The results showed a patent B-T shunt without stenosis and no evidence of aortic insufficiency. His cardiac hemodynamics were considered acceptable for an infant with complex congenital heart disease. The patient was followed in the ICU to improve pulmonary function and to maintain oxygen saturation greater than 70%. The patient was discharged on 29Dec2005.

The patient had his routine follow up visits on 12Jan2006, 9Feb2006 and 9Mar2006 and had a pacemaker evaluation on 23Feb2006 with report of excellent function.

On 27Mar2006, the patient reportedly had been in a good state of health, recovering from a recent upper respiratory infection and had no cyanosis. After feeding, the patient became cranky and spit up a small amount of formula. He was then bathed without incident and was playful. After being put into his crib to go to sleep, his mother heard a high pitched yelp along with crying. The patient became rigid and stopped breathing. CPR was begun and EMS activated. Patient could not be resuscitated and was pronounced dead on the ER.

In the opinion of the Investigator, these two events were definitely not related to the study device.

Patien--------	**Randomization----------**		
SAEs	**Narrowing of Aortopulmonary Shunt**	**9Jan2006 – 10Jan2006**	**Definitely not related**
	Mediastinitis	**20Jun2006 – 22Jun2006**	**Possibly related**

This female infant was born on---------- with a diagnosis of single ventricle with double inlet left ventricle. The patient was enrolled into the study on 28Dec2005. She went to OR on 30Dec2005 for Stage 1 modified Damus-Kaye-Stansel reconstruction, atrial septectomy and placement of a systemic pulmonary artery shunt. Her chest was closed on 31Dec2005.

On 9Jan2006, the patient was noted to have decreased oxygen saturations to 50-60%, echosonography showed a minimal waist or narrowing at the insertion point of the systemic/pulmonary shunt. Heparin therapy and oxygen were started. On 10Jan2005, a stent was placed in the narrowing of her shunt, oxygen saturation stabilized within 24 hours of the procedure.

On 15Jun2006, the patient returned for stage 2 palliation (Bidirectional Glenn shunt). The surgery and immediate post-operative period were uneventful and she was moved to the Peds Special Care Unit on 20Jun2006. Serous drainage was noted from her sternal wound on 19Jun2006 (~25 weeks post randomization and 4 days after 2nd procedure) and cultures were positive for *Staphyolcoccus aureus.* The patient was started on vancomycin and cefepime. Drainage from the sternotomy wound increased, C-Reactive protein was elevated and CBC differential showed increased bands, the patient was also irritable. A mediastinal exploration was performed on 20Jun2006.

The chest and sternum were reopened and the mediastinum was irrigated and debrided. The chest was closed on 22Jun2006, the patient was stable and antibiotic therapy continued.

In the opinion of the investigator, this mediastinitis was possibly related to the study device and the narrowing of aortopulmonary shunt was definitely not related to the device.

Patien-------	**Randomization----------**		
SAEs	**Cardiopulmon---------- t**	**17Jan2006 – 17Jan2006**	**Definitely not related**
	Post-Pericardiotomy Syndrome	**3Feb2006 – 7Feb2006**	**Definitely not related**

This male infant born on---------- was diagnosed with double outlet right ventricle and subpulmonic VSD on 13Ja---------- Jan2006, the patient went to OR for pulmonary artery (PA) banding and Blalock Taussig (B-T) shunt. At that time he was enrolled into this study.

The patient deteriorated on 17Jan2006 with subsequent cardiopulmonary arrest. The chest was opened and the patient was successfully resuscitated. The patient was discontinued from the study due to disturbance of the operative site. The chest was closed on 18Jan2006. He had uneventful recovery and was transferred to ICU on 31Jan2006.

On 4Feb2006, the patient was readmitted with decreased saturations (low 70s) and tachypnea. ECG and chest CT showed fluid in mediastinum and posteriorly around his heart. Antibiotic treatment was started on 3Feb2006. All subsequent wound cultures were negative. On 7Feb2006, the patient was taken to OR for needle drainage of 35 cc of serosanguinous fluid. His wound was healing with no inflammation or drainage noted.

The patient was withdrawn from the study because chest reopening disqualified him from further evaluation (surgical site disturbed). In the opinion of the Investigator, these two events were definitely not related to the study device.

Patien--------	**Randomization----------**		
SAEs	**Hypotension, B---------- ia**	**18May2006 – Ongoing**	**Definitely not related**
	Right Lower Extremity Ischemia	**25May2006 – 27Jun2006**	**Definitely not related**
	Hypoxia	**25May2006 – 2Jul2006**	**Definitely not related**

This male infant was born o----------ith hypoplastic left heart syndrome with intact atrial septum underwent stage I pall---------- ith a right ventricle to pulmonary artery shunt, removal of left ventricular thrombus and partial resection of left ventricular endocardial fibroelastosis on 27Dec2005. At that time, he was enrolled into this study.

The patient was admitted to the hospital on 15May2006 for a planned pre-Glenn echo, cardiac catheterization and Glenn surgery; both procedures are standard clinical care. Preoperatively, he was noted to have poor right systemic ventricular function by ECG. On 16May2006, he underwent cardiac catheterization, which demonstrated severe left pulmonary artery stenosis, hypoplastic right pulmonary artery and severe endocardial fibroelastosis. Cardiac MRI showed what appeared to be a thrombus in the LV.

On 17May2006, the patient underwent take down of his RV to PA conduit, central pulmonary artery plasty with autologous glutaraldehyde-treated pericardium extending into the LPA, bi-directional Glenn connection, excision of LV thrombus, with resection of EFE and mitral valvotomy. On 18May2006, the pressure in his left atrial line increased, and he became hypotensive and bradycardic. The patient's chest was opened when his heart rate and blood pressure could not be sustained without repeated doses of epinephrine and chest compressions. He was successfully placed on ECMO support.

While on ECMO support the patient 's ventricular function appeared to improve but attempts to wean him from the ECMO circuit were unsuccessful due to hypoxemia. On 25May 2006, he underwent a hemodynamic cardiac catheterization and balloon dilation along the length of the left pulmonary artery (LPA). On 27May2006 he had an insertion of modified Blalock-Taussig shunt to improve his pulmonary blood flow and gas exchange. The patient was weaned from ECMO support in the OR, his hypoxia resolved at the time of his extubation on 2Jul2006.

On 27May2006, the patient developed suspected arterial thromboemboli to the lower extremities.

The patient's right leg appeared ischemic with a demarcation line mid-thigh; pulses were not obtained via Doppler. All HITT screens came back negative. The patient has been found to have an unusual coagulatiopathy with lupus anticoagulane and probable antithrombin antibody. Doppler ultrasounds on June 8th and 9th revealed that the right external iliac artery and common femoral artery are patent, but the superficial femoral artery is obliterated immediately distal t its origin. The patient underwent amputation of the right lower extremity at the mid-proximal thigh level on 18Jun2006. He further underwent stump wound closure with a split thickness skin graft on 27Jun2006 and tolerated his surgical procedures well.

In the opinion of the Investigator, all three events were definitely not related to the study device.

Patien---------	**Randomization----------**		
SAEs	**Respiratory Fai------**	**15Feb2006 – 15Feb2006**	**Probably not related**

This female infant was born on ----------with hypoplastic left heart syndrome and underwent stage I Norwood procedure with Blalock Taussig Shunt on 13Jan2006. She was enrolled into this study on 17Jan2006. The patient was discharged on 27Jan2006.

On 15Feb2006 the patient experienced difficulty in breathing at home. Her parents called 911 and began CPR at the time of patient's respiratory and cardiac arrest. Patient was unable to be resuscitated in the emergency room. In the opinion of the Investigator, this event was probably not related to the study device.

Patient--------	**Randomization----------**		
SAEs	**Suspected Necr---- ----------Enterocolitis**	**29Jan2006 – 7Feb2006**	**Probably not related**

This female infant was born on----------with a hypoplastic left heart syndrome and underwent stage I palliative procedure on 23Jan2006. At that time, she was enrolled into this study. Her chest was closed on 26Jan2006.

On 29Jan2006, the patient developed heme positive stools and abdominal distention. She was started on a 5-day course of prophylactic intravenous antibiotics and oral feedings were withheld. On 2Feb2006, the patient's with heme positive stools continued, intravenous antibiotics were prolonged to a 10-day course as a standard precaution for necrotizing entericolitis. This event resolved with no sequelae on 7Feb2006.

In the opinion of the investigator, this event was probably not related to the study device.

11.3.3.2. The Non-Treatment Control

Patien-------	**Randomization----------**		
SAEs	***Staph epidermid-* -------- emia**	**30Mar2004 – 19Apr2004**	**Probably not related**

This female infant was born on----------with DiGeorge Syndrome and congenital heart disease

that was treated by unifocalization of discontinuous pulmonary arteritis and with placement of a RV to RA conduit using 6mm ringed Gore-Tex graft on 5Mar2004. At that time, she was enrolled into this study. The patient was discharged home on 18Mar2004.

On 30Mar2004, the patient was readmitted to the hospital following a 2-day history of bloody stools and a questionable apnea episode. Blood culture was positive for *Staph epidermidis*; and the patient was placed on antibiotics. Bloody stools resolved, and the patient was discharged on 5Apr2004 with continued antibiotic therapy through 19Apr2004.

In the judgment of the investigator, the *Staph Epidermidis* Septicemia was probably not related to the study device.

Patient--------	**Randomization----------**		
SAEs	**Patient Coded a----------**	**13Feb2005 – 27Feb2005**	**Definitely not related**
	Reopened and Placed ECMO		

This male infant was born on----------with hypoplastic left heart syndrome, aortic atresia, and mitral stenosis. He underwe----------d procedure on 20Jan2005, with Sano modification and placement of REPEL-CV. On 13Feb2005 he had hypotension which was treated with fluid boluses and calcium chloride. After the third bolus, he experienced bradycardia and CPR was initiated. Attempted cannulation via the neck was unsuccessful. The chest was opened and the patient was placed on ECMO.

The patient was withdrawn from the study because reopening of the chest disqualified him from further evaluation (surgical site disturbed). In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patient-------	**Randomization----------**		
SAEs	***Staph epidermidis* Infection in Chest Wound**	**21Jun2005 – 8Jul2005**	**Probably not related**
	Sternal Wound Dehiscence	**29Jun2005 – 2Sep2005**	**Probably not related**

This female infant was born on---------- with double outlet right ventricle, ventricular septal defect and hypoplastic left ventricle underwent a pulmonary artery banding procedure. At that time, she was enrolled into this study following pediatric cardiothoracic surgery.

On 21Jun2005, the patient developed an infection in the chest wound and was treated with intravenous antibiotics. On 29Jun2005, the patient's chest incision was opened and needed debridement; dressing changes were started and a plastic surgeon closed the chest.

In the judgment of the investigator, the *Staphylococcus epidermidis* infection in the chest wound and sternal wound dehiscence were probably not related to the study device.

Patien------	**Randomization----------**		
SAEs	**Respiratory Di-------**	**4Jan2004 – 2Feb2004**	**Definitely not related**

This female infant was born on ----------with tetralogy of Fallot and pulmonary atresia. On 10Dec2003 she underwent the placement of a Blalock-Taussig shunt, reapproximation of branch pulmonary arteries and ligation of bilateral ducti. At that time, she was enrolled into this study. The postoperative course was complicated by tachycardia and hypotension post chest closure, respiratory distress following extubation requiring nasal CPAP X 24hr, feeding intolerance and hypoxia. The patient was discharged home on 2Jan2004 (POD#23) on NG feeds and 1/4L O_2 via nasal cannula.

On 4Jan2004, the patient was readmitted for respiratory distress and an increased O_2 requirement. An echocardiogram revealed patency of the shunt. Respiratory specimens for bacterial and viral culture were negative. The patient continues to have an oxygen requirement but is back down to her discharge O_2 level. In addition, the patient tested positive for Di George syndrome.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patient-----	**Randomization----------**		
SAEs	**Desaturation**	**1Feb2005 – 4Feb2005**	**Definitely not related**

This female infant was born on---------- with double outlet right ventricle, pulmonary atresia, transposed great vessels, large ----------ricular septal defect, atrial septal defect, pulmonary coarctation, and patent ductus arteriosus. On 26May2004, she underwent 4mm right modified Blalock-Taussig shunt, ligation of patent ductus arteriosus, ligation and division of main pulmonary artery, and pericardial patch arterioplasty of pulmonary coarctation.

On 1Feb2005, the patient underwent previously noted procedure, post bypass she was noted to have oxygen saturations in the high 70s to low 80s. Bypass was recommended for repositioning of the ventricular septal defect patch. She was then weaned from cardiopulmonary bypass with brief improvement in oxygen saturations to the 90s. She was transported to the ICU where she remained desaturated.

Echocardiogram performed the following day indicated possible communication between the atria. Further evaluation with cardiac catheterization revealed a large communication between the atria and systemic pulmonary artery pressures with elevated right ventricular pressure. She underwent a bidirectional Glenn procedure and closure of the atrial septal defect on 4Feb2005. She returned to the ICU 100% saturated.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien-----	**Randomization----------**		
SAEs	**Wound Infecti---**	**14May2005 – 27Jun2005**	**Probably not related**

This male infant was born on ----------with a diagnosis of hypoplastic left heart syndrome. He underwent a Norwood proced---------- o modification (#5mm Gore-Tex shunt) and ligation of a

patent ductus arteriosus. At that time he was enrolled into this study.

The patient experienced an uneventful postoperative course and was discharged home on 10May2005. He did well until the morning of 14May2005, when he developed a fever of 38.9 degrees rectally. He was taken to the emergency room and noted to be febrile with a reddened area mid-sternotomy. Blood cultures were drawn, and the patient was placed on vancomycin, ampicillin and cefotoxime. The following day an infectious disease consult was obtained and antibiotic therapy adjusted. The vancomycin and ampicillin were discontinued and clindamycin was started along with rifampin. Blood cultures were found to be positive with methicillin sensitive *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and positive mucoid lactose producing gram negative rods. On 16May2005, the cefatoxime was discontinued and he was started on piperacillin and tazobactam. Vancomycin therapy was resumed on 17May2005. Echocardiogram was performed to evaluate for the presence of vegetations and was found to be negative. At the time of this report, the patient was afebrile with no growth from blood cultures and on vancomycin, piperacillin/tazobactam and rifampin therapy.

In the opinion of the investigator, this event was probably not related to the study device.

Patient ----	**Randomization----------**		
SAEs	**Desaturation re----------~~7Oct~~2005 – 7Oct2005**		**Definitely not related**
	reopening of the chest		

This female infant was born on---------- with congenital heart disease and underwent placement of a systemic to pulmonary artery shunt with ligation and division of patent ductus arteriosus and pulmonary arterioplasty on 7Oct2005. This was done with cardiopulmonary bypass. At the end of the procedure the patient was randomized into the study and the chest was closed in the routine fashion.

Upon complete closure of the chest, the subject experienced decrease in oxygen saturations to the 70s; this persisted despite the initiation of nitric oxide. The decision was made to reopen the chest and the oxygen saturations improved to the 80s. The surgical investigation site was not disturbed. A silastic skin patch was placed and the subject was taken to the pediatric intensive care unit in stable condition. Chest closure occurred on 13Oct2005 subject was discharged on 22Oct2005, having recovered completely.

The patient was withdrawn from the study because chest reopening disqualified her from further evaluation. In the opinion of the investigator, this event was definitely not related to the study device.

Patien----	**Randomization----------**		
SAEs	**Cardiac Arrest**	**27Mar2006 – 27Mar2006**	**Definitely not related**
	Desaturation	**6May2006 – 6May2006**	**Definitely not related**
	Cardiac Arrest	**17May2006 – 17May2006**	**Definitely not related**

This male infant was born on---------- with hypoplastic left heart syndrome and I/VI continuous

shunt murmur, right upper sternal border and along sternal border. He underwent Norwood procedure Sano modification with #5 mm gortex shunt and silastic skin patch. The patient was randomized into the study on 26Jan2006.

On 27Mar2006, the infant experienced a bradycardic episode that lead to cardiac arrest and reintubation. Compression was performed and he was given propranolol and digoxin. Echo performed after arrest revealed decreased function and the previous medications was discontinued and patient started on milrinone and dopamine.

On 6May2006, the patient was reported pulseless and a code was called, upon transit to x-ray he became apneic, cyanotic and desaturated to 30% on 4 Liters nasal cannula. Chest compressions were performed (~2minutes), epinephrine and calcium boluses were given which increased his heart rate to 50-60. Atropine was given with return of heart rate to baseline. The patient was taken to the PICU and intubated, Echo revealed severe tricuspid valve regurgitation and moderate to severe global dysfunction.

On 17May2006, the infant's heart rate dropped to 40 requiring chest compression (5minutes). He was asystolic for a short period of time. During the code, he was intubated and received epinephrine and atropine. After heart rate returned to baseline, the patient had a period of hypotension requiring multiple fluid boluses and was restarted on dopamine and dobutamine.

In the opinion of the investigator, all three events were definitely not related to the study device.

Patien-------	**Randomization----------**		
SAEs	**Shunt Insufficie-----**	**13May2004 – 15May2004**	**Probably not related**

This female infant was born on ---------- with hypoplastic left heart syndrome. She underwent stage 1 Norwood palliation and---------- ed home where she did well.

She was admitted to her local hospital with episodes of hypoxia consistent with shunt insufficiency. On 14May2004, she was transferred to Duke University hospital for evaluation. The following day she experienced a cardiac arrest secondary to hypoxia which required extensive medical management. She was taken to the operating room for emergency revision of the shunt. Following surgery, she was returned to the ICU where she developed complications related to the preoperative cardiac arrest. She expired on 15May2004.

In the judgment of the investigator, the serious adverse event was probably not related to the study device.

Patient--------	**Randomization----------**		
SAEs	**Neoaortic Valv----------ncy**	**1May2005 – 1May2005**	**Definitely not related**

An 18-day-old male infant with complex heart disease, hypoplastic left heart syndrome, status post Norwood with Sano modification procedure on 28Apr2005. After chest closure on 1May2005, he presented with persistent lactic acidosis. A transthoracic ECG was performed which suggested

severe neoaortic valve insufficiency. A transesophageal ECG was then performed and confirmed the presence of severe neoaortic valve insufficiency. The sternum was opened, an external annuloplasty procedure was performed to improve his neoaortic valve regurgitation. The patient was extubated on 3May2005 and has shown marked improvement since.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien-------	**Randomization----------**		
SAEs	**Distal Common Bile Duct Obstruction**	**14Feb2006 – 17Feb2006**	**Definitely not related**
	Cardiac Catheterization	**23Mar2006 – 28Mar2006**	**Definitely not related**
	Wound Infection	**4Jul2006 – 8Aug2006**	**Definitely not related**

This male infant was born on----------ith hypoplastic left heart syndrome. He underwent Norwood procedure on 14Jan----------as discharged on 2Feb2006.

On 14Feb2006, patient had increasing jaundice and was admitted for evaluation. GI service work-up demonstrated distal common bile duct obstruction and possible stone. On 17Feb2006, patient noted to have lower saturates and left lung pleural effusion. He had an exploratory laparotomy, cholecystectomy, common bile duct exploration and intraoperative cholangiogram. The patient was discharged on 23Feb2006 following resolution of the obstructive jaundice.

On 23Mar2006, the patient had a cardiac catheterization with balloon dilation.

On 4Jul2006, the patient's sternotomy incision was noted red and draining and he was sent to the emergency department where one dose of antibiotic (Omnicef) was given. The patient was admitted to hospital with redness increasing and where wound cultures were obtained and patient was started on vancomycin. Wound cultures were positive for *Staphylococcus aureus* and alpha hemolytic streptococcus. Patient received a 10-day course and was discharged on 7Jul2006.

In the judgment of the investigator, these three serious adverse events were definitely not related to the study device.

Patien--------	**Randomization----------**		
SAEs	**Cardiopulmona----------t----Secondary to Heart Disease**	**29Dec2003 - 29Dec2003**	**Definitely not related**

The male infant was born on----------ith tricuspid atresia, d-transposition of the great arteries, atrial septal defect, ventricular septal defect, and patent ductus arteriosus. On 4Dec2003, he had palliative surgery (arterial switch operation, over sewing of the aorta, atrial septectomy and a Blalock-Taussig shunt). At that time he was enrolled into this study.

The subject had a prolonged hospital course involving a presumed pre-operative viral pneumonia and postoperative mechanical ventilation for 8 days. The patient was transferred to the ward on

POD #15 (19Dec2003). While on the floor he had a blood culture that came back positive for *Candida parapsilosis* and was started on IV Fluconazole. On 23Dec2003, after discussion with the referring cardiologist, the patient was transferred back to the Las Vegas facility for continued advancement of feeds as well as monitoring of his blood infection and oxygen saturations.

On 26Dec2003 the patient was discharged to home with his parents. The patient was on room air with oxygen saturations in the low to mid 70's. Discharge medications included lasix, aspirin and diflucan.

On 29Dec2003 the patient had a sudden event at home upon awakening. He was irritable, cyanotic and ultimately arrested. According to the patient's cardiologist, the patient was dead on arrival at the ER. No post mortem was ordered on the child. The cardiologist stated that the cause of death was cardiopulmonary arrest secondary to heart disease. Also of note is that the mother told the cardiologist that she had given Tylenol instead of Aspirin because she didn't have any aspirin at home (aspirin is specifically given to maintain patency of the Blalock-Taussig shunt).

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien------	**Randomization----------**		
SAEs	**Necrotizing En----------**	**27Jan2004 – 10Feb2004**	**Definitely not related**

This male infant was born on----------ith hypoplastic left heart syndrome. On 18Dec2003, he underwent a modified Norwo---------- with SANO conduit (RV-PA shunt) and was enrolled into this study.

On 28Jan2004, he presented to emergency department with a one-day history of bloody stools and no change in appetite. The patient had a hematocrit of 35 and was given a blood transfusion and admitted to the ICU. The initial KUB (kidney, ureter, and bladder) x-ray was thought to show the appearance of pneumatosis but repeat KUBs improved. The baby was presumed to have necrotizing enterocolitis and was treated as such. He was made NPO (nothing by mouth), started on TPN (total parenteral nutrition), and placed on triple antibiotic IV therapy.

During hospitalization, he required a second blood transfusion, but continued to have heme-negative stools. After a 10-day course of TPN, and triple antibiotics, the patient was restarted on feeds. He did well on the feeds and advanced to full strength breast milk.

With clearance from both GI and Cardiology services, the baby was discharged home. During a follow-up appointment on 13Feb2004, the baby was evaluated and found to be stable and feeding well without difficulty. He had a slight URI, and the guardian was instructed to call the cardiothoracic nurse practitioner, pediatrician, or cardiologist if he experienced any respiratory distress.

In the judgment of the investigator, the serious adverse event was definitely not related to the study

device.

Patien------	**Randomization ----------**		
SAEs	**Desaturation**	**31Mar2004 – 4Apr2004**	**Definitely not related**

This male infant was born on---------- with hypoplastic left heart syndrome. He underwent Sano Norwood repair on 2Feb20----------d by chest closure on 6Feb2004. On 31Mar2004, he presented to the clinic with oxygen saturation of 73% on room air. ECHO showed the conduit to be working well with a gradient of 40 at the anastamosis. He was sent home with a follow up appointment the next day, when his saturations were found to be 68%. He looked fussy and cyanotic with symptoms of a URI and was admitted for observation.

Intermittent oxygen was administered during episodes of desaturation. He was weaned off the oxygen and became stable on room air. On 4Apr2004, the patient was discharged to home. In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien----	**Randomization----------**		
SAEs	**Gastroesophag----------**	**12Apr2004 – Jun2004**	**Definitely not related**

This male infant was born on ---------- with hypoplastic left heart syndrome and right clavicular fracture at birth. The infant al---------- nged prothrombin time, partial thromboplastin time, low factors V, VII and X. Hematology consult done and vitamin k was given (x3). On 16Mar2004 he was enrolled into the study.

The infant had reflux event pre-randomization. On 12Apr2004, the infant experienced severe gastroesophageal reflux necessitating feeding tube placement. The event was considered recovered until June. In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien------	**Randomization----------**		
SAEs	**Septicemia**	**23Aug2004 – 31Aug2004**	**Definitely not related**
	Deep Vein Thrombosis	**6Oct2004 – 12Oct2004**	**Definitely not related**
	Seizure	**7Oct2004 – Ongoing**	**Definitely not related**

This male infant was born on ---------- ith hypoplastic left heart syndrome and underwent a Sano modification of Norwood----------0Jul2004. At that time he was enrolled into the study.

On 23Aug2004, the infant had fever (greater than 101°F / 38°C) was hospitalized and found to have septicemia.

On 6Oct2004, the patient had thrombus formation, hemodynamic instability requiring inotropic support.

On 7Oct2004, the patient had a seizure and phenobarbital (16.2mg daily) was given orally to manage seizure activity.

In the judgment of the investigator, these serious adverse events were definitely not related to the study device.

Patient------	**Randomization----------**		
SAEs	**Recurrent Coar---------- the Aorta**	**23Jun2005 – 24Jun2005**	**Definitely not related**
	Dehydration	**23Jun2005 – 24Jun2005**	**Definitely not related**

This two and a half-month-old male infant with hypoplastic left heart syndrome underwent Norwood procedure on 3Mar2005. Sternal closure was performed on 6Mar2005. At that time, the patient was enrolled into this study.

This patient presented to his cardiologist with a 2-3 day history of feeding intolerance, reduced oral intake, increased cyanosis and non-productive cough, low-grade fever, emesis and rash consistent with scabies. An echocardiogram demonstrated coarctation of the aorta, the patient was started on dopamine, intubated and hospitalized on 23Jun2005 for further management.

The patient was hydrated started on a milrinone drip and antibiotics to rule out sepsis. A repeated echocardiogram confirmed coarctation of the aorta and demonstrated severe global ventricular dysfunction. On 25Jun2005, the patient went for balloon dilatation with post-cath gradient of 20 mm Hg down from 63 mm Hg. He was kept on dobutamine which was weaned off on 28Jun2005. The patient was extubated to vapotherm on 27Jun2005. Repeat echocardiogram on 29Jun2005 showed persistent but only moderate global dysfunction and slight increase in gradient to 29 mm Hg (discrete narrowing).

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patient-----	**Randomization----------**		
SAEs	**Low Cardiac Output**	**4Oct2004 – 5Nov2004**	**Definitely not related**

This female infant was born on ---------- with hypoplastic left heart syndrome, which was treated with a Norwood procedure. On 7May2004, the patient was enrolled into this study. She was not a candidate for Hemi-Fontan due to poor right ventricular function. She had gone to the OR on 26Oct2004 for revision of the aortopulmonary shunt and repair of the tricuspid valve. She was unable to wean from bypass and was placed on ECMO. She was unable to be weaned from ECMO, and on 4Nov2004, she returned to the OR for tricuspid valve replacement and revision of the shunt. Following the procedure, she sustained a cardiac arrest and could not be resuscitated. She expired on 5Nov2004, secondary to post operative complications.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patient------	**Randomization # 09-02**		
SAEs	**Right Pleural Effusion**	**18Nov2004 – 19Nov2004**	**Definitely not related**
	Cardiac Arrest	**7Dec2004 – 7Dec 2004**	**Definitely not related**

This male infant was born on---------- with hypoplastic left heart syndrome with an intact atrial septum diagnosed in utero. He underwent a radio-frequency ablation of his atrial septum at birth. One week later, on 10Nov2004, he underwent a hybrid procedure (PA bands and PDA stent) and was enrolled into this study. Other than a pneumothorax, all post-op complications were as described as expected in the protocol.

On 18Nov2004, the patient developed a right-sided pleural effusion requiring placement of a chest tube to drain. The event was considered resolved on the next day.

On 7Dec2004, he had a cardiac arrest resulting in death.

In the judgment of the investigator, the two serious adverse events were definitely not related to the study device.

Patient-------	**Randomization----------**		
SAEs	**Gastroenteritis**	**8Oct2004 – 12Oct2004**	**Definitely not related**

This male infant was born on ---------- with hypoplastic left heart syndrome. He underwent Norwood repair.

On 8Oct2004, the infant was admitted for intravenous fluid therapy for gastroenteritis. He recovered fully.

In the opinion of the Investigator, this event was definitely not related to the study device.

Patient------	**Randomization----------**		
SAEs	**Death Resulting from Removal of Life Support**	**7Mar2004 – 7Mar2004**	**Definitely not related**

This male infant was born on---------- with hypoplastic left heart syndrome, tracheo-esophageal fistula, tracheo-bronchiomalacia, horseshoe kidney, and CHARGE syndrome. He was treated by repair of the T-E fistula and Norwood procedure. The patient was enrolled into this study on 11Feb2004.

The infant experienced pulmonary hypertension, but recovered postoperatively with excellent cardiac and pulmonary function. However, he had much difficulty being weaned from the ventilator support due to his tracheomalacia. The parents refused tracheostomy and requested withdrawal of all life support due to his significant visual and hearing deficits. The patient expired on 7Mar2004.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patient-----	**Randomization----------**		
SAEs	**Severe Illness Ending in Death**	**18Mar2005 – 18Mar2005**	**Definitely not related**

This female infant was born on----------with dextrocardia, double outlet right ventricle, complete atrial ventricular canal, s----------nosis and transposition of the great arteries. A B-T shunt was performed. The patient was enrolled into this study on 13Sep2004.

The postoperative course was complicated by multiple problems with compliance. The subject did not return for follow-up. On 18Mar2005, the subject became ill, and the mother took her to the children's hospital in Juarez, Mexico. There she expired from what were believed to have been heart-related problems.

In the opinion of the Investigator, this event was definitely not related to the study device.

Patient-------	**Randomization---------**		
SAEs	**Necrotizing Enterocolitis**	**25Mar2005 – 25Mar2005**	**Definitely not related**

This male infant was born on----------with hypoplastic TV and RV; TGA; PDA; hypoplastic transverse aortic arch and coa---------- ed by Blalock-Taussig shunts. The patient was enrolled into this study on 6Mar2005.

He developed necrotizing enterocolitis and ischemia of the small bowel and stomach following gastrostomy tube placement and fundal plication. He died due to the abdominal pathology on 25Mar2005.

In the judgment of the investigator, the serious adverse event was definitely not related to the study device.

Patien--------	**Randomization----------**		
SAEs	**Allergic Colitis**	**16Nov2005 - -20Nov2005**	**Probably not related**
	Influenza A / Bronchiolitis	**27Feb2006 – 4Mar2006**	**Probably not related**
	Septicemia / CHF	**27Mar2006 – 17Apr2006**	**Probably not related**
	Dehydration / Gastroenteritis	**20Apr2006 – 27Apr2006**	**Probably not related**

This six-month-old male patient with a history of atrioventricular canal with double outlet right ventricle and hypoplastic aortic arch also had hypothyrodism, Trisomy 21 and chronic congestive heart failure. The patient was status post Norwood procedure and also had a left hemidiaphragm plication due to paralysis. The patient enrolled into this study on 30Sep2005.

The patient was admitted to----------on 16Nov2005 due to an increase in the amount of blood in his stool. The final diagnosis was allergic colitis. Patient was kept NPO; a Flexible Sigmoidoscopy was performed and showed inflammation in the colon. All cultures were negative for growth. Patient was switched to Neocate formula.

On 27Feb2006, the patient was hospitalized due to cough, congestion and fever. The patient tested positive for Influenza A and was diagnosed with bronchiolitis and treated with albuterol, atrovent and oxygen.

The patient was admitted on 27Mar2006 for routine cardiac catheterization. The patient has since tested positive for rotavirus and had positive fecal occult blood. The patient demonstrated hyperactive bowel sounds, flatus, diarrhea, oliguria and has been pale. Patient's IV fluids have been increased to a total of 1.5 maintenance. The patient's symptoms resolved completely and he was discharged home on 17Apr2006.

The patient was admitted to---------- --------ue to a 3-day history of emesis, loose stools and decreased urine ---------- ---------- g by mouth and was given IV fluids. All stool studies were negative. The patient's urine input and output was monitored along with his daily weight. The patient fully recovered and was discharged from the hospital on 27Apr2006.

In the opinion of the Investigator, all four events were probably not related to the study device.

Patient----	**Randomization----------**		
SAEs	**Abdominal Distention**	**20Jun2004 – 21Jun2004**	**Definitely not related**
	Cardiopulmonary Arrest/Death	**28Jul2004 – 28Jul2004**	**Probably not related**

This male infant was born on----------with significant congenital heart disease consisting of pulmonary atresia with ventricular septal defect. He underwent placement of a right Blalock-Taussig shunt on 22Apr2004 and at that time was enrolled into this study. Postoperatively, he continued to show symptoms of pulmonary overcirculation with multiple failed extubations, which necessitated ligation of patent ductus arteriosus on 30Apr2004. His postoperative course was complicated by seizures, thought due to hyperglycemia. He also had suspected necrotizing enterocolitis for which he received triple antibiotics for one week.

On 20Jun2004, the infant's abdomen became distended and his respirations increased following a feeding of Enfamil-Neutramigen instead of his usual Progestimil. He was admitted and made NPO. A nasogastric tube was inserted and attached to suction. The following day the NG tube was removed and the patient was started on Pedialyte. His diet was advanced as tolerated, and he was discharged on 21Jun2004.

On 28Jul2004, he was found to be unresponsive. CPR was initiated by the parents, and then continued by EMS while he was transported to the emergency room. He was intubated and given epinephrine X 3 and atropine. Attempts to resuscitate were unsuccessful.

In the judgment of the investigator, the abdominal distension serious was definitely not related to the study device and the cardiopulmonary arrest probably not related to the study device.

Patient----- SAEs	**Randomization---------- Cyanosis with Decreased PO Intake**	**7Nov2004 – 12Nov2004**	**Definitely not related**
	Cyanosis	**4Dec2004 – 6Jan2005**	**Definitely not related**
	Respiratory Distress	**15Jan2005 – 23Jan2005**	**Definitely not related**
	Fever	**28Jan2005 – 31Jan2005**	**Definitely not related**
	Hypoxia	**4Feb2005 – 11Apr2005**	**Definitely not related**

This female infant was born on ----------with double outlet right ventricle, hypoplastic right ventricle, ventricular septal defe---------- ---sition of the great arteries. She underwent Damus-Kaye-Stansel procedure and right Blalock-Taussig shunt on 26Sep2004. She also had a history of right pelvic kidney and gastrointestinal reflux.

The patient developed feeding problems, decreased urinary output, lethargy, and periorbital edema. She vomited twice prior to admission, but had no history of reflux, diarrhea, fever or contact with sick individuals. Echocardiogram was performed on 7Nov2004. The infant's PO intake and electrolyte status were monitored. Stool cultures were negative, and the patient was discharged.

While traveling out of state, the patient became irritable, febrile, and was feeding poorly. She was admitted to a hospital in Texas on 4Dec2004. She was found to have meningitis and was treated with vancomycin and ceftriaxone. She was transferred to the University of Michigan hospital on 4Jan2005. Cardiac catheterization was performed on 6Jan2005. The patient was discharged.

On 15Jan2005, the patient presented to the ER with a 3-day history of rhinorrhea, fever of 100.2^0F, vomiting, cough, and loose watery stool. Blood and urine cultures, RSV and flu washes were negative. Ultrasound of the neck to assess facial swelling was negative, and she was discharged on 23Jan2005.

She had two immunizations on 27Jan2005 and on 28Jan2005, the patient presented to the ER with a fever of 101° F, cyanosis, decreased appetite and fussiness. Blood and urine cultures were negative. The patient was treated with ceftriaxone and discharged on 31Jan2005.

On 4Feb2005 the infant was hospitalized due to mild hypoxia. A septic workup showed positive culture for respiratory syncytial virus (RSV), the patient was started on antibiotics and began doing better. On 12Feb2005, infant had increased wheezing and coughing, chest X-ray was positive for atelectasis. On 13Feb2005, infant intubated for respiratory failure. On 20Feb2005, the blood culture was positive for gram positive *Streptococcus agalactiae*, the infant started vancomycin. On 2Mar2005, the infant extubated and negative for all cultures.

On 8Mar2005, she was doing well on room air but ENT consulted for stridor/hoarseness and received decadron for severe tracjobronchiomalasia with hypomobile vocal cords on 9Mar2005. On 11Mar2005, the infant began desaturating with wheezing and was transferred back to PICU and re-intubated on next day. The following day cardiac catheterization was performed; the BT shunt was not visualized off the right carotid questionable thrombosis. She was transferred to OR for re-sternotomy, central shunt and bilateral pulmonary artery angioplasty and started on a broad-spectrum

antibiotic. The infant was extubated on 17Mar2005 and inotropes being weaned. Infant showed improvement but remained on the cardiology floor as of 25Mar2005.

In the judgment of the investigator, all five serious adverse events were definitely not related to the study device.

---	**Randomization**---		
---	**Shunt Occlusion and Revision**	**29Jul2005 – 30Jul2005**	**Definitely not related**
	Complete Cadiopulmonary Arrest	**4Sep2005 – 4Sep2005**	**Definitely not related**

This male infant was born on--- with Shone's complex. He underwent a Norwood Stage 1 procedure. On16Jun2005 he was enrolled into this study.

On 29Jul2005, the patient underwent a Nissan fundal plication for gastroesophageal reflux disease (GERD). At the time of abdominal closure, the patient experienced an acute episode of desaturation and was placed on cardiopulmonary support. He was found to have cardiopulmonary shunt occlusion and was taken to the Cardiac Cath Lab where a complete thrombosis was confirmed. The shunt was reopened, but the flow was inadequate. He returned to surgery for a new shunt placement the next day. The patient was discharged to home on 2Sep2005.

On 4Sep2005, the patient had a period of crying followed by cardiopulmonary arrest. Emergency medical services (EMS) activated by parents and resuscitation was attempted by EMS personnel. The patient was transferred to local Emergency Department (ED) where resuscitation attempts continued, however, the patient remained unresponsive and resuscitation discontinued.

In the opinion of the investigator, these two events were definitely not related to the study device.

Patient---	**Randomization** ---		
SAEs	**Near Respiratory/Cardiac Arrest**	**21Oct2005 - 21Oct2005**	**Definitely not related**

This male infant was born on --- with hypoplastic left heart syndrome. He underwent a Norwood Stage 1 procedure on --- , complicated by post-operative shunt-site bleeding which required a shunt revision the same day. He remained on cardiopulmonary support until 16Sep2005. His chest was closed on 19Sep2005.

The patient's condition progressed nicely and he remained clinically stable until 21Oct2005. On this date, the patient was found listless and pale in his crib. Noteworthy symptoms at this time included the patient's eyes rolling back and lip smacking. His respiratory effort rapidly deteriorated and he was emergently intubated and placed on ventilatory support. During intubation, the patient's heart rate dropped to 40. Chest compressions were begun. Epinephrine and volume expanders were also given. His condition improved with these interventions and the patient's condition progressed to stable. He was extubated and taken off ventilatory support on 24Oct2005. Due to his symptoms of

eye rolling and lip smacking, which can be significant for seizure activity in infants, an EEG was performed. Seizure activity was confirmed.

In the opinion of the investigator, this event was definitely not related to the study device.

Patient-----	**Randomization----------**		
SAEs	**Right Pulmonary Artery Stenosis**	**18May2006 – 31May2006**	**Definitely not related**
	Suprasternal Abscess	**18May2006 – 31May2006**	**Definitely not related**

This female infant was born on----------with hypoplastic left heart syndrome underwent stage I palliation procedure on 15Dec2005. At that time, she was enrolled into this study. The chest was closed on 16Dec2005. She had an uneventful post-operative course and was discharged home on 27Dec2006 and followed medically. On 18May2006, the patient was admitted to the hospital for an elective pre 2nd stage surgical palliation cardiac catheterization. She was noted to have severe right pulmonary artery stenosis during the catheterization. She remained stable post-catheterization with saturation in the 80s, and was scheduled for the Bidirectional Glenn stage II palliation to resolve her right pulmonary artery stenosis.

During the patient's pre-catheterization assessment, she was noted to have a fluid filled lesion approximately 2.5 cm in diameter over the lower sternotomy scar. The culture of aspirated exudate showed gram + cocci in clusters on 19May2006. Incision and drainage was performed on the area and the patient was placed on antibiotics and cultures were sent again. CT scan results were negative for sternum involvement and 72 hour abscess cultures were negative. The patient continued on antibiotics for prophylaxis until stage II surgery.

In the opinion of the investigator, these two events were definitely not related to the study device.

Patient--------	**Randomization ---------**		
SAEs	**Respiratory Distress**	**21Oct2005 – 24Oct2005**	**Definitely not related**
	Respiratory Distress	**3Nov2005 – 4Nov2005**	**Definitely not related**
	Pleural Effusions	**28Mar2006 – 25Jul2006**	**Definitely not related**
	Seizure	**9Apr2006 – 28Apr2006**	**Definitely not related**

An eleven-day-old female infant with hypoplastic left heart syndrome status post stage 1 Norwood palliation on 12Oct2005. On17Oct2005, she was enrolled into this study. The patient was extubated on 20Oct2005 and within hours of extubation, she experienced respiratory distress exhibited by grunting and retractions. She was treated with albuterol nebulizers and vapotherm. Patient also became acidotic with an elevated lactate level (increase 12.5 mM). Patient was reintubated on 21Oct2005 and again extubated on 24Oct2005.

On 2Nov2005, this three-week-old infant experienced increased work of breathing, tachypnea and decreased oxygen saturations. Patient received an additional dose of lasix, however, her symptoms worsened with tachycardia and respiratory rate 90-100. Patient was transferred to ICU on 3Nov2005. Symptoms improved after albumin infusion. The patient was transferred back to

cardiology on oxygen and discharged from hospital on 14Nov2005.

On 16Mar2006, this five-month-old patient underwent a planned stage II procedure. She had an uncomplicated post-operative shunt course and was discharged home on 22Mar2006. On 28Mar2006 the patient was brought to the cardiology clinic for a routine follow-up visit, and was admitted to the hospital with a 2-day history of poor feeding and a temperature of 102 degrees. A chest x-ray revealed a right pleural effusion. A pigtail catheter was placed in the right pleural space and drained 40 ml of chylous fluid upon replacement. Approximately 140 ml was drained over the following 24 hours.

She was started on prophylactic antibiotics which were discontinued when the culture results came back negative on 29Mar2006. The patient remained in-hospital with the chest tube in place to drain chylous pleural effusion until 24Apr2006. She was transferred back to the cardiac care unit on 1May2006 for respiratory distress. The event was resolved completely on 25Jul2006.

On 9Apr2006 possible seizure activity was noted, left head and eye deviation and left arm extension lasting approximately 10 seconds or less. There had been no neurological issues before this episode. The neurologist recommended an EEG and head ultrasound and started the patient on Phenobarbital. On 28Apr2006, the patient was transferred out of the ICU to the ward. There has been no further seizure activity and she continues to be successfully managed on Phenobarbital. This event has stabilized with treatment.

In the opinion of the investigator, these four events were definitely not related to the study device.

Patien----------	**Randomization----------**		
SAEs	**Hypoxia, Brady----------Arrest**	**28Jan2006 – 28Jan2006**	**Definitely not related**

This female infant was born on ---------- with hypoplastic left heart syndrome (prenatal diagnosis) and underwent stage I palliativ---------- e on 9Jan2006 a Modified Blalock Taussig Shunt. On 12Jan2006, she was enrolled into this study. She had an uneventful post-operative course and was transferred on 17Jan2006 for recovery at a local hospital. She was discharged home on 21Jan2006 with an excellent echocardiogram. The patient was brought to the emergency room on 28Jan2006 with cyanosis. While in the ER she developed profound hypoxia and had a bradycardic arrest. The local hospital team was unable to restore circulation after approximately 40 minutes of resuscitation.

In the opinion of the investigator, this event was definitely not related to the study device.

11.4. Clinical Laboratory Evaluation

11.4.1. Listing of Individual Laboratory Measurements by Patient

Laboratory test results for individual patients are presented in Data Listing 8.

11.4.2. Evaluation of Each Laboratory Parameter

Laboratory tests evaluated chemistry and hematology parameters.

11.4.2.1. 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), are summarized in Statistical Tables 27 and 28, respectively. There is no evidence of changes in laboratory values associated with treatment with REPEL-CV.

11.4.2.2. Individual Patient Changes

Data Listings 8 shows a listing of laboratory values for individual patients at screening, 3 days post-chest closure (or day of discharge) and safety follow-up visits as clinically indicated.

11.4.2.3. Individual Clinically Significant Abnormalities

All laboratory abnormalities were specified as normal if within the normal range or abnormal if outside the normal range for the chemistry and hematology parameters (Section 13.1, Statistical Tables 29 and 30, respectively). There is no evidence of more frequent clinically significant laboratory abnormalities associated with treatment with REPEL-CV.

11.5. Physical Findings and Other Observations Related to Safety

11.5.1. Observations at Second Sternotomy

Observations at the time of the Second Sternotomy are summarized for the ITT population in Statistical Table 31. 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 processe--------- tological evaluation. For the other 4 specimens: one specimen was lost (Randomizat----------; for one observation, the material was discarded by the surgeon (Randomization ----------- or two observations, there was not sufficient material to biopsy (Randomization No---------- The one control specimen was processed and evaluated. Table 18 below shows the patient randomization number and the time to observation for the available specimens.

Table 18. Samples to Pathology and Time to Observation

Patient Randomization Number	Time from randomization to obtaining specimen (2nd Sternotomy) in Months
REPEL-CV	
----------	---------- ~ 3
----------	---------- ~ 9
----------	---------- ~5.5
----------	---------- ~4
----------	---------- 0.25

[redacted]	~ 6
[redacted]	~4
[redacted]	~2.5
[redacted]	~4
[redacted]	~4
[redacted]	~ 3.5
[redacted]	~3.5
[redacted]	~4.5
CONTROL	
[redacted]	~ 6.5

Histology slides for the above 14 cases were received for hi[redacted] from the study sites and evaluated under light microscopy[redacted] consulting pathologist to SyntheMed (See Appendix 15.4).[redacted] Report is in Appendix 15.4.1 and his histological evaluation with a diagnosis and a description for the 14 cases is in Appendix 15.4.2. Finally, the pathology reports for the 14 cases as evaluated by the respective study site's pathologist is in Appendix 15.4.3.

Overall, 13 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[redacted] ty sufficient for diagnosis were identified in the one remaining case (Randomization No. [redacted]

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 to be 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.

11.5.2. Wound Healing Assessment One Month Post Second Sternotomy

Wound Healing assessments at one month post second sternotomy indicated that the sternotomy site healing appeared normal and had no infection for 91.1% (51/56) of REPEL-CV patients and 92.6% (50/54) of Control patients (Statistical Table 31). There was no significant difference between these two groups (p=0.7570).

11.5.3. 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. The summary of vital signs and the physical exam results at baseline are provided in Section 13.1 Statistical Tables 4 and 6, respectively. There is no evidence of adverse effects on vital signs or physical examination associated with treatment with REPEL-CV.

11.5.4. Concomitant Medications

Concomitant medication and common medications include medications associated with the patients' surgical procedures and clinical conditions. Data Listing 18 presents concomitant medications by individual patient. The common medications used during the study by visit are summarized in Statistical Table 7. The number of concomitant and common medications used was similar for both the REPEL-CV and control patients.

11.6. 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 ($p=0.6405$). The number of concomitant and common medications used was similar for both the REPEL-CV and control patients and there is no evidence of more frequent clinically significant laboratory abnormalities associated with treatment with REPEL-CV.

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% were patients with a single ventricle. In addition, greater than 85% of patients had their sternum left open for several days as a routine prior to closure. 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 cardiothoracic surgery.

12. Discussion and Overall Conclusions

The study has met the desired study objectives for the primary effectiveness measure. Results were established in the ITT and PP populations and confirmed for masked evaluators and key subgroups including Norwood, on bypass, and chest closure delays. Multiple prospectively defined statistical analyses were all confirmatory of significance for the ITT and PP populations. Although the standard deviation was somewhat higher than expected (leading to 74% power as opposed to the desired 80% power), the magnitude of the differences detected always exceeded the pre-defined 20% clinically meaningful difference used to plan the study as well as the 21.7% difference required

to achieve 80% power. In addition, many secondary effectiveness outcomes are also significant. The potential for bias from withdrawals, time to withdrawal, and times to second sternotomy have been ruled out as have site and site-treatment interactions.

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% were patients with a single ventricle. In addition, greater than 85% of patients had their sternum left open for several days as a routine prior to closure. 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 cardiothoracic surgery.

REPEL-CV, a bioresorbable barrier, has been shown to safely reduce the formation of post-operative cardiovascular adhesions.