

REPEL-CV

Bioresorbable Adhesion Barrier

FDA Review of P070005

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Division of Cardiovascular Devices

Office of Device Evaluation

September 19, 2007

FDA PMA Review Team

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- Epidemiology – Mingdong Zhang, M.D., Ph.D.
- Manufacturing – Mary Ann Fitzgerald
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FDA IDE Review Team

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Device Description

- Single use, bioresorbable adhesion barrier
- Designed to be resorbed in 28 days
- 52% by weight poly-lactic acid (PLA) and 47% by weight polyethylene glycol (PEG)
- Designed to prevent interconnection as a result of the fibrin bands that develop during the course of normal healing
- Typically, device used when re-operation likely

Proposed Indications for Use

- REPEL-CV is a surgical adjuvant indicated for reducing the incidence, severity and extent of post-operative adhesion formation in patients undergoing cardiac surgery via sternotomy.
- Contraindications - REPEL-CV is contraindicated in patients in whom a Ventricular Assist Device (VAD) is implanted.

Pre-Clinical Review

- Biocompatibility/Sterilization
- Mechanical/Chemical Properties
- Animal Studies
- FDA has no major concerns regarding the pre-clinical review

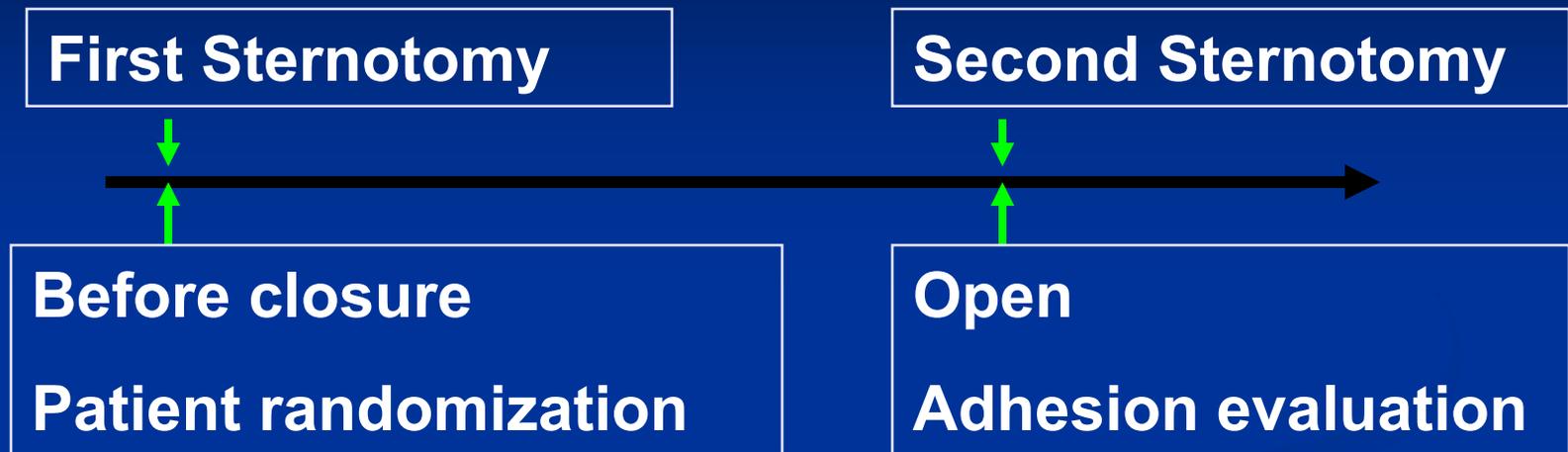
Clinical Studies

- Feasibility – 3 studies
 - Study 1 – Safety in adult patients
 - Study 2 – Safety and effectiveness in pediatric patients
 - Study 3 – Safety in OUS pediatric patients
- Pivotal - Study 4
 - Safety and effectiveness
 - 144 enrolled pediatric patients at 15 centers

Pivotal Study Design

- Neonate patients undergoing planned second surgery
- One continuous piece of the REPEL-CV is placed to the area directly below the sternotomy site
 - Placed directly over the heart, between the epicardium and the sternum
 - Not studied for placement between any pericardial surfaces
- Severity of adhesions were evaluated using grading scale 0-3 after 2nd sternotomy

Adhesion Evaluation



- Adhesion grading:

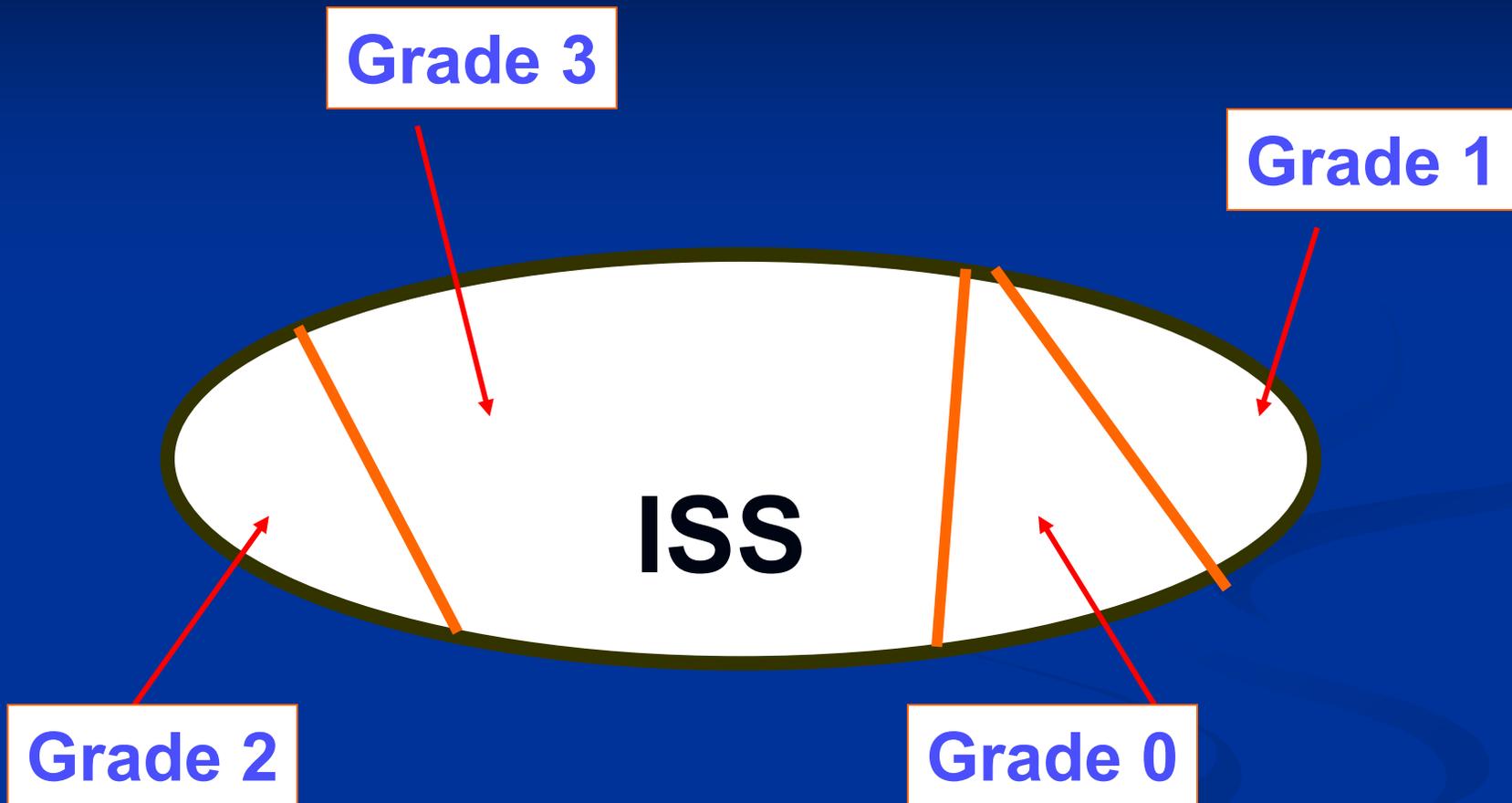
Grade 0: No adhesion

Grade 2: Moderate

Grade 1: Mild

Grade 3: Severe

Adhesion Measurement



Recording % area with grade 0, 1, 2 and 3 respectively for each patient

FDA Presentation

- Statistical Review – Yunling Xu
- Clinical Review – Wolf Sapirstein
- Epidemiology Review – Mingdong Zhang

FDA Statistical Review REPEL-CV

Yunling Xu, Ph.D.

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September 19, 2007

Outline

- Pivotal study design
- Primary effectiveness endpoint results
- Summary

Studies in the PMA

- Feasibility studies
 - S1: Randomized, controlled (adults, n=27)
 - S2: Randomized, controlled (neonates, n=13)
 - S3: Single-arm, European (neonates, n=19)
- Pivotal study (S4): Randomized, controlled, multi-center study of neonates

Pivotal Study Design

- Randomized, controlled
 - REPEL-CV vs. Standard of care
 - Randomized 1:1 at each center
- Multi-center
 - 17 centers planned
 - 15 centers actually enrolled patients

Primary Effectiveness Endpoint

- The percentage of area with grade 3 adhesion measured at the second sternotomy
- Hypotheses:

$$H_0: \mu_t \geq \mu_c \text{ vs. } H_a: \mu_t < \mu_c$$

where μ_t and μ_c represent the mean percentage of area with grade 3 adhesion for the REPEL-CV (Treatment) and Control, respectively

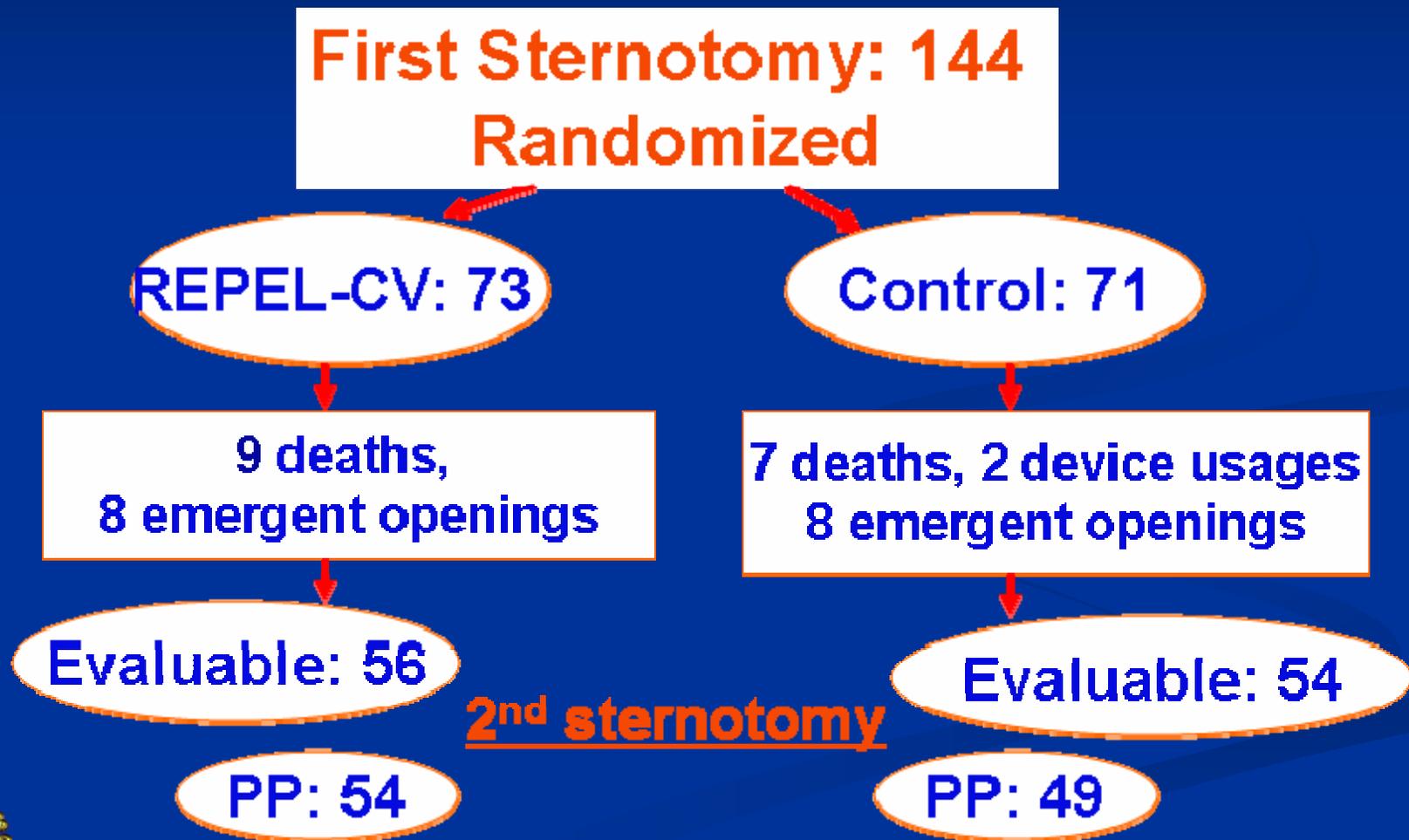
Analysis Population

- **Evaluable patients:** (Referred to as “**Intent-to-treat**” **by sponsor**): randomized patients who had the adhesion evaluation at the second sternotomy
- **Per-protocol (PP):** evaluable patients who had the second sternotomy at least 2 months after the first sternotomy and had no major protocol violations

Sample Size Estimation

- Driven by the primary effectiveness endpoint
- $\alpha = 0.025$ (one-sided), power = 80%
- Assumptions: standard deviation $SD = 35$, difference of mean $D = 20$
- Calculated sample size = 100 (50 per arm)
- Total approved study sample size = 156
 - Expected loss to follow-up = 56

Study Result: Patient Accountability

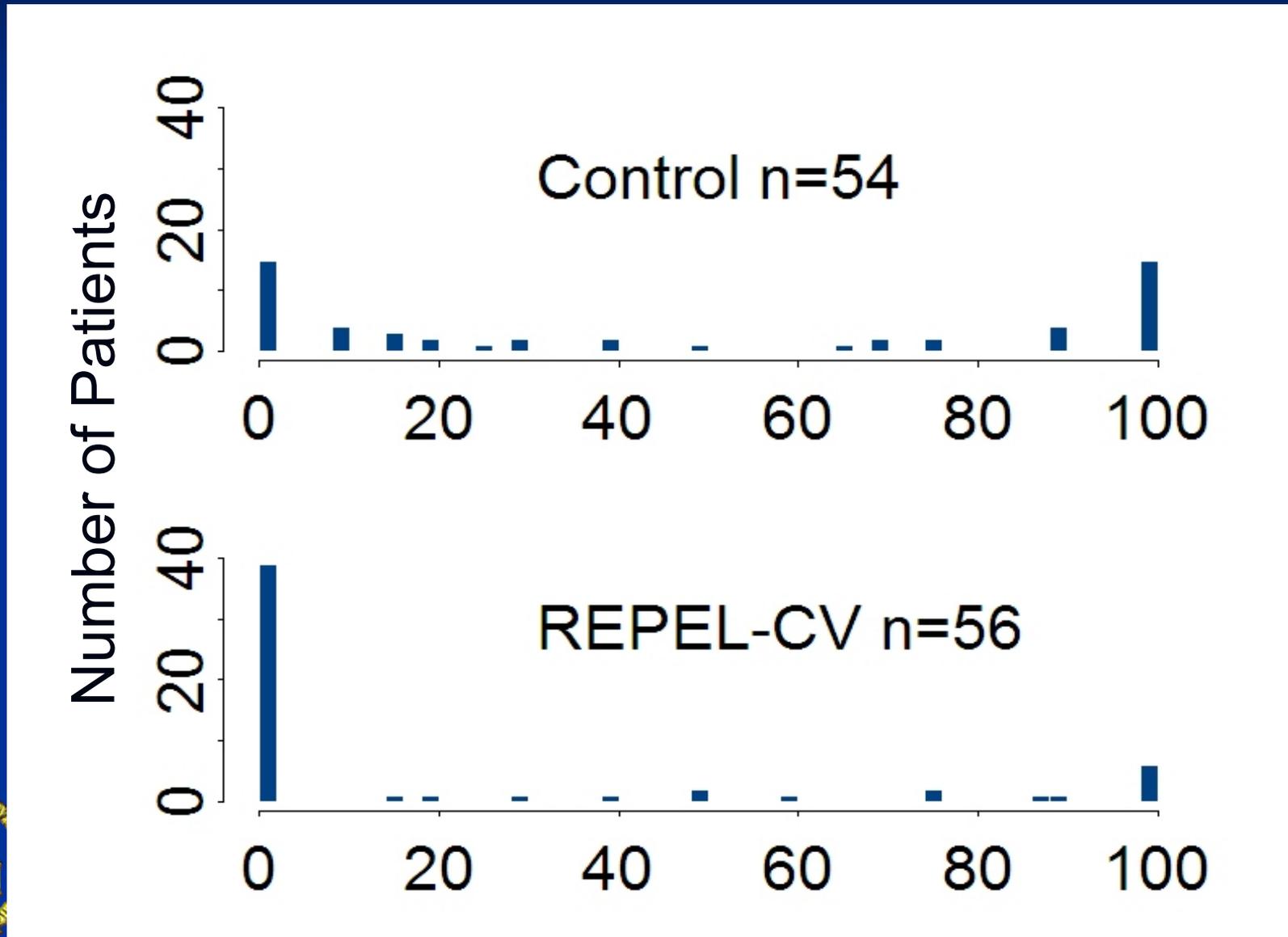


Primary Effectiveness Endpoint Result

% area with grade 3 adhesions (evaluatable patients)

| | REPEL-CV (n=56) | Control (n=54) | Difference (REPEL-CV – Control) |
|---------------------|--------------------|-------------------|---------------------------------------|
| Average | 21.3% | 47.3% | -26% |
| SE | 4.9% | 5.8% | |
| 95% CI | | | (-41%, -11%) |
| P-value (t-test) | | | .0004 |

Histogram of % Area with Grade 3 Adhesions



Is the t-Test still Valid ?

- Maybe yes. By the central limit theorem (due to the moderately large sample size)
- Nevertheless permutation test, **with raw observations themselves as the scores**, was performed to support the t-test results

Randomization Test

- A type of **non-parametric** statistical test
- Inference based on the random assignment of available subjects to treatment arms

Primary Effectiveness Endpoint Result: Randomization Test

- Hypotheses:

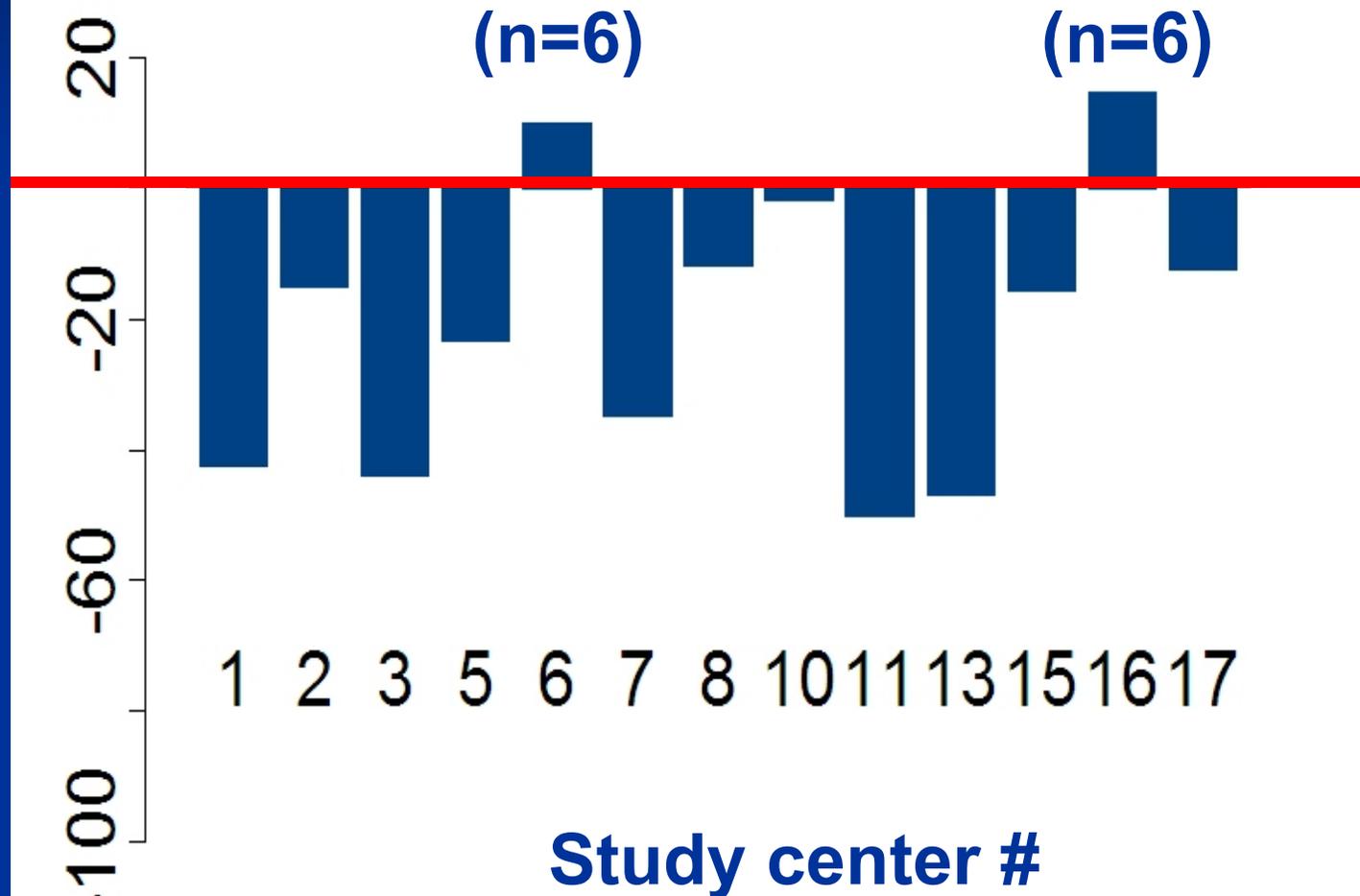
$$H_0: \mu_t \geq \mu_c \text{ vs. } H_a: \mu_t < \mu_c$$

- One-sided p-value = 0.0005

FDA analysis of evaluable patients

Treatment Effect by Center

Difference in average % area with grade 3 adhesion



Primary Effectiveness Endpoint Result: Randomization Test (stratified by study center)

Hypotheses:

$$H_0: \mu_t \geq \mu_c \text{ vs. } H_a: \mu_t < \mu_c$$

- Adjust for center effect
- One-sided p-value = 0.0013

FDA analysis of evaluable patients

Un-blinded Evaluation

- Pivotal study designed with blinded evaluators
- However, about 25% of patients were evaluated by un-blinded evaluators

?Potential confounding problem?

Statistical Modeling for Adjusting Covariates

- Dichotomize % area with grade 3 adhesion for each patient using three different cut-points
- Cut-point at 25%: If $> 25\%$ ➤ 1; otherwise ➤ 0
- Cut-point at 50%: if $> 50\%$ ➤ 1; otherwise ➤ 0
- Cut-point at 75%: If $> 75\%$ ➤ 1; otherwise ➤ 0

For logistic regression modeling

Primary Effectiveness Endpoint Result: Logistic Regression

Covariates (Gender, Heart-lung bypass machine usage, Chest closure delay, Procedure type & **Blinding status**)

Adjusted analysis

| Treatment effect | Dichotomization (cut-off points) | | |
|------------------|----------------------------------|-------|-------|
| | > 25% | > 50% | > 75% |
| p-value | 0.002 | 0.003 | 0.006 |

FDA analysis of evaluable patients

Primary Effectiveness Endpoint

Analysis of all randomized patients

- So far, all results were for evaluable patients only
- 17 patients (about 25% of the randomized patients) from each arm were missing primary effectiveness measures (% area with grade 3 adhesion)
- Multiple imputation

Primary Effectiveness Endpoint Result: Logistic Regression

| Treatment effect | Dichotomization (cut-off points) | | |
|------------------|----------------------------------|-------|-------|
| | > 25% | > 50% | > 75% |
| p-value | 0.016 | 0.010 | 0.033 |

Same Covariates were used in the multiple imputation model and the analysis model: Gender, Heart-lung bypass machine use & Chest closure delay

FDA analysis of all randomized patients



Summary

- It appears that statistically the mean % area with grade 3 adhesion in the REPEL-CV arm is significantly smaller than that in the control arm for the pediatric population studied

Secondary Effectiveness Endpoints

Comments on the analyses in the PMA

- No pre-specified hypothesis tests on secondary effectiveness endpoints
- P-values presented in PMA were not adjusted for multiple comparison

FDA Clinical Review REPEL-CV

Wolf Sapirstein, M.D.

Division of Cardiovascular Devices

Office of Device Evaluation

September 19, 2007

Clinical Presentation Objectives

- Feasibility study data and endpoints
- Pivotal study
 - Study design
 - Safety Endpoint
 - Pre-specified primary endpoint
 - Secondary endpoints
 - Adverse Events analysis
 - Summary of Data

Feasibility Studies

- Study 1: Single Center - 1998
 - Randomized 27 adult Patients
 - Operations on 20 CABG, 5 Valve, 2 VAD (REPEL-CV group)
 - Severe adhesions noted in VAD patients
- Study 2: Single Center - 2001
 - Randomized 13 pediatric patients;
 - 5/7 REPEL-CV; 1/6 Control “less than usual adhesions”
 - Mediastinum events in 2 REPEL-CV patients (severe)
 - Grading scale was 0-2
- Study 3: Multi-center - 2002
 - 15 pediatric patients OUS completed study
 - Grading scale changed to 0-3
 - 10% treated areas had Grade 0; 60% Grade 1; 20% grade 2; 11% Grade 3

Pivotal Study Objective

Determine safety and effectiveness of REPEL-CV for reducing post-operative adhesions in pediatric patients undergoing cardiothoracic surgery

Pivotal Study Design

- Multi-center – 15 sites
- Randomized to REPEL-CV or Control (no device)– 144 pediatric patients
- Evaluator-masked – adhesions were graded by surgeon on surgical team, blinded to device placement
- Grading Scale

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)

Inclusion Criteria

- FDA acknowledges reasons for enrollment of only pediatric patients
 - Assurance for re-operation
 - Pathogenesis similar for all ages
- Required staged cardiovascular sternotomy procedures
- No previous sternotomy
- Weight greater than 2.5 Kg
- Anticipated that the second sternotomy procedure to be performed two to eight months subsequent to the initial sternotomy procedure

Assessment Schedule

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

Assessment of Adhesion Grade

- Masked evaluators were members of the site's cardiac surgical team
- Evaluators independently assessed the adhesions
- Other surgical team instructed to refrain from comments about the extent and severity of the adhesions

Randomization Process

| | REPEL-CV | Control |
|----------------------------|----------|---------|
| Block Randomized | 73 | 71 |
| Protocol Deviation | | 2 |
| No Re-exploration | 17 | 15 |
| Evaluable Patients (“ITT”) | 56 | 54 |
| Re-explored at < 2 months | 2 | 5 |
| Per Protocol | 54 | 49 |

Safety Endpoint

- Assessed by comparing the type, severity, relationship, and timing of adverse experiences for REPEL-CV and Control group
- Safety population evaluated
 - 73 REPEL-CV
 - 69 Control
 - 142 TOTAL
 - 2 Control protocol deviations were excluded

Primary Effectiveness Endpoint

Percent of the study-defined investigational surgical site (ISS) with severe (Grade 3) adhesions at the second sternotomy procedure

Secondary Effectiveness Endpoints

- Percentage of patients with Grade 0, 1, or 2 as worst degree adhesions
- Patient-specific percentage of the study-defined surface area (the investigational surgical site) with Grade 0, 1, and 2 adhesions
- Dissection time for freeing up adhesions
- Number of patients by worst degree of adhesions within the investigational surgical site

Results



Safety – Adverse Event Rates

| | REPEL-CV | Control |
|--------------------------------|-----------------|----------------|
| ■ Patients with AE | 51 (69.9%) | 49 (71%) |
| ■ Treatment related | 6 (8.2%) | 1 (1.4%) |
| ■ Patients with Serious Events | 37 (50.7%) | 32 (46.4%) |
| ■ Deaths | 12 (16.4%) | 9 (13.0%) |

Safety – Adverse Events

| | REPEL-CV | Control |
|-------------------------|----------|---------|
| ■ Mediastinitis | 4 | 1 |
| ■ Wound Infection | 6 | 5 |
| ■ Wound Dehiscence | 1 | 1 |
| ■ Cardiac complication | 2 | 4 |
| ■ Thoracic complication | 2 | 4 |

Safety – Mediastinitis

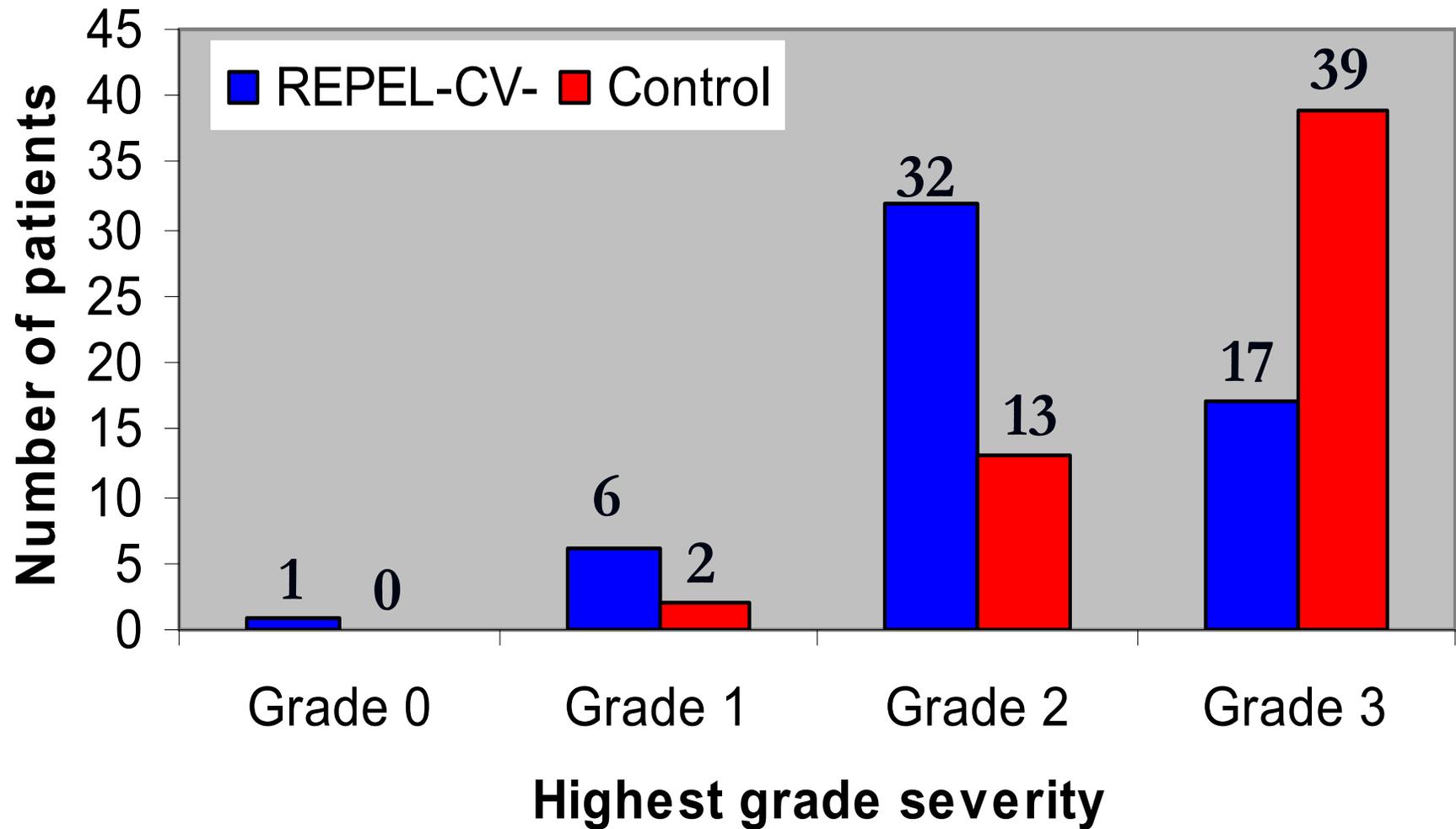
- Occurring after First Sternotomy:
 - REPEL-CV – at 120 days and at 14 days
 - 2.7% (2/73 patients)
 - Control – at 20 days
 - 1.4% (1/69 patients)
- Occurring after Second Sternotomy:
 - REPEL-CV – at 30 days and at 4 days
 - 3.6% (2/56 patients)

Primary Effectiveness Endpoint Results

- Mean Percent of the study-defined investigational surgical sites (ISS) with severe (Grade 3) adhesions (Evaluable patients).
- Mean \pm SE
 - 21.3% \pm 4.9% (n=56) for the REPEL-CV group
 - 47.3% \pm 5.8% (n=54) for the Control group

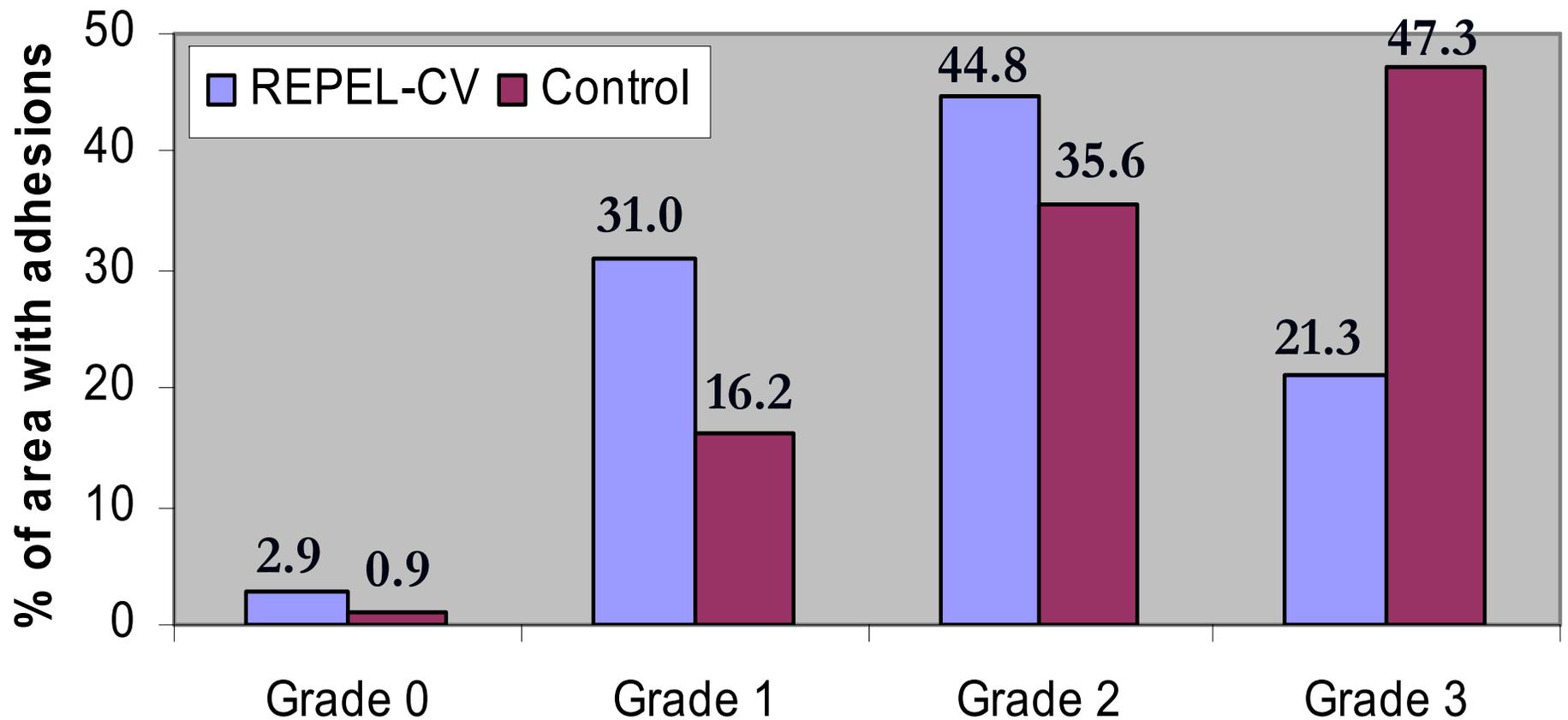
Secondary Effectiveness

Patient Distribution for Highest Adhesion Grade



Secondary Effectiveness

Extent of Adhesions (Mean % Area)



Secondary Effectiveness Endpoints

Median Dissection Times

| Grade 3 Adhesions | REPEL-CV | Control |
|-------------------------------|-----------|-----------|
| Patients | 17 | 39 |
| % Study Area | 21.3 | 47.3 |
| Time to Lyse (minutes) | 38 | 23 |
| No Severe Adhesions | REPEL-CV | Control |
| Patients | 38 | 15 |
| % Study Area | 78.7 | 52.6 |
| Time to Lyse (minutes) | 13 | 14 |
| ALL PATIENTS | | |
| Time to Lyse (minutes) | 20 | 18 |

Summary – Safety

- Mortality rates are consistent with literature reported values for this patient population
- SAEs and AEs show observational trend for similarity between REPEL-CV and Control
- Mediastinitis events
 - Foreign body introduced into operative field exposed to repeated potential contamination

Summary – Effectiveness

- Significant difference in Grade 3 adhesions in favor of REPEL-CV
- No planned hypothesis testing for secondary endpoints
- Other findings
 - Grades 2+3 similar study and control
 - No clear dissection time advantage
- FDA requests panel input on clinical benefit of device

Summary – Labeling Considerations

- Can the study results be extrapolated to adult patients?
- Do the study results support the use of the device to prevent adhesion of pericardial surfaces?
- Should the indications for use specify patients expected to undergo re-operation?
- Is the experience in VAD patients applicable to other prosthetic devices?

FDA Epidemiological Review REPEL-CV

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September 19, 2007

Outline

- General Principles
- Rationale/Postmarket Questions
- Proposed Post-Approval Study (PAS) Protocol
- Assessment of PAS Protocol
- PAS Issues for Panel Discussion

Disclaimer

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating **a reasonable assurance of safety and effectiveness** in order for the device to be found approvable.

General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population (within approved indication for use) over an extended period of time after premarket establishment of reasonable device safety and effectiveness.
- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Need for Post-Approval Studies

- Gather postmarket information
 - Longer-term performance
 - Community performance
 - Effectiveness of training programs
 - Sub-group performance
 - Rare adverse events and real world experience
- Account for Panel recommendations

Issues to Consider for the REPEL-CV Post-Approval Study

- General issue: Long-term safety profile in a larger number of individuals within the intended use population, under general conditions of use.
- Specific issue: Incidence of mediastinitis

Overview of Sponsor's PAS Protocol

| | |
|---------------------|--|
| Study Design | Multi-center, longitudinal, observational study, historical/concurrent controls, non-inferiority. |
| Population | <p>Patients undergoing single cardiac procedure.</p> <p>Age group to be determined by indication for use.</p> <p>REPEL-CV: enrolled in up to 15 study sites in US.</p> <p>Controls: from the Society of Thoracic Surgeons (STS) Registry, all patients treated after Jan 2003.</p> |
| Sample Size | 170 patients |
| Follow-up | Screening, Hospital stay, 4-weeks, 8-weeks |
| Primary Endpoint | Incidence of mediastinitis. |
| Secondary Endpoints | Complications; mortality; readmission. |



Assessment of Proposed PAS

- Sample Size Assumptions
 - Mediastinitis rate:
 - 6% REPEL-CV and 2% Controls
 - 4% non-inferiority margin
 - One sided test, alpha 0.05
- Enrollment ratio (REPEL-CV:Control) not specified
- Claim 80% power to test non-inferiority hypothesis
 - Not able to replicate

Assessment of Proposed Post-Approval Study

- 4% Non-inferiority margin for the primary endpoint
 - Clinical justification not provided
- Length of Follow-up
 - No justification for 8-week follow-up
 - Unclear if sufficient for long-term safety evaluation

Assessment of Proposed PAS

- Statistical Analysis

- Interim analysis to assess futility or non-inferiority of REPEL-CV once 100th patient completes 8-week assessment.
 - The interim analysis method is not specified.
- Unclear what methods will be used to address differences between study groups.

PAS Issues for Panel Discussion

- Primary study endpoint:
 - Mediastinitis vs. a composite safety endpoint
- 4% Non-inferiority margin
- Length of follow up: 8 weeks

Questions?

DISCUSSION SLIDES

STATISTICAL – DISCUSSION SLIDES

Comparison Stratified by Blinded/Un-blinded Evaluators

Average % area with grade 3 adhesion (evaluative patients)

| | Control | REPEL | (REPEL – Control) |
|---------------------------|-------------|-------------|-----------------------|
| Blinded | 50.4 (n=41) | 24.0 (n=43) | -26.4 |
| Un-blinded | 37.7 (n=13) | 12.5 (n=13) | -25.2 |
| (Blinded – Un-blinded) | 11.5 | 12.3 | |

Covariate-Adjusted Analysis

logistic regression coefficient (p-value)

| Effect | | Cut-off point | | |
|---------------------------|---------|----------------|---------------|---------------|
| | | > 25% | >50% | >75% |
| Treatment | REPEL | 1.357 (0.002) | 1.392(0.003) | 1.375(0.006) |
| Gender | Male | 0.893(0.056) | 1.285(0.010) | 0.885(0.087) |
| Heart-lung bypass machine | On | 0.745(0.468) | -0.715(0.574) | -0.235(0.863) |
| Chest closure delay | Yes | -1.117(0.243) | -0.758(0.451) | -2.133(0.057) |
| Procedure | Norwood | -0.577 (0.528) | -0.564(0.562) | 0.974(0.336) |
| Blinding | Yes | -0.563(0.270) | -0.194(0.722) | -1.278(0.050) |



FDA analysis of evaluable patients

Covariate-Adjusted Analysis (Cont')

With random center effect in the model
p-values from logistic regression

| Effect | | Cut-off point | | |
|---------------------------|---------|---------------|-------|-------|
| | | > 25% | >50% | >75% |
| Treatment | REPEL | 0.011 | 0.021 | 0.050 |
| Gender | Male | 0.057 | 0.020 | 0.130 |
| Heart-lung bypass machine | On | 0.457 | 0.634 | 0.875 |
| Chest closure delay | Yes | 0.340 | 0.606 | 0.140 |
| Procedure | Norwood | 0.671 | 0.710 | 0.533 |
| Blinding | Yes | 0.052 | 0.577 | 0.092 |



FDA analysis of evaluable patients

Primary Effectiveness Endpoint

Average % area with grade 3 adhesion for subgroups

Difference (REPEL – Control)

| Gender | | Norwood procedure | | Heart-lung bypass machine use | | Chest closure delay | |
|----------------|----------------|-------------------|-------------|-------------------------------|-------------|---------------------|-----------|
| Male (n=69) | Female (41) | Y (n=81) | Non (29) | Y (n=96) | N (n=14) | Y (n=83) | N (27) |
| 29% | 28% | 24% | 27% | 24% | 23% | 23% | 29% |



Evaluable patients

Covariate-Adjusted Analysis

Randomization test stratified by subgroup

- By Gender: one-sided p-value = 0.0001
- By Blinding status: one-sided p-value = 0.0004

FDA analysis of evaluable patients

Covariate-Adjusted Analysis

All randomized patients with multiple imputation

Logistic regression coefficient (p-value)

| Effect | | Cut-off point | | |
|---------------------------|-------|---------------|---------------|---------------|
| | | > 25% | >50% | >75% |
| Treatment | REPEL | 0.978 (0.016) | 1.076(0.010) | 0.969(0.033) |
| Gender | Male | 0.388(0.101) | 1.102(0.0240) | 0.885(0.054) |
| Heart-lung bypass machine | On | -1.086(0.935) | -1.809(0.154) | -1.472(0.262) |
| Chest closure delay | Yes | -1.552(0.104) | -0.883(0.233) | -0.747(0.329) |

FDA analysis



Primary Effectiveness Endpoint Result

All randomized patients with “worst case” imputation

All missing values were imputed as 100%

| | REPEL (n=74) | Control (n=71) | (REPEL – Control) |
|---------------------|-----------------|-------------------|----------------------|
| Average | 39.6% | 59.9% | -20.3% |
| 95% CI | | | (-35.1%, -5.5%) |
| P-value (t-test) | | | 0.004 |

FDA analysis

Primary Effectiveness Endpoint

All randomized patients

- If the observed average difference in % area with grade 3 adhesion between the REPEL arm and the control arm **for those (34) patients who had missing adhesion measures** is less than (about) 30%, the conclusion will hold

FDA analysis

Primary Effectiveness Endpoint

All randomized patients

excluding deaths and protocol violations

- If the observed average difference in % area with grade 3 adhesion between the REPEL-CV arm and the control arm for those (16) patients who had missing adhesion measures is less than (about) 40%, the conclusion will hold

FDA analysis

% Area with Grade 0, 1, or 2

| Grade of adhesion | REPEL (n=56) | Control (n=54) | (REPEL - Control) | p-value (one-sided) | |
|-------------------|--------------|----------------|-------------------|---------------------|---------------|
| | | | | t-test | randomization |
| Grade 2 | 44.8% | 35.6% | 9.2% | 0.0889 | 0.0883 |
| Grade 1 | 31.0% | 16.2% | 14.8% | 0.0079 | 0.0080 |
| Grade 0 | 2.9% | 0.9% | 2.0% | 0.1608 | 0.1630 |

Mortality Rate

Safety population

| | REPEL | Control | (REPEL – Control) |
|-----------|---------------|------------|----------------------|
| Mortality | 16.4% (12/73) | 13% (9/69) | 3.4% |
| 95% CI | | | (-8.7%, 15.4%) |

Secondary Effectiveness Endpoints

Mean Dissection Times

| Grade 3 Adhesions | REPEL-CV | Control |
|-------------------------------|--------------------|--------------------|
| Patients | 17 | 39 |
| % Study Area | 21.3 | 47.3 |
| Time to Lyse (minutes) | 33.1 ± 19.1 | 28 ± 23.0 |
| No Severe Adhesions | REPEL-CV | Control |
| Patients | 38 | 15 |
| % Study Area | 78.7 | 52.6 |
| Time to Lyse (minutes) | 22.7 ± 21.4 | 17.5 ± 16.9 |
| ALL PATIENTS | | |
| Time to Lyse (minutes) | 25.9 | 25 |

Average Dissection Time

| | REPEL (n=55) | Control (n=53) | (REPEL – Control) |
|----------------------|-----------------|-------------------|----------------------|
| Average (minutes) | 25.9 | 25 | 0.9 |
| 95% CI | | | (-7.3, 9.0) |

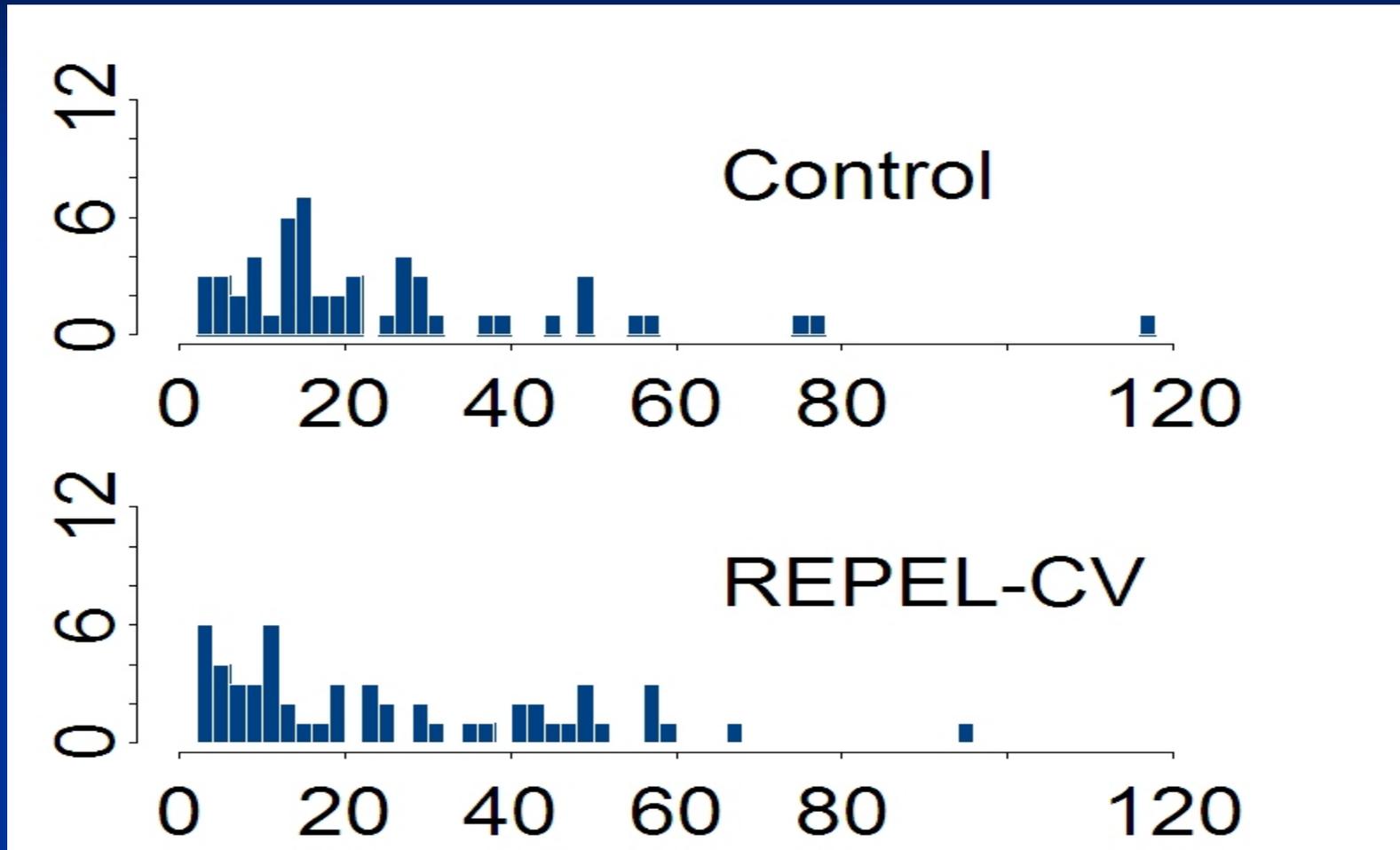
Secondary Effectiveness Endpoints

Median Dissection Times

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| ALL PATIENTS | | |
| Time to Lyse (minutes) | 20 | 18 |

Histogram of Dissection Time

Number of patients



Dissection time (minutes)

Comparison of Mean Dissection Time Between REPEL and Control

| Type of test | One sided p-value |
|--|-------------------|
| t | 0.418 |
| Randomization* | 0.421 |
| randomization stratified by blinding status* | 0.421 |

Hypotheses:

$H_0: T_t \geq T_c$ vs. $H_a: T_t < T_c$

**POST-APPROVAL
STUDY –
DISCUSSION SLIDES**

PAS Issues for Panel Discussion

- Composite Safety Endpoint
 - Superficial Surgical Infections
 - Soft Surgical Site Infections
 - Deep Sternal Infections (Mediastinitis)
 - Sternal Instability
 - Sternal Dehiscence