ACORN CORCAP CSD

Expert Comment on Scientific Issues in Dispute

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Draft – December 13, 2006

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METHODOLOGY OF REVIEW

- Each expert consultant independently reviewed all relevant data, including:
  - PMA as amended December 13, 2005
  - Relevant published literature
  - Proceedings from FDA Advisory Panel Meetings
  - August 12, 2005 and February 2, 2006 Not-Approvable letters
  - Study protocol
- The experts jointly provided consensus opinion

CONCLUSIONS

- Primary endpoint clinically meaningful
- Small amount of missing information does not compromise result
- No evidence that bias affected primary endpoint
- Analysis of primary endpoint in accord with proper statistical methods, and as specified in study protocol
- Results in MVR/non-MVR strata clinically relevant
- Results for secondary endpoints supportive
- Product has reasonable safety profile and benefits outweigh risks

EXPERT COMMENT OVERVIEW

- Overview
- Primary Endpoint
- Secondary Endpoints
- Safety
- Benefit – Risk
- Conclusions on Issues in Dispute

STUDY OVERVIEW

- Well-designed and well-executed
- Surgical trial – not blinded
- 4 techniques to reduce bias
  - Blinded core lab NYHA, echo, BNP, exercise
  - CERC
  - DSMB
  - Acorn and investigators blinded to aggregate results
- Primary endpoint is a composite
- Incorporated more than one stratum
- Protocol-specified secondary endpoints

PRIMARY ENDPOINT

Design & Analysis

Steven Piantadosi, MD, PhD

Draft – December 13, 2006

PRIMARY ENDPOINT STATISTICALLY MEANINGFUL

- What is it?
  - Composite of 3 clinical outcomes selected to assess disease progression coherently: NYHA, MCPs, mortality
  - Each patient classified as Improved, Same, Worsened
- Designed and powered for composite endpoint
  - Clinical benefits and changes in same direction important
  - Mortality designed as safety endpoint per FDA letter
  - Not designed or powered to analyze components
- Small amount of missing information for the composite, multiple imputation appropriate

PRIMARY ENDPOINT

Statistical Comment

Donald B. Rubin, PhD

Draft – December 13, 2006

SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

- Some missing information in composite primary endpoint, which involved change in lab-assessed NYHA from baseline
- Baseline lab-assessed NYHA only recorded in latter part of trial for final 126 – data missing by design for first 174
- Baseline site-assessed NYHA was recorded for all 300 patients
- FDA appropriately suggested handling missing data in NYHA by Multiple Imputation (MI)

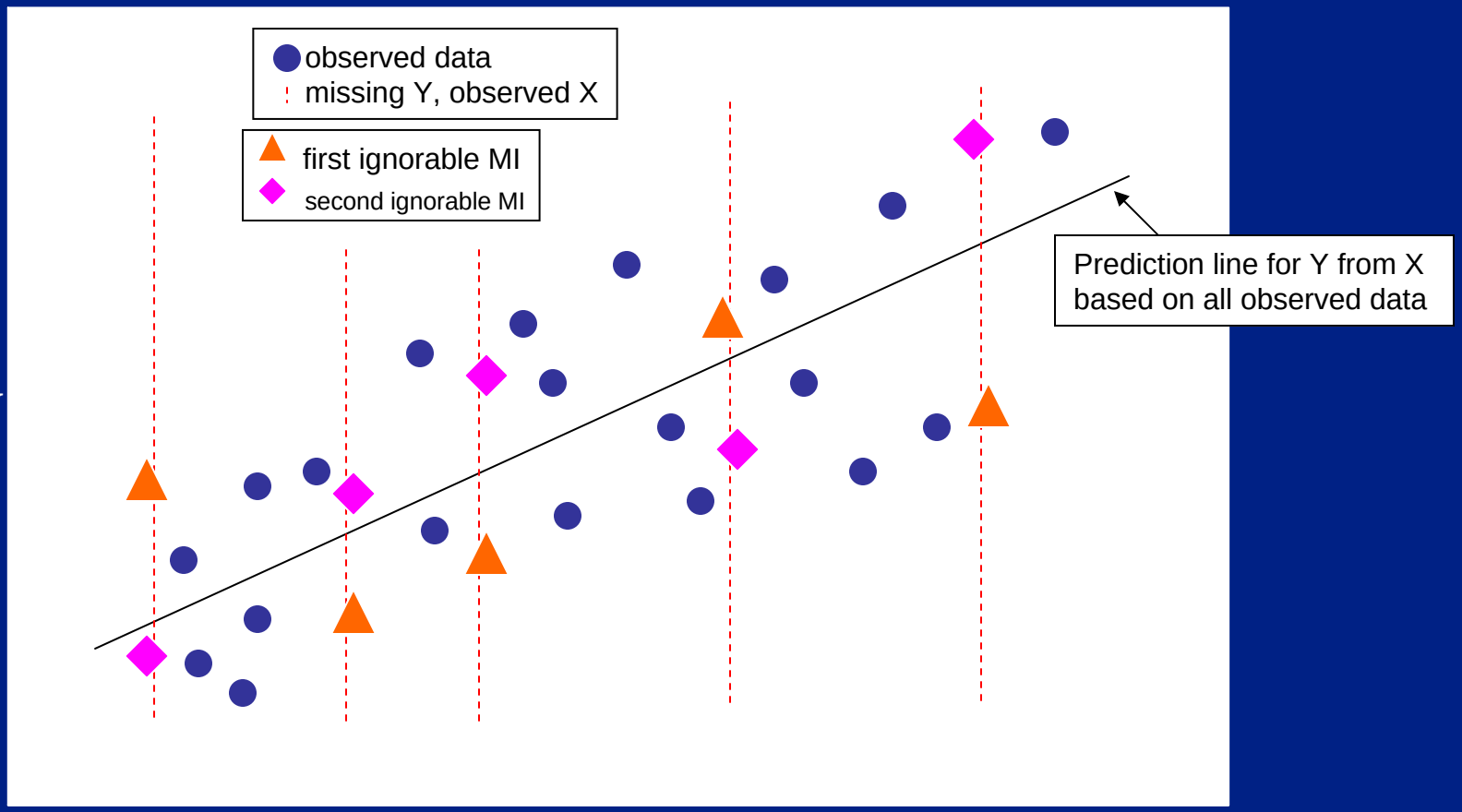
SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

MI is well-established as a valid method of dealing with missing data when realistic MI model is used

- Each missing datum is replaced by multiple values
  - Reflects uncertainty about the correct value to impute
  - Allows standard complete-data methods of analysis
- MI proposed by Rubin in the 1970s and has a very large number of evaluations supporting its validity and robustness to modeling assumptions
- Standard MI assumes "ignorable" missingness
  - "ignorable" in a particular technical sense

SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

Illustrative Example of MI



SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

Acorn's PMA MI Model

- Developed in collaboration with a local outside expert and implemented using SAS (8.2) PROC MI and PROC MIANALYZE
- Assumed:
  - ignorable missingness
  - normally distributed NHYA
  - only baseline predictors in MI model
- Analysis of primary endpoint after MI favored CorCap over control at p=0.024, odds ratio = 1.73

SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

Criticisms of PMA MI Model (Panel Meeting June 2005)

1. The missingness was *not ignorable* because of the *fraction of missing values* of baseline NYHA
2. Too few predictors included and possibly improperly selected
3. Missing NYHA not normally distributed but ordinal

- Criticism 1 represents a misunderstanding of the technical definition of "non-ignorable"
  - By construction, the missingness *is* "ignorable" for comparisons of CorCap and control
- Criticisms 2 and 3 deserve consideration

SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

Fraction of *Missing Data* versus Fraction of *Missing Information*

- Suppose 1000 patients where primary endpoint is change in weight from baseline in *pounds*
- First 500 patients: weight in *kilograms*
- Second 500 patients: weight in *pounds* and *kilograms*
- Fraction of *missing data* on weight in pounds: 50%
- Fraction of *missing information* on primary endpoint is tiny because weight in pounds is so highly correlated with weight in kilograms

SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

Ignorable versus Nonignorable Missing Data

- *Nonignorable* means missing *because* of its value
- If nonignorable, value to impute is
  - Unpredictable from observed values
  - Systematically off prediction line
- Lab-assessed NYHA missing because of administrative decision, not because of its value
  - Early versus late enrollment in trial
  - Blocked (in time) randomization to CorCap and control
  - Therefore, the missingness is ignorable for comparing CorCap and control

SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

Three Additional SAS-Based MI Models Support Robustness Of Original Conclusions

- Updated (version 9.1) was used
  - Allowed more flexible and realistic models
- All three models assumed ordinal NYHA and used 100 multiple imputations
  1. More predictors, some post-baseline, which is valid and usually more efficient:
     - p for primary endpoint = 0.029, odds ratio = 1.69
  2. More predictors but none post-baseline:
     - p for primary endpoint = 0.033, odds ratio = 1.67
  3. Like model 1 but distinct models for the two randomized groups to avoid cross-contamination of the MI models:
     - p for primary endpoint = 0.021, odds ratio = 1.79

SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

Final MI Model Used Special State of the Art Method

- Designed for CDC Anthrax Vaccine trials
  - Extends method in Rubin (2003) used to address missing data in National Medical Expenditure Survey
- Application to Acorn data
  - NYHA ordinal
  - Allowed over 100 baseline and post-baseline variables
  - Done separately by randomized group
  - Implemented by blinded third party
  - Used 5 multiple imputations
  - p for primary endpoint = 0.014, odds ratio = 1.77

SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

Percentage of Missing Information for Primary Endpoint

$$= \frac{\text{(Between Variance in estimated Primary Endpoint across MIs)}}{\text{(Between Variance + Average Within Variance)}}$$

- Under MI Model 0 → 9%
- Under MI Model 1 → 5%
- Under MI Model 2 → 7%
- Under MI Model 3 → 16%
- Under MI Model 4 → 2%

SMALL AMOUNT OF MISSING INFORMATION FOR COMPOSITE ENDPOINT: MULTIPLE IMPUTATION APPROPRIATE

Effect of MI on Estimate and Significance of Primary Endpoint

- Each of the four new MI models confirmed the conclusion of the PMA's MI model
- There is a significant and beneficial treatment effect of CorCap relative to control on primary endpoint
- The most sophisticated MI model resulted in the most significant result
  - p for primary endpoint = 0.014
  - Odds ratio = 1.77

PRIMARY ENDPOINT

Clinical Comment

Randall C. Starling, MD, MPH

Draft – December 13, 2006

PRIMARY ENDPOINT RESULTS

Result	Treatment	Control	Odds Ratio 95% CI	p-value
Improved	38%	27%	1.73* (1.07, 2.79)	0.024
Same	25%	28%		
Worsened	37%	45%		

As of common closing date (4 July 2004)
Median Follow-up = 23 months

* Proportional odds ratio indicates treatment patients had a 73% greater odds of being in a better category than control patients

COMPONENTS OF COMPOSITE IMPORTANT CLINICAL OUTCOMES

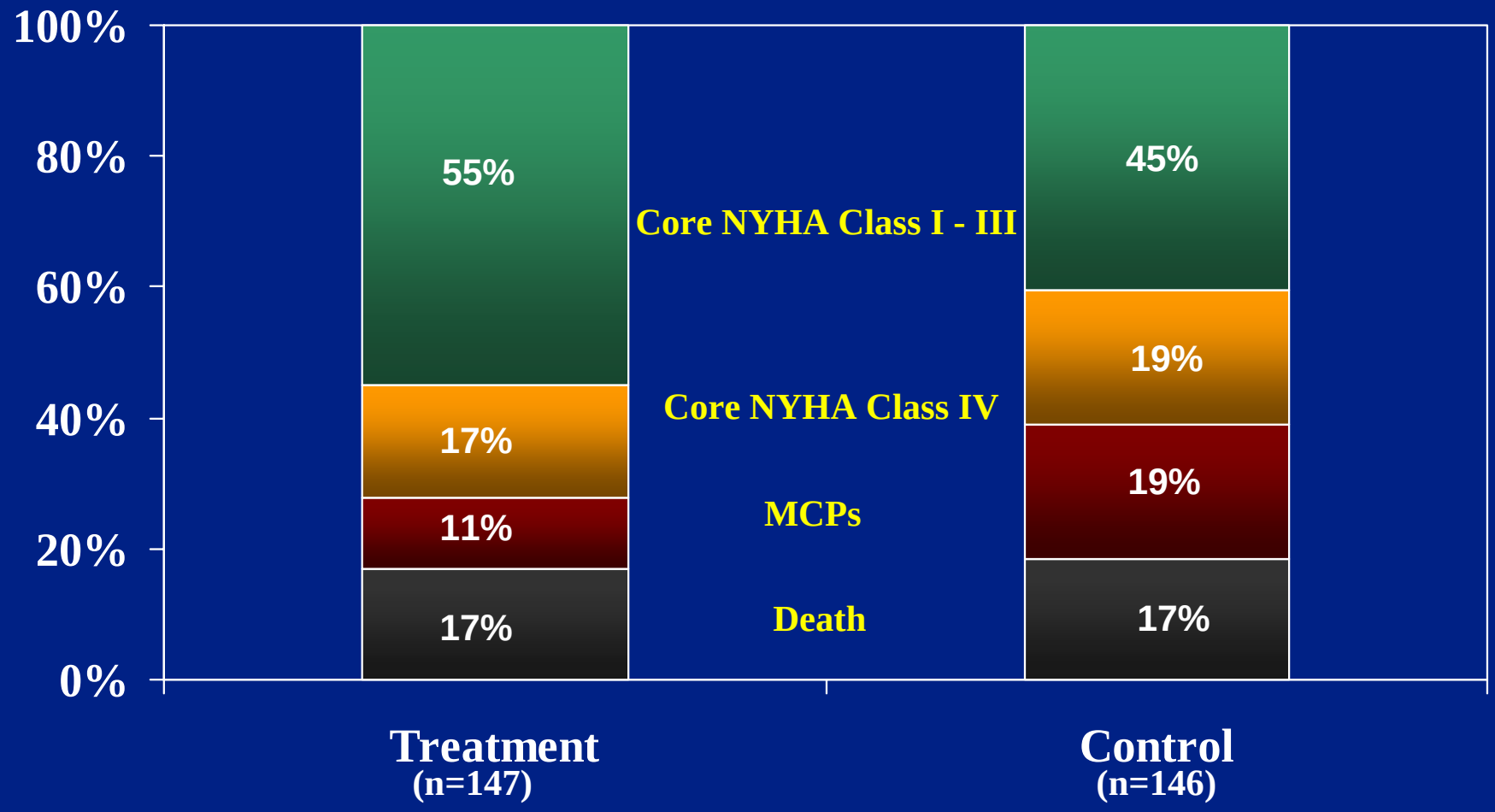
- Three clinically meaningful components:
  - Blinded NYHA
  - MCPs
  - Mortality
- Results consistent
  - NYHA: improved
  - MCPs: improved significantly
  - Mortality: neutral

INVESTIGATOR BIAS DID NOT AFFECT MCP COMPONENT

- Methodology
  - CERC adjudicated events
  - Composite endpoint
- If bias existed, expect to see more patients in CorCap group in NYHA Class IV and higher mortality
- Data on death or re-hospitalization does not reflect bias

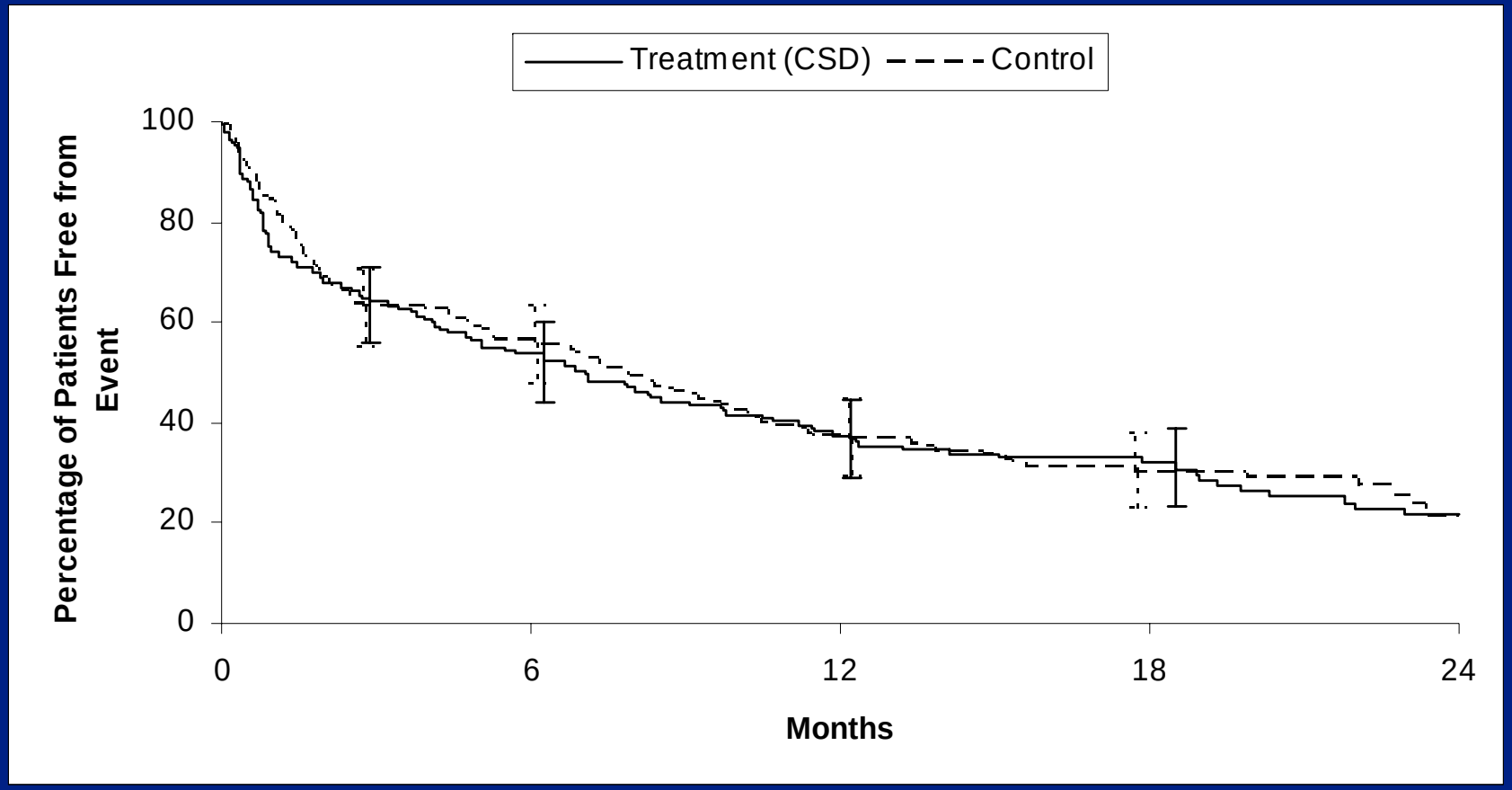
INVESTIGATOR BIAS DID NOT AFFECT MCP COMPONENT

Primary Endpoint: Status at End of Trial



INVESTIGATOR BIAS DID NOT AFFECT MCP COMPONENT

Freedom from Death or All-Cause Re-Hospitalization Full Cohort (n=300)



PRIMARY ENDPOINT

Stratification

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STRATIFICATION

- Clinical and statistical rationale for stratification MVR/no-MVR
  - Reduce variance, control heterogeneity, induce balancing
  - Increase precision in detecting treatment effect
  - Stratification does not require or dictate stratum treatment effect estimates
- Each stratum expected to have different baseline characteristics and outcomes
- Study designed to estimate average relative treatment effect across strata
- Both strata favor CorCap over control

POSITIVE RESULTS IN BOTH MVR/NO-MVR STRATA

Primary Endpoint Results

Cohort n = T/C	OR	95% CI	p-value
Overall	1.73	1.07 – 2.79	0.02
MVR Stratum (n = 91/102)	1.51	0.84 – 2.72	0.17
No-MVR Stratum (n = 57/50)	2.57	1.09 – 6.08	0.03

SECONDARY ENDPOINTS

Statistical Comment

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Draft – December 13, 2006

PROPER ANALYSIS OF SECONDARY ENDPOINTS

- Selected for clinical utility
- Explicitly named as secondary outcomes, not primary
- Protocol-specified analysis of variance at months 6 and 12
- Longitudinal regression models through end of efficacy phase across all follow-up visits
- Proper interpretation depends on direction and magnitude of differences, not on p-values

MULTIPLICITY ADJUSTMENT NOT REQUIRED

- Not appropriate, necessary, or mandatory
  - Sole purpose to provide supportive evidence to protocol-specified statistically significant primary endpoint
  - Not independent basis for establishing safety and efficacy
- Variations in statistical significance not unexpected due to complexity of disease

SECONDARY ENDPOINTS

	Secondary Endpoints	Treatment Difference (T-C)	Individual p-value
Structural	LVEDV	-17.9ml	0.008
	LVESV	-15.2ml	0.02
	LVEF	0.83	0.49
	Sphericity Index	0.042	0.031
	Mass Index	-5.9g/m2	0.15
	LVEDD	-1.8mm	0.02
	LVESD	-1.2mm	0.21
Functional	MLHF	-4.47	0.04
	SF-36 (GH)	9.13	<0.0001
	SF-36(PF)	5.41	0.015
	NYHA (Site Assessed)	-0.04	0.60
	6-minute Walk Distance	1.27 (odds ratio)	0.24
	Peak VO_2	1.37 (odds ratio)	0.15
Lab	BNP	77.33 pg/ml	0.014
Clinical	All Cause Re-Hospitalizations	1.0	0.44
	Mortality or Re-Hospitalizations	1.02 (odds ratio)	0.88

MAJOR SECONDARY ENDPOINTS SUPPORTIVE

- Protocol-specified major secondary endpoints:
  - LVEDV
  - LVEF
  - MLHF
  - Site-assessed NYHA
- Hochberg adjustment implemented in response to FDA request to pre-specify "a type I error rate"

HOCHBERG'S METHOD: WHAT IS IT?

- Assists with interpretation of statistical significance for multiple endpoints
- Provides joint success criterion for major secondaries
- Hochberg's manuscript* discusses testing of "intersection hypotheses," what Acorn describes as a "joint success criterion"
- Manuscript also provides for testing each endpoint one by one using Hochberg's method
  - Nominal p-value obtained for each outcome
  - P-value adjusted based on its ranking relative to other outcomes

* Hochberg Y. 1988. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 75:800-803.

MAJOR SECONDARY ENDPOINTS

Major Secondary Endpoints	Treatment Difference*	P-value	
		Individual	Hochberg
LVEDV	-17.9 ml	<0.01	0.03
MLHF	-4.47	0.04	0.12
LVEF	0.83	0.49	0.60
NYHA (Site-Assessed)	-0.04	0.60	0.60

- LVEDV statistically significant (nominal $p < 0.01$), meeting collective success criterion under Hochberg ($p < 0.0125$)
- Equivalent to finding at least one Hochberg-adjusted individual p-value < 0.05 (e.g. LVEDV = 0.03, also significant under Bonferroni)

* Treatment difference: all favor CorCap

SECONDARY ENDPOINTS

Clinical Comment

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SECONDARY ENDPOINTS

Secondary Endpoints	Treatment Difference (T-C)	Individual p-value
LVEDV	-17.9ml	0.008
LVESV	-15.2ml	0.02
LVEF	0.83	0.49
Sphericity Index	0.042	0.031
MLHF	-4.47	0.04
SF-36 (GH)	9.13	<0.0001
SF-36 (PF)	5.41	0.015

SECONDARY ENDPOINTS CLINICALLY RELEVANT

- Structural endpoints show improvements:
  - Ventricular size
  - Ventricular shape

- Significant improvements in quality of life
  - MLHF
  - SF-36

SAFETY

Perioperative Mortality

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Michael A. Acker, MD

Draft – December 13, 2006

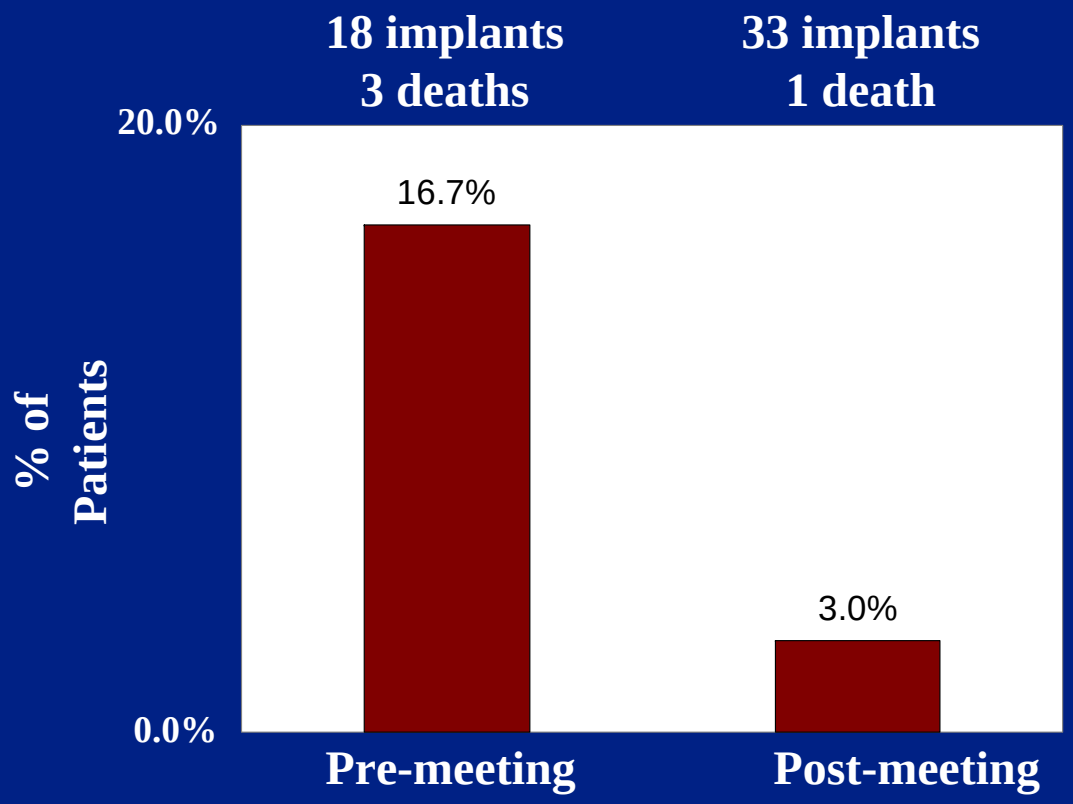
PERIOPERATIVE DEATHS

CorCap No-MVR Stratum

Pt ID	Patient Characteristic	CPB	Hemodynamic Instability Observed	Post-Op Days to Death	Cause of Death
3153	Peak VO_2 = 8.5	Off Pump*	Yes	1	Ventricular Arrhythmia
3807	Peak VO_2 = 9.9 LVEF = 10%	Off Pump	Yes	24	Multi-organ Failure
3904	LVEDD = 89mm LVEF = 9%	Off Pump	No	12	Ventricular Arrhythmia
4407	LVEDD = 98mm	Off Pump*	Yes	1	Multi-organ Failure

* Case started off pump; patient was subsequently placed on pump due to hemodynamic compromise

LEARNING CURVE REDUCES PERIOPERATIVE MORTALITY



After third death, use of IABP and cardiopulmonary bypass, as needed, reinforced
Information disseminated at investigator meeting April 5, 2002

SAFETY

Risks of Re-Operation

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ADHESIONS AT RE-OPERATION DID NOT AFFECT OUTCOMES

Re-Operations for Transplant

	CorCap	No-CorCap
Total # Patients	7	16
Deaths	0	2*
AEs per Patient	1.7	1.9
Total AEs within 30 days of transplant	4	10
Return to OR for bleeding	0	1
Post-Operative Stay (days)	12.3 (6 – 17)	19.6 (8 – 46)
CPB Time	207 min** (158-270)	193 min** (128-284)

* 1 patient died within 30 days of re-operation

** CPB times only noted in operative reports for 5 treatment and 5 control patients

ADHESIONS AT RE-OPERATION DID NOT AFFECT OUTCOMES

- No evidence that adhesions had significant adverse effect on outcomes of subsequent surgery
- Longer dissection times in some cases
- Issue is effectively managed with proper training and experience

SAFETY

Risk of Pericardial Constriction

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Steven Piantadosi, MD, PhD

Draft – December 13, 2006

NO CLINICAL EVIDENCE OF PERICARDIAL CONSTRICTION

- No pre-clinical evidence of constrictive pericarditis in animals studied
- Echocardiographic data do not demonstrate consistent evidence of constrictive physiology in any patients
- No clinical evidence of constrictive pericarditis in any patients in trial in up to 331 patient years of follow-up (as of April 2005)
- Continue monitoring IDE patients for up to 5 years

BENEFIT – RISK ANALYSIS

Randall Starling, MD, MPH

Draft – December 13, 2006

CLINICALLY IMPORTANT BENEFITS

- Functional Class - 38% improved by one or more NYHA class vs. 27% in control
- Quality of Life - Improved MLHF and SF-36
- Need for MCPs - 41% reduction in need for major cardiac procedures related to worsening heart failure in CorCap group vs. control
- Heart size - Decreased volume by 7.7% vs. control
- Mechanism consistent with other effective therapies (device and pharmacologic)

CORCAP CSD IN CLINICAL PRACTICE

- Symptomatic despite optimal management
- Class III/IV NYHA
- Limited treatment options
- Risk-benefit

CONCLUSIONS ON OMBUDSMAN'S QUESTIONS TO PANEL

Steven Piantadosi, MD, PhD

Draft – December 13, 2006

CONCLUSIONS

1. Overall trial results for the primary effectiveness endpoint are interpretable and clinically meaningful.

2. Secondary endpoint results are supportive of the safety and effectiveness of the device.

3. FDA's safety concerns have been addressed by the data provided.

4. Data submitted by Acorn adequately address FDA's safety and effectiveness concerns for the original patient population.

5. The focused cohort is a post-hoc analysis. Issues can be resolved on the basis of the original patient population.