Medtronic

HAMMOCK PAS Clinical Study

MDT16002SUR001

Statistical Analysis Plan (SAP)

Rev 2.0

14 April 2017

NCT03139721

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Approvals

The undersigned have reviewed this document and agree with its contents.

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Statistical Analysis Plan

Clinical Investigation Plan Title	Medtronic **Ha**ncock II ® and **M**osaic **M**itral and Aortic Valves: A Study to **O**bserve the Effects of the Stent Material **C**hange to PEE**K** **P**ost **A**pproval **S**tudy (HAMMOCK PAS)
Clinical Investigation Plan Identifier	MDT16002SUR001
Clinical Investigation Plan Version	2.0 06 Jan 2017
Sponsor/Local Sponsor	Medtronic Coronary Structural Heart Clinical 8200 Coral Sea Street N.E. MVS66 Mounds View, MN 55112 USA Medtronic Bakken Research Centre BV (Europe) Coronary and Structural Heart Endepolsdomein 5 6229 GW Maastricht The Netherlands
Document Version	2.0

Confidentiality Statement

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Cathy Zeng / Principal Statistician

2.0	• To align with CIP version 2.0
	  • Add wording "valve-related" to death
	  • Change word "hemodynamic" to "clinical"
	  • Update site information
	  • Update inclusion/exclusion
	  • Update data collection
	  • Update minimizing bias
		Cathy Zeng / Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CIP	Clinical Investigational Plan
SAP	Statistical Analysis Plan

3. Introduction

The Mosaic and Hancock II bioprostheses received CE Mark in 1995, and FDA approval in 2000 and 1999 respectively. The Mosaic and Hancock II have been in the market worldwide for over 20 years. The devices have a safe history of use as indicated by the published clinical data and by the low complaint and adverse event rates collected through product surveillance.

The current stent material used for the bare stent in the Mosaic and Hancock II bioprostheses, acetal homopolymer (AHP), has been discontinued by the supplier. Medtronic completed a formal material selection process to evaluate replacement materials and selected polyether ether ketone (PEEK) as the optimal replacement material for the stent. As part of the pre-clinical qualification for the substitution of acetal homopolymer (AHP) with Polyetheretherketone (PEEK) material in Mosaic and Hancock II valve stents, Medtronic completed a thorough analysis to identify potential risks associated with the material change. Design verification testing demonstrated equivalent functional performance and non-inferior structural performance and durability of the PEEK stented valves versus the prior stented valve with AHP stent material.

The purpose of the study is to complete a prior agreed upon requirement for the continuation of CE Mark by providing the Notified Body with supplemental post market clinical follow-up data on the safety and performance of the Mosaic and Hancock II devices with PEEK material at 1 year post implant for the primary endpoint with a pre-determined and agreed upon study follow-up duration of 3 years post treatment..
This Statistical Analysis Plan (SAP) is designed to document, before data are analyzed, the rationale for the study design of the Medtronic HAMMOCK PAS Study, and the planned analyses that will be included in study reports. The design and analyses are consistent with the objectives of the Clinical Investigational Plan (CIP).

This Statistical Analysis Plan (SAP) applies to the publications and the final study report. The publications may request additional analyses that are not included in this SAP.

4. Study Objectives

4.1. Primary Objective(s)

The primary objective of the study is to characterize the freedom from valve related death, re-intervention of, or
explant related to the Mosaic and Hancock II valves with PEEK stent material in a patient population undergoing aortic or mitral valve replacement of his/her native aortic or mitral valve at 1 year post implant.

4.2. Secondary Objective(s)

The secondary objective of the study is to characterize the clinical performance of Mosaic and Hancock II valves containing PEEK stent material at 1 year post implant.

5. Investigation Plan

This is a prospective, interventional, non-randomized, worldwide, multi-center study, with each site following a single common protocol. The design of the study adheres to the principles of International Conference on Harmonization Guidelines on Good Clinical Practice (GCP), Declaration of Helsinki and ISO 14155:2011.

The study will be conducted at up to 15 sites worldwide with approximately up to 7 sites in the US and up to 8 sites in Europe with a maximum of 110 total subjects enrolled and a minimum of 100 study subjects implanted. Enrolled subjects who exit the study will not be replaced. Subjects eligible for aortic or mitral valve replacement and compliant with the enrollment criteria will be considered by the investigator for inclusion in the study.

Adverse Events collection is limited to all Serious Adverse Events, all device and procedure related Adverse Events and all Device Deficiencies.

Enrollment is estimated to take approximately 15 months to complete and subjects will consent to be followed annually up to 3 years post procedure. A minimum of 89 subjects is required to be followed to 1-year to satisfy the primary endpoint requirements: freedom from valve related death, re-intervention of, or explant study valve related to the Mosaic and Hancock II valves with PEEK stent material. Total expected duration of the study is approximately 5 years. The study will be considered
complete when the last active implanted subject completes the 3 year required follow-up.

Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical study. Selection of subjects, treatment of subjects and evaluation of study data are potential sources of bias.

Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- For sites that are participating in other Aortic or Mitral valve studies which may have similar enrollment criteria as the HAMMOCK PAS Study, a written process for avoiding selection bias is strongly recommended
- Demographics and medical history will be collected at baseline in order to later assess possible characteristics that may influence endpoints

- Data collection requirements and study procedures will be standardized across all geographies
- All geographies will follow the same version of the CIP and eCRFs
- No more than 20% of expected implants may come from a single site
- All study investigators will be required to meet the requirements of 21 CFR Part 54, Financial Disclosure by Clinical Investigators
- All study site and Medtronic personnel will be trained using standardized training materials
- Study sites should follow their institutional procedures for maintenance of echocardiography and laboratory equipment used for assessing the study variables.Regular monitoring visits will be conducted to verify adherence to the CIP and source data
- An independent Clinical Events Committee (CEC) will be utilized to regularly review and adjudicate reported endpoint related adverse events

Subjects must meet all of the following criteria to be included in the study.

1. Subjects who require aortic or mitral valve replacement of his/her native a Mosaic or Hancock II bioprosthesis with PEEK Material.
2. Subject is geographically stable and willing to return to the implanting site for all follow-up visits.
3. Subject is of legal age to provide informed consent in the country where they enroll in the study.
4. Subject has been adequately informed of risks and requirements of the study and is willing and able to provide informed consent for participation in the clinical study.

Subjects who meet any of the following criteria will not qualify for participation in the study.

1. Subject requires concomitant replacement of the aortic and mitral valves.
2. Subject requires a replacement of a previously implanted failed prosthetic aortic or mitral valve.
3. Subject requires a Bentall procedure for replacement of aortic valve or aortic root.
4. Subject presents with active endocarditis, active myocarditis, or other active systemic infection.
5. Subject has a non-cardiac major or progressive disease, with a life expectancy of less than 1 year. These conditions include, but are not limited to:
    a. Child-Pugh Class C liver disease
    b. Terminal cancer
    c. End-stage lung disease
6. Subject has chronic renal failure, defined as dialysis therapy or GFR<30 mL/min/1.73 m2.
7. Subject has hyperparathyroidism.
8. Subject is participating in another investigational device or drug study or observational competitive study.
9. Subject is pregnant, lactating, or planning to become pregnant during the study period.
10. Subject has systolic EF<20% as assessed by echocardiography.
11. Subject has Grade IV Diastolic Dysfunction.
12. Subject requires emergency surgery.
13. Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable such that subject cannot provide informed consent.

6. Determination of Sample Size

PASS (2013) software was used to calculate the sample size. Confidence interval method for one proportion was utilized. When the sample event free proportion assumed to be 97% at 1 year post implantation, to achieve a one-sided 95% confidence interval width of 5.0% or less, a sample size of 89 subjects with the exact (Clopper-Pearson) confidence interval method for one proportion. Allowing for attrition rate of up to 20% in the first year, a total of up to 110 subjects will be enrolled.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Analysis Sets

The primary analysis will be evaluated for the implanted population. The implanted population consists of all enrolled subjects who are actually implanted with a Mosaic or Hancock II device. To be considered implanted, the subject's device disposition form must show at least one device with a final disposition of "Implanted." Time zero begins at the date of the procedure.

7.2. General Methodology

All continuous variables will be summarized with means, standard deviations, medians, interquartile ranges, minimums, and maximums. Categorical variables will be summarized with frequencies and percentages.

For comparisons of categorical data between sub-groups, chi-square tests will be used unless there are expected cell counts of less than 5. In those cases, Fisher's exact test will be used. No multiplicity adjustments will be made to control the familywise Type I error rate. Caution needs to be taken when interpreting statistical significance or making statistical inference.

All statistical tests and/or confidence intervals, as appropriate, will be performed at α=0.05 (2-sided), except when specified otherwise. All reported p-values greater than or equal to 0.001 will be rounded to three decimal places. P-values less than 0.001 will be displayed as "<0.001".

7.3. Center Pooling

The study will be conducted at up to 15 sites worldwide with approximately up to 7 sites in the US and up to 8 sites in Europe with a maximum of 110 total subjects enrolled. Per site there is no minimum enrollment requirement, however, a maximum of 20 enrolled subjects per site will be allowed. Data from all the sites will be pooled for the analyses.

7.4. Handling of Missing Data and Dropouts

Unless specified otherwise in each objective, no statistical techniques will be used to impute missing data. If a subject's data are missing for any reason, that subject will not be included in that portion of the analysis. The number of subjects included in each analysis will be reported so that the potential impact of missing data can be assessed.

In the case of partial dates, the general rule is as follows:

- If only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15th of that month.
- If only the year is known, the event or assessment will be analyzed as if it occurred on June 30th of that year.

These resolutions of partial dates are subject to the restrictions that pre-procedure events and assessments must occur between the enrollment date and the procedure date, and post-procedure events and assessments must occur no earlier than the procedure date. If additional information about the partial dates might be known, for example, the event occurs after 15th of the month, then data may be analyzed as if it occurred on the 16th of the month.

7.5. Demographic and Other Baseline Characteristics

Descriptive statistics will be used to report demographic and clinical characteristics at baseline. Major baseline demographic and clinical variables will be summarized for the implanted populations. Information to be summarized includes, but is not limited to:

- Demographics (age, gender)
- Cardiovascular conditions and risk factors
- Previous cardiac interventions

7.6. Evaluation of Objectives

7.6.1. Primary Objective(s)

The primary objective of the study is to characterize the freedom from valve related death, re-intervention of, or explant related to the Mosaic and Hancock II valves with PEEK stent material in a patient population undergoing aortic or mitral valve replacement of his/her native aortic or mitral valve at 1 year post implant.

7.6.1.1. Hypothesis and/or Parameters to Be Estimated

No specific hypotheses have been set for the overall analysis of freedom from deaths, re-intervention, or explant related to the Mosaic and Hancock II valves with PEEK stent material. Kaplan- Meier estimates will be provided for freedom from death, re-intervention of, or explant related to the Mosaic and Hancock II valves with PEEK stent material with its lower 95% confidence interval at 1 year.

7.6.1.2. Endpoints

The primary endpoints are valve related death, re-intervention of, or explant related to the Mosaic and Hancock II valves with PEEK stent material at 1 year.

7.6.1.3. Data Collection and Analysis Methods

Death, re-intervention, or explant related to the Mosaic and Hancock II valves will be adjudicated by the Clinical Events Committee (CEC) and collected on the CEC form. CEC adjudication shall overwrite the Medtronic classification of the events or site classification of the events.

Kaplan-Meier method will be used for time to the first valve related death, re-intervention of, or explant of the study valve related to the Mosaic and Hancock II valves with PEEK stent material at 1 year after procedure. Subjects not experiencing the event through 1 year after procedure will be censored. One year is defined at timepoint of 365 days post procedure. The product-limit estimate of the event-free rate (or event rate), the number of subjects at risk, the number of
subjects with event, the number of subjects censored, and the log-log transformed lower one-sided 95% confidence interval using the Greenwood standard error will be presented.

Specifically, Kaplan-Meirer estimate is as follows.

$$\hat{S}(t_k) = \prod_{j=1}^{k}(1 - \frac{d_j}{n_j})$$

Greenwood variance is estiemated as below.

$$Var\left(\hat{S}(t_k)\right) = \hat{S}(t_k)^2 \sum_{j=1}^{k} \frac{d_j}{n_j(n_j - d_j)}$$

Pointwise one-sided lower 95% confidence interval at 365 days post procedure after log-log transformation (Kalbfleisch and Prentice; 1980) is as below.

$$\hat{S}(t)^{\exp(z_\alpha * tao))}$$

$$where\ tao = \frac{\sigma(\hat{S}(t))}{\hat{S}(t) * \log\left(\hat{S}(t)\right)}$$

A Kaplan-Meier plot will also be presented.

This objective will be analyzed for the implanted population.

7.6.2. Secondary Objective(s)

The secondary objective of the study is to characterize the clinicalperformace of Mosaic and Hancock II valves containing PEEK stent material at 1 year post implant with regard to NYHA Functional Classification and hemodynamic performance.

7.6.2.1. Hypothesis and/or Parameters to Be Estimated

No specific hypotheses have been set for the analysis of hemodynamic performance of Mosaic and Hancock II valves containing PEEK stent material at 1 year post implant.

7.6.2.2. Endpoints

The clinical performance endpoints are:

- NYHA Functional Classification (at 1 year and annually thereafter through 3 years)
- Clinically acceptable hemodynamic performance obtained from echocardiography (at discharge or 30 days), 1 year and annually thereafter through 3 years) including:
  - effective orifice area (EOA)
  - effective orifice area index (EOAI)
  - peak pressure gradient
  - mean pressure gradient
  - performance index
  - cardiac output
  - cardiac index
  - valve regurgitation

7.6.2.3. Data Collection and Analysis Methods

NYHA data will be collected at baseline, 1 year and annually through 3 years on the site follow-up form. Echo data will be collected at baseline, discharge through 30 days, 1 year and annually through 3 years. All transthoracic (TTE) echoes will be analyzed by an echo core lab which will determine the values for the Hemodynamic Performance endpoints.

Data Collection Requirement	**Assessment Intervals**					
	Baseline	Implant	Discharge though 30 days	1 Year	Annually years 2-3	Exit
Window from implant	-45 days/ -180 days for TTE	Date of Mosaic and Hancock II valves with PEEK material Implant	≤ 30 days	± 30 days	± 60 days	Date of Exit
Demographics	X					

Data Collection Requirement	Assessment Intervals					
	Baseline	Implant	Discharge though 30 days	1 Year	Annually years 2-3	Exit
Window from implant	-45 days/ -180 days for TTE	Date of Mosaic and Hancock II valves with PEEK material Implant	≤ 30 days	± 30 days	± 60 days	Date of Exit
Physical Examination	X					
Pregnancy Test	X*					
Medical History	X					
NYHA Classification	X			X	X	
12-Lead ECG	X		X	X	X	
Blood Labs				X	X	
Transthoracic Echo (TTE)	X		X	X	X	
Transesophageal Echocardiogram (TEE)		X				
AE/Device Deficiency		X	X	X	X	X
Relevant Medications	X		X	X	X	
EuroScore II	X					
STS Risk Score	X					
Operative Information		X				
Protocol Deviations		X	X	X	X	X
Study Exit						X

*Pregnancy test is required for female subjects who are not exempt, see CIP section 10.3.1.

NYHA functional classification and echocardiographic (TTE) hemodynamic data will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables. NYHA functional class will be evaluated based on the percentage of subjects in each specific NYHA class at each follow-up time-point.

Hemodynamic Performance endpoints will be summarized as with continuous data. These data will be summarized by aortic and mitral position.

This objective will be analyzed for the Implanted population.

8. Validation Requirements

Validation requirements will follow SAS Programmers group guidance.

9. References

Kalbfleisch, J. D. and Prentice, R. L. (1980), *The Statistical Analysis of Failure Time Data*, New York: John Wiley & Sons.