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FAMILY OF COMPANIES

Statistical Analysis Plan (SAP)

36 mm CERAMAX® Ceramic Hip System PMA POST-APPROVAL STUDY:
Short to Mid-Term Follow-up of New Study Subjects
Protocol Version: D

SAP Revision: 1
SAP Revision Date: 20DEC2023

36 mm CERAMAX® Ceramic Hip System PMA POST-APPROVAL STUDY:
Short to Mid-Term Follow-up of New Study Subjects
Protocol Version: Rev D

The following individuals have reviewed this version of the Statistical Analysis Plan and are in agreement with the content:

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Revision History

Revision Number	Revision Date (DD/MM/YYYY)	Reasons for Revision
1	20/12/2023	Initial Version (SAP template rev 5)

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1 Study Design

This is a prospective, non-controlled, non-randomized, multicenter study of the 36 mm Ceramic on Ceramic (COC) device.

A new enrollment cohort of a minimum of 170 subjects will be prospectively enrolled into the study. Study sites will be comprised of both IDE study sites, as well as newly recruited sites. These subjects will be seen for a pre-op clinic visit at the time of consent, and then at 6 weeks, 1 year, 2 years, 3 years, 4 years, and a minimum of 5 years. The purpose of the pre-op visit will be to obtain patient medical history and baseline information. At the post-op clinic visits the following information will be obtained: a Harris Hip evaluation, radiographic evaluation, subject evaluation and adverse event information (if applicable). The primary endpoint in this study is device survivorship at 5 years post-op. A minimum of 80% of enrolled subjects will be confirmed to either have a surviving implant or to have had a revision at a minimum of 5 years post-op with a clinical evaluation.

For a given Subject, their study participation will end if they withdraw consent, as per Principle Investigator (PI) decision, undergo a revision of either the acetabular shell and/or liner, are reported as deceased or when they have reached the final endpoint at 5 years.

2 Treatment Assignment

Treatment assignment in this study was not randomized. All subjects received the 36mm COC device, and this was the only device configuration of interest in this PAS. Details regarding sample size are presented in Section 8.

3 Randomization and Blinding Procedures

This was a non-randomized, open-label study, and the sponsor was not blinded to any part of the study or data at any time during the study.

4 Interval Windows

The study includes the following time periods: Pre-op, 6 Wk, 1 Yr, 2 Yr, 3 Yr, 4 Yr, and 5 Yr Min. Intervals related to each are shown in Table 4-1 below.

Table 4-1 Interval Windows for Study Visits

Visit	Mininum Day	Maximum Day
Pre-op	-90 (-180 for Radiographic Data)	0
6 Weeks (Optional)	1	92
1 Yr	275	455
2 Yr	640	820
3 Yr	1005	1185
4 Yr	1370	1550
5 Yr Min	1825	2555

Time point specific data which were collected for the primary and secondary efficacy-related objectives will be assessed for compliance with these intervals. Only data which can be attributed to the Visit intervals in Table 4 1 will be used in the analysis of primary and secondary endpoints. If multiple measurements fall into the specified windows, the last value within the window will be utilized for analysis.

5 Levels of Significance

There are no pre-specified hypotheses and all analyses are exploratory. Summaries of the primary and secondary endpoints in this study are being undertaken without established statistical power. Any p-values and confidence intervals which are provided are only intended to facilitate clinical judgement.

6 Analysis Sets

There is only one analysis set defined for this study:

Safety Analysis Set - Subjects are considered to be in this analysis set if they have provided informed consent and treated as indicated in the protocol.

All analyses will be conducted on the Safety Analysis Set.

7 Sample Size Justification

The sample size will be a minimum of 170 prospectively enrolled subjects. This sample size will provide data upon which to obtain a 5-year survivorship estimate from newly enrolled subjects who did not participate in the COC36 IDE study. The sample size of 170 subjects in this PAS is approximately the same sample size of COC36 IDE investigational subjects, and hence will provide sufficient data on a new cohort of subjects to further support mid-term clinical success.

The objective of this study is to obtain an estimate of device survivorship at 5-years post-operatively. The 170 enrolled subjects will provide a minimum of 136 subjects (80% of enrolled subjects) with 5-year follow-up. This will yield a 5-year survivorship estimate that has an approximate 3.6% margin of error. In particular, Peto's estimate[1] for the variance of a Kaplan-Meier survival estimate is

$$var\big(\hat{S}(t)\big) = \frac{\big(\hat{S}(t)\big)^2\big(1-\hat{S}(t)\big)}{n(t)}$$

where $\hat{S}(t)$ is the estimate of survival at time *t* and $n(t)$ is the number of unrevised subjects at risk (still being followed) at time, and *t*. Hence, if it is assumed that the point estimate of survival is at a minimally acceptable level of 95.1% for subjects in this PAS, and there is a minimum of 136 subjects (80% of enrolled subjects) at 5-years post-operatively upon which this estimate is based, then an estimate for the variance of the Kaplan-Meier survival estimate at 5 years is

$$var\big[\hat{S}(5)\big] = \frac{[0.951]^2(0.049)}{136} = 0.00034\,,$$

and a two-sided 95% confidence interval margin of error for survival at 5 years is anticipated to be approximately

$$1.96 * \sqrt{0.00034} = 3.6\%.$$

A sample size of 170 enrolled subjects is therefore justified in order to obtain a 3.6% margin of error on a 5 year survivorship estimate.

8 Statistical Analysis Methods

8.1 General Conventions

Study data will be analyzed for all subjects in the Safety Analysis Set using SAS v9.3 or higher. Planned tabulations are described below and table, figure, and listing shells are provided separately.

Standard descriptive summaries for continuous data will include the number of subjects with non-missing data (n), mean, standard deviation (SD), median, minimum, and maximum values. For categorical data, counts and percentages will be provided. Percentages will be based on the number of subjects who do not have missing data for the respective endpoint.

[1] Cantor, A. Estimates of the Variance of the Kaplan-Meier Estimator. In: *Extending SAS® Survival Analysis Techniques for Medical Research.* 2nd ed., Cary NC: SAS Institute, 2003:24.

8.2 **Disposition of Study Subjects**

The number of study subjects, withdrawals before study completion, and those who have completed the study (All Safety Analysis Set subjects that were recorded to have completed the study requirements as outlined in the protocol) will be summarized.

8.3 **Demographic and Baseline Characteristics**

Descriptive statistics (at time of index surgery) will be displayed for subjects in the Safety Analysis Set:

- Age at time of index surgery (in years);
- Gender;
- Height;
- Weight;
- BMI (kg/m2);
- Ethnicity;
- Race;
- Any Known Allergies;
- Primary Diagnosis;
- Other Joint Involvement;
- General Medical Conditions;

8.4 **Endpoint(s) *and Associated Hypotheses***

8.4.1 **Primary Endpoint(s)**

The primary endpoint of this study is device survivorship at 5 years post-op. A revision is defined as the removal of any THA component(s), and device survival is defined as the lack of revision. No hypothesis tests of the primary endpoint are planned.

8.4.2 Secondary Endpoints

The secondary endpoints of this study are Harris Hip total and sub-score means, radiographic evaluations, device survivorship annually through 5 years post-op, and adverse event outcomes at each protocol defined post-op interval. No formal hypothesis tests of the secondary endpoints are planned. Confidence intervals and p-values may be provided (such as for the Cox proportional hazards model) to facilitate clinical judgement.

8.4.3 Additional Endpoints

Questions pertaining to function, pain, plans for any upcoming revisions, and satisfaction with the index hip replacement procedure were asked of study subjects, some by telephone if telephone follow-up was utilized. Responses to these endpoints are considered to be exploratory endpoints and will be summarized.

8.5 **Analysis of Primary Endpoint(s)**

8.5.1 Plans for Interim Analysis

There were no planned interim analyses for the purpose of terminating the trial early. Interim analyses of the primary and secondary endpoints were carried out to provide interim PAS progress reports to the FDA.

8.5.2 Plans for Final Analysis

A Kaplan-Meier survivorship analysis will be provided, with device survivorship as a function of post-op time. Implant survivorship will be reported for each year where greater than 40 hips are still at risk of revision. The 5 year KM survivorship estimate is the primary endpoint analysis.

8.6 **Handling of Missing Data**

In the analyses of all primary and secondary endpoints, no missing data imputation methods will be implemented.

8.7 Safety Analyses

Adverse events which occurred during subjects' participation in this PAS will be summarized. Adverse Events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 or higher.
An overall summary of the AE incidence will be presented, broken down by systemic and surgical site, and will include the number and percentage of subjects having one or more:

- Serious adverse event (SAE)
- Operative Site AEs
- Systemic AEs
- Device related AEs
- Procedure related AEs

The number and percent of subjects with adverse events and the 95% binomial exact confidence interval for this percent will be presented by MedDRA system organ class (SOC) and preferred term (PT) for all AEs and stratified for systemic and operative site adverse events. A subject-level listing will be provided to display details of all AEs.

8.8 Analyses of Secondary Endpoints

Harris Hip score summary statistics and change from baseline statistics will be reported for each protocol defined post-op visit interval. These will be provided for total Harris Hip score as well as the Harris Hip sub-scores (pain, function, activity, deformity, and range of motion). Results will be presented overall, as well as stratified by obesity (non-obese vs. obese) according to BMI (subjects with BMI < 30 vs. subjects with BMI ≥ 30, respectively). Responses to questions on the Subject Hip Outcomes questionnaire will be summarized at each post-op visit interval. Radiographic summaries will be provided for each protocol defined post-op visit interval. Device survivorship will be estimated at each year post-operatively. A proportional hazards model will be provided, in which device survivorship is a function of post-op time, and BMI (at the time of index surgery) is a covariate.

8.9 Additional Endpoint Analyses

All analyses which are described in sections 8.3, 8.5, 8.7, 8.8. will also be provided for the following subgroups:

- Each stem type (e.g., S-ROM, Summit, etc.) for which there are 10 or more subjects
- Each cup type (e.g. Pinnacle 100, Pinnacle Sector, etc.) for which there are 10 or more subjects

KM survivorship and cox proportional hazards models will only be conducted for subgroups which have more than 40 subjects.

9 Data Monitoring Committee (DMC)

A DMC was not used to monitor safety or efficacy in this study.

10 Appendix: Tables, Listings and Graphs Shells

A separate document will illustrate presentation for all planned Tables and Listings.

11 Reference(s)

[1] Cantor, A. Estimates of the Variance of the Kaplan-Meier Estimator. In: Extending SAS® Survival Analysis Techniques for Medical Research. 2nd ed., Cary NC: SAS Institute, 2003:24.

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Revision History for SAP Template

SUMMARY OF CHANGES	
Revision No.	Description of Change
1	New Document – Procedure Harmonization
2	Update role names for consistency across SOPs Added statement to randomization and blinding procedure section regarding a randomization plan Moved section related to primary and secondary endpoint analysis to be part of the analysis to be conducted section Added Safety Analysis section Added Adjustments for Multiplicity section Moved DMC section to bottom of template
3	Update approver to reflect 'Franchise Clinical Platform Lead' instead of 'Franchise Platform Head of Clinical Research' to reflect current structure
4	Updated footer to match version and added revision history table
5	Added company logo to the title page Require adding SAP template version in the history of revisions Added list of acronyms and abbreviations Replaced TOC with a working one Updated footnote to include version, confidential, and page number Added text to Introduction Made changes to the wording and order of section 8, which resulted in shifting of subsections Description added to Analyses of Secondary Endpoints Updated Appendix description and made it optional Added Reference section

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