STATISTICAL ANALYIS PLAN (SAP)

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Contents

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CRF	Case Report Form
FAS	Full Analysis Set
HHS	Harris Hip Score
HOOS	Hip Disability and Osteoarthritic Outcome Score
LOCF	Last Observation Carried Forward
N (or n)	Total Sample Size (or subgroup sample size)
SAP	Statistical Analysis Plan
TFL	Table, Figure and Listing
WOMAC	Western Ontario and McMaster Universities Arthritis Index

2 INTRODUCTION

The following Statistical Analysis Plan (SAP) details the statistical considerations, including the data analysis methods, for the Study Protocol D10070. Related documents to this SAP are the Study Protocol, Case Report Form (CRF), and Tables, Figures and Listings (TFL) Templates Shells.

The POLARSTEM™ is a commercially available cementless hydroxyapatite (HA) coated primary hip stem that has been in clinical use since 2002. The aim of this multicenter study is to validate the short-, mid- and long-term outcome of the POLARSTEM™ by evaluating standard efficacy and safety parameters. The preoperative status of the patients including demographic information, the surgical data, clinical and radiological outcomes will be documented.

3 STUDY DESIGN

The study is a prospective long-term multicenter clinical observation study. Overall a minimum of 225 patients were enrolled consecutively into the study at 3 sites. Patients enrolled into the study had at least one of the following indications:

- Primary or Secondary coxarthrosis
- Rheumatoid arthritis
- Developmental dysplasia of the hip
- Fracture or avascular necrosis of the femoral head

The patients were enrolled consecutively over 12 months and followed up for 10 years with observations at 3 months, 1 year, 3 years, 5 years and 10 years.

4 STUDY OBJECTIVES

The goal of this multicenter clinical observation study is to validate the short-, mid- and long-term outcome efficacy and safety of the POLARSTEM.

4.1 Primary Objective(s)

- Evaluation of function, range of motion (ROM), and pain as assessed by the Harris Hip Score (HHS), Hip disability and osteoarthritis outcome score (HOOS), an extension of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).
- Radiographic changes as defined by radiolucent lines, osteolysis, hypo- and hypertrophy implant loosening.

4.2 Secondary Objective(s)

- Intra- and perioperative implant-related "Adverse Events" (AE) and complications until discharge.
- Postoperative AE up to 10 years after the surgery

4.3 Exploratory Objective(s)

Not applicable.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

Short term, medium term and long term survival rates at 3 months and at 1, 3, 5, and 10 years.

5.2 Secondary Endpoints

- Harris Hip Score (HHS)
- HOOS Score (Hip Dysfunction and Osteoarthritis Outcome Score), which includes the complete WOMAC Osteoarthritis Index
- Radiological: radiolucent lines, osteolysis, hypo- and hypertrophy of the cortex, loosening of the implant or migration

5.3 Exploratory Endpoints

Not Applicable.

5.4 Safety Endpoints

- Intra- and perioperative implant-related "Adverse Events" (AE) and complications until discharge
- Postoperative AE up to 10 years after the surgery

6 STATISTICAL CONSIDERATIONS

6.1 Determination of Sample Size

A minimum of 225 patients were planned to be enrolled at all investigational sites.

6.2 Randomisation

Not Applicable.

6.3 Interim Analysis

Interim analyses were planned and carried out for this study at 5 year follow-up. The outcome from the analyses has previously been reported.

7 STATISTICAL ANALYSIS

7.1 General

Smith & Nephew's Global Biostatistics group will conduct the statistical analysis for this study. Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. All p-values will be rounded to three decimal places, p-values less than 0.001 will be presented as '<0.001' in all tables.

Baseline data, outcome variables and adverse events will be summarized according to the nature of the variable. Categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: number of observations, mean, median, standard deviation, minimum and maximum values. The outcome variables will be summarized for all recorded time points.

Appropriate parametric and/or non-parametric analyses will be chosen for statistical analysis. The analysis of continuous variables will be done using a paired-sample t-test if appropriate, to test for differences between the baseline and end of study outcomes. The Wilcoxon rank-sum tests will be explored if the data is non-normal.

If data allows, Kaplan-Meier estimates will be calculated for the survival data otherwise only the survival proportion with a 95% confidence interval will be reported..

All analyses will be performed in SAS version 9.4 (or later).

7.2 Analysis Populations

All subjects who provide informed consent are considered study participants. Study populations are defined as follows:

- **Full analysis population (FAS)**, including all subjects that were included in the study, who received study treatment and attended at least one post baseline assessment.
- **Per protocol analysis population**, including all subjects in the full analysis population, have no significant protocol deviations and meet the inclusion/exclusion criteria.
- **Safety population**, including all subjects who have received study treatment.

Statistical analysis will be performed using each of the subject populations as follows: Analysis of primary, secondary and exploratory variables will be performed separately using both the FAS and the Per-Protocol Set. All safety analyses will utilise the Safety Population. Demographic characteristics will be summarized for each analysis population. Demographic characteristics will be summarized on a subject level. For bilateral subjects the data corresponding to the date of the hip's first enrolment into the study will be used.

7.3 Handling of Missing, Incomplete and Repeat Data

Missing and incomplete data are usually due to lost to follow-up, revision, death and patient withdrawal. A complete accountability along with the explanation for lost-to-follow-up, death, revision, and withdrawn patients will be provided in the final study report and these subjects will be treated as censored at the date of lost-to-follow up in the survival analysis. The missing due to revision will be treated as device failure. A complete assessment of the informative/non-informative missing data will be performed. In case of missing outcome values at designated time points, the last observation carried forward (LOCF) method will be used.

7.4 Derived Data

The following variables will be derived from the collected data:

- **Age:** The age will be calculated as the exact number of days between the date of birth and date of entry into study converted to years (i.e. difference in days/365.25).
- **Body Mass Index (BMI):** BMI is obtained by dividing the weight (kg) at enrollment by the square of height (m) i.e. weight (kg)/ height^2 (m).

- **Baseline:** Preoperative examination visit is considered as the baseline visit for all parameters for which data is collected at that time point.
- **Safety population indicator variable**: A binary variable will be defined if the patient receives study treatment then the patient is included in the safety population or not. Only patients indicated as included in the safety population will be used in the safety population analysis.
- **FAS set indicator variable**: A categorical variable will be defined to indicate if the patient receives study treatment and attends at least one post-baseline assessment then the patient is included in the full analysis set. Only the patients in the included category will be included in the full analysis set.
- **Per-protocol set indicator variable**: A categorical variable will be defined to indicate if the patient is in the full analysis set and have no significant protocol deviations and meet the inclusion/exclusion criteria. Only the patients in the included category will be included in the per-protocol analysis set.
- **Visit Interval**: days between baseline assessment and Study Visit defined as: Date of Study Visit – date of baseline assessment.
- **Survival time (days)**: End of study/Death/Loss to Follow-up/revision date – baseline assessment date+1; In months, divide days by 30.4375; In years, divide days by 365.25.
- **Revision**: Binary indicator variable for presence of revision
- **Adverse event**: Binary indicator for whether a patient experiences at least one adverse event.
- **Scores (HHS and WOMAC from HOOS):** The global scores or scores under each dimension of the questionnaire under consideration will be determined per specific scoring instructions for each questionnaire.
  - Harris Hip Score (HHS)
  - Algorithms used for scoring each of the 10 items (components) of the HHS as well as the domains (pain, function, AoD and ROM) of the HHS and total HHS are presented below:
  -

Harris Hip Score (HHS) scores per item and domain			
Item	Original Response	Likely scores per Item	Domains (Range of Scores)
Pain	None or ignores it	44	**Pain Domain (0 to 44)**
	Slight, minimal, no compromise in activities	40	
	Mild pain, no effect on average activities, rarely moderate pain with unusual activity; may take aspirin	30	
	Moderate pain; tolerable but makes concessions to pain. Some limitation of ordinary activity or work. May require occasional pain medication stronger than aspirin	20	
	Marked pain, serious limitation of activities	10	
	Totally disabled, crippled, pain in bed, bedridden	0	
Limp	None	11	**Function Domain (0 to 47)** **{Sum of all items within subdomain}**
	Slight	8	
	Moderate	5	
	Severe	0	
Support	None	11	
	Single cane for long walks	7	
	Single cane most of the time	5	
	One crutch	3	
	Two canes	2	
	Two crutches or not able to walk	0	
Distance walked	Unlimited	11	
	Six blocks	8	
	Two or three blocks	5	
	Indoors only	2	
	Bed and chair only	0	
Sitting	Comfortably in ordinary chair	5	
	On a high chair for 30 minutes	3	
	Unable to sit comfortably in any chair	0	

Public transportation	Yes, possible	1	
	No, unable	0	
Stairs	Normally without using a railing	4	
	Normally using a railing	2	
	In any manner	1	
	Unable to do stairs	0	
Socks/Shoes	With ease	4	
	With difficulty	2	
	Unable	0	
Range of Motion (ROM)	Flexion = FLEX+EXT-FLEX_ZERO	N/A	
	Movement = ABD+ADD-ABD_ZERO	N/A	
	Rotation = ER+IR-ER_ZERO	N/A	
ROM subscore	Flexion+Movement+Rotation		**Range of Motion Domain (0 to 5))**
	0 to 29	0	
	30 to 59	1	
	60 to 99	2	
	100 to 159	3	
	160 to 209	4	
	≥ 209	5	
Leg Length Difference (in mm)	None	N/A	
	Ipsilateral longer (LL_DIF_LONG)	N/A	
	Ipsilateral shorter (LL_DIF_SHORT)	N/A	
Absence of Deformity (AOD)	IF (FLEX_ZERO = . OR FLEX_ZERO < 31) AND (ABD_ZERO = . OR ABD_ZERO < 11) AND (ER_ZERO = . OR ER_ZERO < 11) AND LL_DIF_LONG < 33 AND LL_DIF_SHORT < 33 THEN AODScore = 4	0 or 4	**Absence of Deformity Domain (0 to 4)**
Total HHS		Sum of all domain scores per subject	Sum of all domain scores per subject

Note: The maximum possible score for the HHS is 100.			

For the WOMAC from HOOS, algorithms used in deriving the pertinent endpoints are as presented below.

WOMAC from HOOS Stiffness, Pain, and Physical Function Raw Scores			
Items/Questions within each domain		Range of Individual RAW Scores for each item	Possible Range of Scores by Domain
	Stiffness		
S1	Stiffness in the morning	None = 0; Slight = 1; Moderate = 2; Severe = 3; Extreme = 4	0 to 8
S2	. Stiffness later in the day		
	Pain		
P1	Walking on flat	None = 0; Slight = 1; Moderate = 2; Severe = 3; Extreme = 4	0 to 20
P2	Stair climbing		
P3	At night while in bed		
P4	Sitting or lying		
P5	Standing upright		
	Physical Function		
A1	Descending stairs	None = 0; Slight = 1; Moderate = 2; Severe = 3; Extreme = 4	0 to 68
A2	Ascending stairs		
A3	Rising from sitting		
A4	Standing		
A5	Bending on floor		
A6	Walking on flat		
A7	Getting in/out of car		
A8	Going shopping		
A9	Putting on socks		
A10	Rising from bed		
A11	Taking off socks		
A12	Lying in bed		
A13	Getting in/out bath		
A14	Sitting		
A15	Getting on/off toilet		
A16	Heavy domestic		
A17	Light domestic		
Total RAW WOMAC Score		Sum of Stiffness, Pain, and Physical Function scores	0 to 96

Algorithms for Calculating Transformed WOMAC from HOOS scores

WOMAC Subdomain	Original score = sum of the following items from Table 2	Possible Raw score range
Pain	P1 to P5	20
Stiffness	S1 to S2	8
Function	A1 to A17	68
Total	Sum{(P1 to P5), (S1 to S2), (A1 to A17)}	96
Transformed Score (per subdomain) = 100 – {(actual raw score/possible raw score range)x100}		

Each WOMAC subdomain score is transformed independently to a value that would range between 0 and 100. For each transformed score, a value of 100 is indicative that the subject has no problems while a score of 0 is indicative of severe problems within each subdomain.

- **Enrolled Subject:** A subject is considered to be enrolled into the trial when they sign informed consent forms.
- **Withdrawn Subject:** A withdrawn subject will be considered as one who does not complete the study because of to loss to follow-up or the early termination or any other known reason.
- **Completed Subject:** This study has been terminated early, a subject will be considered as having completed the study if he/she completed the 10 year visit for the study prior to its termination.

7.5 Baseline Data

Baseline characteristics with information available either at the preoperative or at the operative visit would be summarized using descriptive characteristics for continuous[1] or categorical[2] data but not only limited to the following variables:

- Body Mass Index (BMI)[1]
- Operative data[2] (i.e. surgery access)
- Charnley classification[2]
- Physical activity[2]
- Medication[2]
- Previous ipsilateral surgeries[2]
- Local risk factors[2]
- General risk factors[2]
- Type of anesthesia[2]
- Surgery time[1]
- Cup type[2]
- Cup size[2]
- Cup cemented[2]
- Stem size[2]
- Stem cemented[2]
- Head type[2]
- Head size[2]
- Neck length[2]
- Articulation[2]
- Operated Hip[2] (Right, Left, Bilateral).
- Fixation with additional screws[2]
- Tribological pairing[2]
- Primary diagnosis at enrollment[2]
- Intraoperative complications[2]
- Medical History[2] (i.e. general risk factors, diabetes, heart/circulatory, etc.)
- Local early postoperative complications[2]
- General early postoperative complications[2]

7.6 Disposition Data

- This would be summarized as the number of subjects (and hips) that were prematurely terminated on-study would be presented as frequency (n) and percentage (%). The reasons for premature termination would also be presented. Additionally, a listing of all terminations would be presented.
- The disposition of subjects (and hips) would also be summarized as clinical follow-up of the subjects' hip from the operative through the 10 year postoperative follow-up. Information to be summarized in these tables would include but not only restricted to theoretically due, revisions, terminations, expected at visit and present at visit.

7.7 Protocol Deviations

The frequency of protocol deviations will summarized along with the number of subjects experiencing each. Subjects with protocol deviations deemed as significant enough to exclude the subject from the Per Protocol analysis will be listed.

7.8 Measurement of Treatment Compliance

Not Applicable.

7.9 Multiplicity

Not Applicable.

7.10 Analysis of Primary Endpoint

- Short term, medium term and long term survival rates.
- Survival rates will be presented with a 95% confidence intervals at 3 months and at 1 year, 3 year, 5 year and 10 year postoperative time points from Kaplan-Meier product limit estimates.
- The revisions (by type of revision) will be tabulated and/or listed.

7.11 Analysis of Secondary Endpoints

- Harris Hip Score (HHS)

- HOOS Score (Hip Dysfunction and Osteoarthritis Outcome Score), which includes the complete WOMAC Osteoarthritis Index
    - The different dimensions of and the overall HHS, and WOMAC from HOOS scores at all recorded time points and end of study will be will be summarized using mean, median, SD, minimum, and maximum. A paired sample t-test (or a non-parametric equivalent such as the Wilcoxon signed-rank test) will be used to test the difference between preoperative and postoperative scores.
- Radiological: At all recorded time points (from the perioperative through the 10 year postoperative follow-up), the following analyses would be carried out:
    - For general findings: At the acetabulum position, cranial migration (mm), medial migration (mm) and tilted angle would be summarized using descriptive characteristics for continuous variables; At the stem position, varus tilting, valgus tilting and sunken (mm) will be summarized using descriptive statistics for continuous variables; Integration in general/acetabulum, integration in general/stem and ectopic ossification will be summarized using descriptive statistics for categorical variables.
    - Within the cup and the stem (by zone): The number and percent of hips with osteolysis will be summarized; for seams (0mm, 1mm, 2mm &>2mm), atrophy (none, mild, moderate & severe) and hypertrophy (none, mild, moderate & severe) their frequencies (n) and percentages will be presented.

7.12 Analysis of Exploratory Endpoints

Not Applicable.

7.13 Analysis of Safety Endpoints

- Intra- and perioperative implant-related "Adverse Events" (AE) and complications until discharge will be summarised
- Postoperative AE up to 10 years after the surgery
    - Adverse Events (as defined in Safety Reporting) – All adverse events will be tabulated classified by seriousness, relationship to the study device and given by frequency and percentages.

7.14 Other Data Summaries

Any other data from the CRF that was not planned for analysis but may help in the interpretation of the results will be summarised.

7.15 Changes in Analysis Methods Specified in the Protocol

There is a discrepancy in the protocol in regards to the sample size requirements for this study. In the "Study Design" section of the protocol, it is stated that a minimum of 225 subjects will be enrolled in 3 sites whereas in the "Sample Size Consideration" of the protocol, it is stated that "Sample size estimations have been made on the assumption that for a valid statistical data analysis according to Kaplan-Meier, at least 100 implants surviving 10 years are necessary. Over a period of 10 years, a drop-out rate of 30% should be considered. Therefore, 150 initial implantations are needed in each group".
A total of 225 subjects was eventually enrolled an implanted with the study device.

8 REFERENCES

1. Peacock JL, Kerry S. Presenting medical statistics from proposal to publication: a step-by-step guide. Oxford University Press; 2007.

2. Petrie A, Sabin C. Medical statistics at a glance. John Wiley & Sons; 2013.

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Witness Events	Signature	Timestamp

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Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	01-Dec-2021 | 12:31
Signing Complete	Security Checked	01-Dec-2021 | 12:32
Completed	Security Checked	01-Dec-2021 | 12:32

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