Statistical Analysis Plan (SAP)

Multi-Center, Non-Controlled, Prospective Radiostereometric Analysis of the Pinnacle Acetabular Shell

Protocol Version: REV 4

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1 Study Design

This study is designed as a prospective, multi-center, non-randomized, non-controlled study. This study does not limit the procedures involved in the treatment of the subject as long as the protocol specified products are utilized.

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective is to establish the mean superior cup migration of the Pinnacle Acetabular Shell using model-based RSA over the first two years post-implantation. The primary endpoint is the mean vertical subsidence (Y translation, also known as superior cup migration) at 2 years as measured with RSA. This will be summarized for each surgical approach separately, as well as combined.

1.1.2 Secondary Objectives

The secondary objectives are:

- To establish the subsidence profile of the Pinnacle Acetabular Shell; this will be accomplished by determining the mean subsidence at 3 months, 6 months and 1 year as measured with RSA.
- Other RSA measurements (X and Z translations in mm, X, Y, and Z rotations in degrees, and maximal total point motion in mm) at all time points.
- Functional and health status will be measured with Harris Hip Score, HOOS Jr. and Forgotten Joint Score (FJS-12).
- Analysis of cup positioning (inclination and version)
- Linear head penetration: Linear head penetration (in mm) will be performed by examining the change in distance between the center of the femoral head and the center of the acetabular shell between the 6-week (baseline) exam and the 3 months, 6 months, 1 year and 2 year exam. The femoral head center is determined

by fitting a CAD sphere to the articular region of the femoral head (ignoring the trunnion area). The acetabular shell center is determined in a similar manner but also uses the silhouette of the cup face to determine its' centerpoint.

1.1.3 Exploratory Objectives

The following will be summarized as exploratory analyses:

- Subsidence for subset of subjects where RSA data was obtained prior to discharge
- Analyses to examine the correlation of functional and health status outcomes vs. RSA observations may be explored.

2 Interval Windows

The study includes the following periods: Pre-op, Operative, Prior to Discharge, 6 Weeks, 3 Months, 6 Months, 1 Year, 2 Years. Intervals related to each are shown in Table 3, below.

Table 3 Interval Windows for Non-Radiographic Study Visits

Visit	Minimum Day	Maximum Day	Midpoint Day
Pre-Op*	**-90**	**0**	
Operative	**0**	**0**	**0**
Prior to Discharge	**1**	**Discharge**	
6 Weeks	**28**	**56**	**42**
3 Months	**60**	**120**	**90**
6 Months	**135**	**225**	**180**
1 Year	**275**	**455**	**365**
2 Years	**640**	**820**	**730**

* For radiographs Pre-Op study film window is from -270 days to DOS.

Time point specific data collected to satisfy 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 3 will be used in the analysis of primary and secondary endpoints. This visit will be hereafter referred to as the Analysis Visit and the originally recorded visit as the Nominal Visit. If multiple measurements fall into the pre-

operative window, or into the ‘Prior to Discharge’ post-operative window, the result collected most promimate to surgery will be utilized. For all post-operative visits after the ‘Prior to Discharge’ visit, if multiple measurements fall into the window then the last value within the window will be utilized for analysis.

3 Levels of Significance

There are no specific hypotheses being tested in this study. To facilitate clinical interpretation, confidence intervals will accompany primary and secondary endpoint estimates and will be 2-sided 95% confidence intervals; these confidence intervals are considered to be exploratory.

4 Analysis Sets

The following analysis sets are defined:

- **All Enrolled** – Subjects will be considered enrolled if they have consented and authorized release of their personal health information.
- **Safety** – The Safety Analysis Set consists of all enrolled subjects who receive THA surgery. Subjects will be analyzed according to the surgical approach applied during of the study.
- **Per Protocol** – The Per Protocol (PP) Analysis Set will be a subset of Safety Set subjects who have no major inclusion/exclusion protocol violations, and who have a 6 weeks RSA exam and at least one post-baseline RSA exam. Subjects will be analyzed according to the actual treatment (surgical approach) received during of the study.

5 Sample Size Justification

This study sample size was established to provide adequate precision on the mean subsidence estimate at 2 years for each surgical approach. A common standard deviation of 0.2 mm is anticipated. Based upon this standard deviation and a sample size of N=30, a

2-sided 95% confidence interval for each respective surgical approach is anticipated to have a margin of error equal to approximately $2SE = 2 * \frac{SD}{\sqrt{N}} = 2 * \frac{0.2}{\sqrt{30}} = 0.073mm$. This margin of error was deemed to be an adequate level of precision by the Sponsor.

6 Analyses to be Conducted

6.1 General Conventions

All statistical analyses will be performed using SAS® Version 9.4 or higher, unless otherwise noted. Standard descriptive summaries for continuous data include the number of subjects with non-missing observations (n), mean, standard deviation (SD), median, minimum, and maximum values. For categorical data, the count and percentage will be provided. Percentages will be based on the number of subjects without missing data. If exploratory tests of hypotheses are performed, t-tests will be performed for continuous variables, and Fishers' Exact Test will be performed for categorical variables. Baseline for the RSA analysis is 6 weeks with the exception of the exploratory analysis of the subset where RSA data is available prior to discharge. Baseline for the Forgotten Joint Score and for linear head penetration is also 6 weeks. Baseline for all other endpoints is the pre-operative measurements collected before surgery. Unless specifically stated otherwise, all endpoints will be analyzed by surgical approach and overall, pooling all surgical approaches.

6.2 Disposition of Study Subjects

Counts of the following categories of subjects by surgical approach and in total will be provided: All Enrolled dataset, Safety, major inclusion/exclusion protocol violations, Per Prototol, non inclusion/exclusion major protocol violations, deaths, withdrawals, study completion, ongoing in the study.

A subject accounting table using the Safety set will also be provided to account for the following at each follow-up interval:

- Treated: the count of subjects treated. This should not vary per visit;
- Not Yet Due: the count of subjects who do not have an evaluation at the visit and who, based on date of surgery and date of data extract, are not yet in-window for the visit;
- Theoretical Due: the count of subjects treated and not counted in Not Yet Due.
- Death: the count of theoretical subjects who died after the start of the window and who do not have data at the visit;
- Revision: the count of subject theoretically due, without data at the visit, who were revised. Revisions will be identified through consensus between Medical Affairs and the clinical study team using the data from the AE and study completion CRFs;
- Not Yet Overdue: count of theoretical subjects within the evaluation time window. Do not count subjects who have data at the visit or subjects who are counted in Death or Revision;
- Expected Due: the count of subjects theoretically due who are not counted in Death, Revision, Not Yet Overdue;
- Actual data on file (records with a date): the count of Expected subjects with a record with a date for each of the following endpoints: RSA measured subsidence, cup positioning (6 Weeks only), Harris Hip, HOOS Jr., Forgotten Joint Score, and Linear Head Penetration. A count of subjects with a record with a date in any of the listed endpoints will also be provided and a follow-up rate will be calculated using the number of Expected subjects in the interval as denominator;
- Scorable data: the count of Expected subjects with a record with a date and where the endpoint was scorable/non-missing for the following endpoints: RSA measured subsidence, cup positioning (6 Weeks only), Harris Hip, HOOS Jr., Forgotten Joint Score, and Linear Head Penetration. A count of subjects with a record with a date of all of the listed scorable endpoints will also be provided and a follow-up rate (complete data) will be calculated using the number of Expected subjects in the interval as denominator.

6.3 Demographic and Baseline Characteristics

Descriptive statistics will be summarized for the subjects in the Safety Analysis Population and for the subjects in the Per Protocol population (both in total and by surgical approach):

- Age at consent (in years);
- Sex;
- Child's bearing potential if Sex is Female;
- Height (cm);
- Weight (kg);
- BMI (kg/m^2);
- Clinical (30 <= BMI < 40) & morbid obesity (BMI >= 40);
- Primary diagnosis;

6.4 Operative details

Operative details will be summarized for the subjects in the Safety Analysis Population and for the subjects in the Per Protocol population (both in total and by surgical approach):

- ASA Risk;
- Surgical time (Duration) (min);
- Anesthesia time (Duration) (min);
- Surgical approach;
- Use of wires/cables;
- Use of screws. Additional details regarding the use of screws will be provided in a listing;
- Acetabular bone graft;
- Acetabular bone class;
- Acetabular osteophytes removed;
- Femoral bone graft;
- Femoral bone class proximal;

- Femoral bone class distal;
- DORR class.

6.5 Device Deficiencies and Protocol Deviations

Listings of device deficiencies and protocol deviations will be provided.

6.6 Primary Endpoint and Associated Hypotheses

RSA Measured Subsidence at 2 years

The primary endpoint of RSA measured subsidence (Y translation from week 6 in mm, also known as superior cup migration) results in the 2-year visit window will be summarized on the subset of subjects in the Per Protocol Analysis Set (primary analysis) who have 6 week and 2 year data for the analysis. The analysis will also be conducted on the subset of subjects in the Safety Analysis Set (supportive analysis) who have 6 week and 2 year data for the analysis. Standard continuous summaries will be provided along with 95% confidence intervals. These summaries will be provided for each surgical approach, as well as combined.

6.7 Secondary Endpoints

6.7.1 RSA Measured Subsidence and maximal total point motion at 3 months, 6 months, 1 year, and 2 years

X, Y, and Z translations from week 6 in mm and A, Y, and Z rotations in degrees, and maximal total point motion in mm will be summarized at the 3 month, 6 month,1 year, and 2 years visit windows using the Per Protocol Analysis Set and the Safety Set. Standard continuous summaries will be provided along with 95% confidence intervals. These summaries will be provided for each surgical approach, as well as combined.

6.7.2 Cup Positioning at 6 weeks

Inclination and version will be assessed at 6 weeks from the AP radiographs using Martell software. Summaries will be provided using the Per Protocol Analysis Set.

6.7.3 Linear head penetration at 6 weeks, 3 months, 6 months, 1 year, and 2 years

Linear head penetration (in mm) is the change in distance between the center of the femoral head and the center of the acetabular shell between the 6-week (baseline) exam and the 3 months, 6 months, 1 year and 2 year exam. The distance between the centers within each visit window will be summarized and the change from baseline will be provided using the Per Protocol Analysis Set.

6.7.4 Harris Hip Score at Pre-Op, 6 weeks, 3 months, 6 months, 1 year, and 2 years

Harris hip scores are assessed at the Pre-Op visit and at 6 weeks, 3 months, 6 months, 1 year and 2 years. Results within each visit window will be summarized and changes from baseline will be provided using the Per Protocol Analysis Set. Standard continuous summaries will be supplemented with 95% confidence intervals.

6.7.5 HOOS Jr. Score at Pre-Op, 6 weeks, 3 months, 6 months, 1 year and 2 years

HOOS Jr. scores are assessed at the Pre-Op visit and at 6 weeks, 3 months, 6 months, 1 year and 2 years. Results within each visit window will be summarized and changes from baseline will be provided using the Per Protocol Analysis Set. Standard continuous summaries will be supplemented with 95% confidence intervals.

6.7.6 Forgotten Joint Score (FJS-12) at 6 weeks, 3 months, 6 months, 1 year and 2 years

FJS-12 scores are assessed at 6 weeks, 3 months, 6 months, 1 year and 2 years. Results within each visit window will be summarized and changes from baseline will be provided

using the Per Protocol Analysis Set. Standard continuous summaries will be supplemented with 95% confidence intervals.

6.7.7 Hip Evaluation at Pre-Op, 6 weeks, 3 months, 6 months, 1 year and 2 years

Hip evaluation questions will be summarized at Pre-Op, 6 weeks, 3 months, 6 months, 1 year and 2 years as categorical data using the Per Protocol Analysis Set. The first two questions (“How satisfied are you with this procedure?” and “Would you have this procedure again?”) will not be summarized at the Pre-Op visit.

6.8 Exploratory Endpoint Analysis

Exploratory analyses will include the following:

- Summaries of RSA measured subsidence at 6 Weeks, 3 months, 6 months and 1 year and 2 years will be conducted on the subset of subjects where RSA data was obtained prior to discharge;
- Correlation of cup position at 6 weeks and cup migration across surgical approaches (pooled) as well as by surgical approach;
- Correlation of functional and health status outcomes (Harris Hip Score, HOOS Jr., and FJS-12) vs. RSA observations may be explored.

6.9 Safety Endpoint Analysis

Adverse Events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1. Analyses will be conducted for all subjects in the Safety Analysis Set.

An overall summary of the AE incidence within each surgical approach group as well as in total will be presented and will include the number and percentage of subjects having one or more:

- Any AE

- Intra-operative AEs
- Post-operative AEs
- Serious adverse event (SAE)
- Device related AEs (AEs marked Unlikely, Possible, Probable, or Causal Relationship by investigator)
- Procedure related AEs (AEs marked Unlikely, Possible, Probable, or Causal Relationship by investigator)
- AE leading to withdrawal
- Deaths

The number (%) of subjects with adverse events will be presented by MedDRA system organ class (SOC) and preferred term (PT) for all AEs, device related AEs, procedure related AEs and SAEs. In these summaries, AEs will be sorted by decreasing frequency within each MedDRA SOC and PT. A subject-level listing will be provided to display details of all reported AEs.

6.10 Plans for Interim Analysis

There are no formal interim analyses that are designed to potentially stop or change the study design. A planned interim summary analysis will take place after all subjects have completed the 1 year visit in order to give product development an understanding of acetabular cup subsidence that might be expected for future product development purposes. There is no intention to utilize this interim analysis as a means to justify stopping the study early.

6.11 Handling of Missing Data

Only subject data which is collected in the study will be utilized in analyses; there will be no imputation of missing data.

6.12 Adjustment for Multiplicity

P-values and confidence intervals will not be adjusted for multiplicity.

6.13 Sensitivity Analyses

No sensitivity analyses will be conducted.

6.14 Subgroup Analysis

Although no additional subgroup analyses are prospectively planned, post-hoc analyses may be conducted.

6.15 Assessment of Site Homogeneity

No formal assessment of site homogeneity will be conducted.

7 Data Monitoring Committee (DMC)

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

8 Appendix A – Questionnaire Scoring

8.1 Harris HIP Score

The Harris Hip Score[1] was developed for the assessment of the results of hip surgery, and is intended to evaluate various hip disabilities and methods of treatment in an adult population. Scores range from 0 (worse disability) to 100 (less disability).
To calculate the overall score, score each answer according to table 8.1.1, then sum up those scores to obtain the total score. Do not allow score to be greater than 100. If a question was left unanswered then the total score cannot be calculated..

8.1.1 HHS Scoring

Domain	Item	MHHS Question	Response Scoring
Hip evaluation	1	Pain	None = 44 Slight = 40 Mild = 30 Moderate = 20 Marked = 10 Totally disabled = 0
Gait	3	Limp	None = 11 Slight = 8 Moderate = 5 Severe = 0 Unable to walk = 0
Gait	4	Distance Walked	Unlimited = 11 6 blocks (600 meters) = 8 2-3 blocks (200-300 meters) = 5 Indoors only = 2 Bed and chair = 0
Gait	5	Support	None = 11 Cane long walk = 7 Cane full time = 5 Crutch = 3 Two canes = 2 Two crutches/Walker = 0 Unable to walk = 0
Activities	7	Stairs	Normally = 4 Normally with banister = 2 Any method = 1

			Not able = 0
Activities	8	Socks/Shoes	With ease = 4 With difficulty = 2 Unable = 0
Activities	9	Sitting	Any chair, 1 hour = 5 High chair, ½ hour = 3 Unable to sit, ½ hour, any chair = 0
Activities	10	Public Transportation	Able to enter = 1 Unable to enter = 0
Deformity	11	Deformity	If subject did not respond then missing **else** If Fixed adduction >= 10 degrees **or** Fixed internal rotation (in extension) >= 10 degrees **or** Leg length discrepancy > 3.2 cm or 1.25 in. **or** Fixed flexion >= 30 degrees **Then 0** **Else 4**
Range of motion	12	Flexion + Abduction + Adduction + External rotation + Internal rotation	Sum all ranges then score as following: Sum >= 161 = 5 101 <= Sum < 161 = 4 61 <= Sum < 101 = 3

			31 <= Sum < 61	=	2
			0 <= Sum < 31	=	1
			Sum < 0	=	0

8.2 HOOS Hip Jr. Scoring

This is a patient reported joint-specific score designed to evaluate outcomes after total hip arthroplasty. Scores range from 0 to 100 with a score of 0 indicating total hip disability and 100 indicating perfect hip health.

To calculate the overall score, score each answer according to table 8.2.1, then sum up those scores to obtain the total raw score. The overall score can be obtained from the total raw score using table 8.2.2. If at least one question is not answered then the overall score cannot be calculated. [Source: https://www.hss.edu/files/HOOS-JR-Scoring-Instructions-2017.pdf]

8.2.1 HOOS Hip Jr. Raw Score

Domain	**Item**	**MHHS Question**	**Response Scoring**
Pain	1	Going up or down stairs	None = 0 Mild = 1 Moderate = 2 Severe = 3 Extreme = 4
Pain	2	Walking on an uneven surface?	None = 0 Mild = 1 Moderate = 2 Severe = 3 Extreme = 4

Function, daily living	3	Rising from sitting	None = 0 Mild = 1 Moderate = 2 Severe = 3 Extreme = 4
Function, daily living	4	Bending to floor/pick up an object	None = 0 Mild = 1 Moderate = 2 Severe = 3 Extreme = 4
Function, daily living	5	Lying in bed (turning over, maintaining hip position)	None = 0 Mild = 1 Moderate = 2 Severe = 3 Extreme = 4
Function, daily living	6	Sitting	None = 0 Mild = 1 Moderate = 2 Severe = 3 Extreme = 4

8.2.2 HOOS Hip Jr. Scoring

Raw score	**HOOS Hip Jr. Score**
0	100.000
1	92.340
2	85.257

3	80.550
4	76.776
5	73.472
6	70.426
7	67.516
8	64.664
9	61.815
10	58.930
11	55.985
12	52.965
13	49.858
14	46.652
15	43.335
16	39.902
17	36.363
18	32.735
19	29.009
20	25.103
21	20.805
22	15.633
23	8.104
24	0.000

8.3 Forgotten Joint Score (FJS-12):

For scoring the FJS-12, all responses are summed (never, 0 points; almost never, 1 point; seldom, 2 points; sometimes, 3 points; mostly, 4 points) and then divided by the number of completed items. This mean value is subsequently multiplied by 25 to obtain a total score

range of 0 to 100. Finally, the score is subtracted from 100, to change the direction of the final score in a way that high scores indicate a high degree of “forgetting” the artificial joint, that is, a low degree of awareness. If more than 4 responses are missing, the total score should not be used. [Source: The “Forgotten Joint” as the Ultimate Goal in Joint Arthroplasty: The Journal of Arthroplasty Volume 27, Issue 3 , Pages 430-436.e1, March 2012 H Behrend et al.]

8.3.1 FJS-12 Scoring

FJS-12 Question	**Item**	**Response Scoring**
…in bed at night	1	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3 Mostly = 4
…when you are sitting on a chair for more than one hour?	2	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3 Mostly = 4
... when you are walking for more than 15 minutes	3	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3 Mostly = 4
... when you are taking a bath/shower	4	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3

		Mostly = 4
... when you are traveling in a car	5	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3 Mostly = 4
... when you are climbing stairs	6	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3 Mostly = 4
... when you are walking on uneven ground	7	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3 Mostly = 4
... when you are standing up from a low-sitting position	8	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3 Mostly = 4
... when you are standing for long periods of time	9	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3 Mostly = 4
... when you are doing housework or gardening	10	Never = 0 Almost never = 1 Seldom = 2

		Sometimes = 3 Mostly = 4
... when you are taking a walk/hiking	11	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3 Mostly = 4
... when you are doing your favorite sport	12	Never = 0 Almost never = 1 Seldom = 2 Sometimes = 3 Mostly = 4

9 References

- W. H. Harris, “Traumatic Arthritis of the Hip after Dislocation and Acetabular Fractures: Treatment by Mold Arthroplasty. An End-Result Study Using a New Method of Result Evaluation,” The Journal of Bone & Joint Surgery, Vol. 51, No. 4, 1969, pp. 737-755.

10 Tables, Listings and Graphs Shells

Draft shells tables, listings and graphs shells are included in “DSJ_2018_02 - Table Shells - 2019-12-17.docx”

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