Intraoperative case series study: trial rasp position versus SL-PLUS™ MIA Ti/HA femoral hip stem position

Short Title: SL-PLUS™ MIA Ti/HA femoral hip stem
15-4567-03

Statistical Analysis Plan
-Final Version-
Version: 1.0 (2017/09/21)

Contents

1. SIGNATURE PAGE

Study Title:	Intraoperative case series study: trial rasp position versus SL-PLUS™ MIA Ti/HA femoral hip stem position
Study Number:	15-4567-03
Product:	SL-PLUS™ MIA Ti/HA
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Position	Signature	Date Approved
Fiona Schlomowitsch Clinical Study Manager		28-Sep-2017
Nick Bornschein Biostatistician STATWORX		16-Oct-2017
Alan Rossington Reviewing Biostatistician		12-Oct-2017

2. REVISION HISTORY

Version Number	Reason for Change or Change Control Number	Document Author
0.1	Initial Draft Version	Nick Bornschein
0.2	Draft Version	Nick Bornschein
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0.9	Draft Version	Nick Bornschein
1.0	Final Version	Nick Bornschein

3. ACRONYMS

Table 1: Acronyms

Acronyms	Term
ADE	Adverse Device Effects
AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
DD	Device Deficiency
FAS	Full Analysis Set
m_{50}	Median
Max	Maximum
Min	Minimum
MRT	Multiple Response Table
N	Available Records (count)
SADE	Serious Adverse Device Effects
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
THA	Total Hip Arthroplasty

4. INTRODUCTION

With an increasing life expectancy, the demand of total hip arthroplasties is rising while the success of the hip implant depends to the position of the femoral stem. The correct position of a cemented hip stem is planned preoperatively. During surgery, the final

position of the rasp should correspond to the preoperatively determined position and the same position should be adopted by the cemented femoral stem.
The SL-PLUS™ MIA Ti/HA femoral hip stem study is going to evaluate the difference between the final position of the stem and the last trial rasp.

5. STUDY OBJECTIVES

The study objective is to evaluate if there is a difference between the femoral position of the last trial rasp and the final implant position of the SL-PLUS™ MIA Ti/HA femoral hip stem.

Primary Endpoint:

The primary endpoint is the mean difference D between the position of the last trial rasp and the final implant position of the SL-PLUS™ MIA Ti/HA femoral hip stem. The difference D is determined by analyzing standardized fluoroscopic images taken during surgery.
The difference D is given in mm and is defined as D = x1 – x2 with x1 being the distance between the shoulder of the trial rasp and the tip of the greater trochanter and x2 being the distance between the shoulder of the implant and the tip of the greater trochanter.

The study hypothesis is defined as:
H_0: The null hypothesis is that there is no mean difference between the position of the last trial rasp and the final implant position of the SL-PLUS™ MIA Ti/AH femoral hip stem.
H_1: The alternative hypothesis is that there is a mean difference between the position of the last trial rasp and the final implant position of the SL-PLUS™ MIA Ti/AH femoral hip stem.

Secondary Endpoints:

The secondary endpoints include a measurement of leg length discrepancy preoperatively and after insertion of the SL-PLUS™ MIA Ti/HA femoral hip stem. In addition, intraoperative complications will be collected.

6. INVESTIGATION PLAN

6.1. STUDY DESIGN

This is an observational, single arm, prospective, multi-center, case series study to collect intraoperative data from 40 subjects implanted with the SL-PLUS™ MIA Ti/HA femoral hip stem at 4 sites in Europe.
Data from eligible subjects, who have provided written and informed consent for the collection of their coded data, will be recorded on specially designed case report forms (CRFs).

No follow-up visits after surgery is planned for study participants. Therefore, total study duration for study participants is completed with surgery.
A final data analysis describing the study outcome is planned after completion of study assessments.

6.2. RANDOMIZATION PLAN

No randomization algorithm was followed for patient recruitment.

6.3. SAMPLE SIZE DETERMINATION

The following hypotheses will be tested:

H_0: The null hypothesis is that there is no mean difference between the position of the last trial rasp and the final implant position of the SL-PLUS™ MIA Ti/AH femoral hip stem.

H_1: The alternative hypothesis is that there is a mean difference between the position of the last trial rasp and the final implant position of the SL-PLUS™ MIA Ti/AH femoral hip stem.

$$H_0: \mu = 0 \; vs. \; H_1: \mu \neq 0$$

In 2007, a non-published cadaver test was performed to measure the difference D between the position of the last trial rasp and the implant position of the SL-PLUS™ MIA Ti/AH femoral hip stem. A total of 4 femoral hip stems were implanted into the cadaveric femur. The range of the measured difference was found to be between 0mm and 6mm. However, it is most likely that the maximum difference will be greater 6mm when more cases are studied. To compensate for the small number of evaluated cases, the anticipated variation in D will be extended to 10mm with an estimated standard deviation of 2.5mm. A correlation ρ between the distances x_1 and x_2 is certainly positive but it is unknown how strong the correlation is. The standard deviation sd of the difference D has the following relationship with the standard deviations sd_1 and sd_2 for distances x_1 and x_2:

$$sd^2 = sd_1^2 + sd_2^2 - 2\,\rho sd_1 sd_2$$

Since ρ>0 and assuming that ρ=0 will lead to a larger sd and therefore a larger sample size. If assumed that sd_1=sd_2, then sd^2=$2sd_1^2$. So assuming sd_1 and sd_2 being equal, the sd will also lead to a larger sample size. Therefore, assuming that the correlation is zero and allowing for both standard deviations sd_1 and sd_2 to be 2.5mm is a conservative approach for computing sample size.
According to orthopaedic surgeons, the maximum difference between the position of the rasp and implant without clinical significance is considered to be 2mm. The standard deviations of sd_1 and sd_2 are estimated as approximately 2.5mm estimated based on the assumptions above and data for the range of difference.
The sample size calculation is based on a two-sided test. The significance level and power of the study are chosen to be 0.05 and 0.90; the minimum mean difference Δ is identified as 2 mm; the standard deviations sd_1 and sd_2 are 2.5mm; the correlation between x_1 and x_2 is set to 0. The following formula can be used to calculate the sample size:

$$N \geq \frac{2(T_{N-1,\alpha/2} + T_{N-1,\beta})^2 sd^2}{\Delta^2}$$

The SAS POWER procedure is used to compute the sample size and at least 35 subjects are needed for the study.

6.4. VISIT SCHEDULE AND VISIT WINDOW

Table 1 shows the evaluations completed at each visit.

Table 2: Visit Schedule

Study Visit Schedule	Pre-Operative	Surgery Peri-Operative
Patient Information and Informed Consent	**x**	
Inclusion/Exclusion Criteria	**x**	
Demographics/Medical History	**x**	
Radiographic assessment	**x**	
Operative Data Collection		**x**
Fluoroscopic assessment		**x**
Measurement of leg length discrepancy	**x**	**x**
Adverse Event Assessment	**x***	**x**
End of Study/Exit		**x**

* if applicable

6.5. PRIMARY ENDPOINT EVALUATION

Once a subject has completed the informed consent procedure and signed the Informed Consent Form (ICF)[1], the Principal Investigator (PI) or delegated study research staff can complete the screening process with the subject. All potential subjects who undergo the screening process will be documented on a Screening and Enrollment Log, on which reasons for exclusion from or denial to participate should be noted. The primary endpoint analysis of the mean difference D between the position of the last trial rasp and the final implant position of the SL-PLUS™ MIA Ti/HA femoral hip stem will be based on full analysis set (FAS) population. The FAS population includes all subjects implanted with a SL-PLUS™ MIA Ti/HA femoral hip stem device in combination with a Smith & Nephew cup with consecutive enrollments to the study. Subjects being a screen failure (CRF plate 99, question 1. Screen Failue Yes) will be excluded from the FAS.
A primary endpoint analysis of a sub-group might be performed excluding subjects with low image quality as per defined image review criterias (e.g. trochanter not visible). This depends on the assessment of the independent Image Reviewer.

6.6. SECONDARY ENDPOINTS EVALUATIONS

The secondary endpoint analysis of measurement of leg length discrepancy preoperatively and after insertion of the SL-PLUS™ MIA Ti/HA femoral hip stem (and in addition, collecting intraoperative complications) will also be based on full analysis set (FAS) population.

6.7. SAFETY

Safety evaluations include the listing of Adverse Events (AE), Serious Adverse Events (SAE), Adverse Device Effects (ADE) and Serious Adverse Device Effects (SADE).

Additionally, listings about Device Deficiency (DD) will be reported.

7. STATISTICAL METHODS

7.1. GENERAL REPORTING CONVENTIONS

Analyses will be generated using Stata version 15.0 or higher.

General summary statistics for **numeric data** include the available records (N), the mean (Mean), the standard deviation (SD), the median (m_{50}), the minimum (Min), and the maximum (Max) value. Summary statistics can also be grouped by all relevant categorical variables, for example between lateral / standard or Pre-Op / Surgery/Peri-Op.

For **categorical data**, the count / available records (N) and percent (%) of data will be presented with the percent based on the number of subjects within the data. Additionally, bar charts will be provided.

[1] To eliminate the potential for selection bias, Investigators should consecutively pre-screen all subjects undergoing THA with the SL-PLUS™ MIA Ti/HA femoral hip stem. In order to do so, only the existing information obtained per standard routine medical procedures will be used. No study-specific screening procedures, activities or questionnaires will be performed during pre-screening.

For **missing data**, a complete accountability report, along with the explanation for lost-to-follow-up, death, revision and withdrawn subjects, is to be provided in the study report. No other adjustment or imputations will be made for missing data.

Multiple response answers (marked with "check all that apply") offer several ways to determine the number of valid observations. By default, all cases with at least one valid response are taken into account. All other observations are treated as missing. Furthermore, one might want to consider cases with complete information only and neglect all cases with one or more missing values (Stata option "casewise"). The results will be provided as multiple response table (MRT).

For any **two-group comparison**, a paired or unpaired t-Test (depending on the data) will be performed. All t-Tests will be fitted using Stata "ttest" command. No 2+ group comparison is planned in this study, so no baseline must be chosen.

If not mentioned otherwise, all results are reported as a two-sided significance test. Significance values of less than 5% ($p < 0.05$) are considered as statistically significant. Any confidence intervals (CI) will be based on 95% CIs.

7.2. STUDY POPULATIONS

All subjects who meet the study inclusion and exclusion criteria will be included in the statistical analysis. **Subjects being a screen failure as documented on "End of Study" – CRF (plate 99) (answer "yes") will be excluded from the statistical analysis.** Statistical analyses will be conducted for demographics, pre-operative information, surgical information and safety data. Demographics will include, but not limited to, gender, age, weight and height. Pre-operative information and surgical information will include any data collected as defined in this protocol. Safety data will include adverse events, serious adverse event, adverse device effect, serious adverse device effect, unanticipated serious adverse device effect, and device deficiency.

Descriptive statistics for continuous variables will include mean, median, minimum, maximum, standard deviation, and 95% confidence interval, if appropriate. Descriptive statistics for discrete variables will include count and percentage.

Subgroup analyses will be provided if they are necessary. The following sections define the details of primary endpoint and secondary endpoints analyses.

7.3. ADJUSTMENTS FOR INTERIM ANALYSES AND MULTIPLE ENDPOINTS

No interim analyses are planned and no adjustments will be made for multiple endpoints. Testing for secondary measures is provided as an aid in interpreting study results and no specific claims are being sought based on secondary measures.

8. STATISTICAL METHODS AND EVALUATIONS

8.1. SUBJECT DISPOSITION AND ACCOUNTABILITY

Summaries of subject disposition information will be provided and will include the number of subjects screened, enrolled and completed overall and by site (FAS population), the

number of subjects with data by time point and site (theoretical due), deaths, stem revisions, the expected number (expected) and the number of subjects completing the study (actual and %).

Table 3: Subject Disposition by screening and enrollment

	N
Screened	
Enrolled	
Completed	
Total	

8.2. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic characteristics including age at surgery, gender, operated study hip side and bilateral subjects, will be listed. Height and weight at surgery will be listed for all subjects who allowed use of this information. All pre-operative observations will be summarized descriptively. Summaries for demographic characteristics will be provided in total and by femoral stem type.
Additionally, pre-operative outcome information will be listed as frequency table and all "other" outcomes will be listed separately.

All tables are provided in the appendix, chapter **Error! Reference source not found.**.

8.3. TREATMENT ADMINISTRATION

Implant information of SL-PLUS™ MIA Ti/HA will be summarized descriptively including the operated side (left or right) and use of lateral or standard stem. A graph will show the use of lateral and standard stem per site by gender.

8.4. EFFECTIVENESS EVALUATIONS

8.4.1. Primary Analysis

If the difference between x_1 and x_2 measured from fluoroscopic images approximately follows a normal distribution, then a two-sided paired T test will be used to test the mean. The test statistic is a t-score defined by the following equation:

$$T = \frac{\bar{D}}{\frac{sd}{\sqrt{N}}}, \text{ where } \bar{D} = N^{-1}\sum_{N}^{i=1}(x_{i1} - x_{i2}), \text{ and } sd = \sum_{i=1}^{N}\frac{(x_1 - D^2)^2}{N-1} \text{ with } x_i = x_{i1} - x_{i2};\ i = 1, \ldots N$$

If the difference does not follow a normal distribution, then the signed rank test will be used to test the hypothesis.

8.5. SAFETY EVALUATIONS

8.5.1. Adverse Events, Serious Adverse Events and Device Deficiency

Definitions for safety reporting are outlined in chapter 8.1 of the study protocol and in chapter 6.7 of this document.

General and local intra- and post-operative observations will be summarized as frequency tables.

An overall summary of AEs will be provided including the number and percent of subjects with any AE, any related (definitely, probably, possible) AE, any severe AE, any severe and related AE, any AE resulting in death, and any AE resulting in removal or revision of component(s).

All AE will be summarized with count and percent, such as:

- Category of AE (medical diagnosis)
- Severity
- Relationship to study device and procedure
- Outcome
- Study participation
- Actions taken (multiple response)
- Seriousness

If the AE is serious (SAE), a frequency table of SAE categories will be provided.

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

8.5.2. Radiographic Data

There are no radiographic data.

8.6. OTHER EVALUATIONS

There are no other evaluations.

9. CHANGES TO PLANNED ANALYSES

No changes were made to planned analyses as outlined in the protocol.

10. REFERENCES

None.

11. LIST OF TABLES

Table 4: Table of Tables

12.9. End of Study	
Table 47	Screen Failure
Table 48	Completion of study
Table 49	Comments

12. APPENDIX

12.1. INCLUSION/EXCLUSION & INFORMED CONSENT

Table 5: Enrollment Eligibility

Eligibility criteria	Total N = xx
No	
Yes	
If no, reason	

12.2. DEMOGRAPHICS

Table 6: Age, Height and Weight by Subject

Variable	Statistic	Total* N = xx
Age at surgery (in years)	N	
	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	
Height	N	

(in cm)	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	
Weight (in kg)	N	
	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	
BMI	N	
	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	

Table 7: Age, Height and Weight by Hip

Variable	Statistic	Total N = xx
Age at surgery (in years)	N	
	Mean	
	Min	
	Max	
	SD	

	-95% CI	
	+95% CI	
Height (in cm)	N	
	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	
Weight (in kg)	N	
	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	
BMI	N	
	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	

Table 8: Gender

Gender	Total N = xx (%)
Female	
Male	

Table 9: Study Side

Study Side	Total N = xx (%)
Left	
Right	

Table 10: Bilateral Subject Identification

Contralateral hip enrolled	Total N = xx (%)
No	
Yes	
If yes, Subject ID	

12.3. PRE-OPERATIVE ANALYSIS

Table 11: Preoperative Planning

	Statistic	Total N = xx
Distance X	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	

Table 12: Planned Stem Size

Stem Size	Total N = xx (%)
01	
00	
1	
2	
3	
4	
5	
6	
7	

Table 13: Planned and used Stem Size

	Planned Stem Size									
Used Stem Size	**01**	**00**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Total N = xx (row %)**
01										
00										
1										
2										
3										
4										
5										
6										
7										
Total N = xx (row %)										

Table 14: Planned Stem Type

Stem Type	Total N = xx (%)
Standard	
Lateral	

Table 15: Planned and used Stem Type

	Planned Stem Type		
Used Stem Type	**Standard**	**Lateral**	**Total N = xx (row %)**
Standard			
Lateral			
Total N = xx (row %)			

Table 16: Diagnostic Reason for THA

Reasons for THA	Total N = xx (%)
Osteoarthritis	
Rheumatoid Arthritis	
Post-Traumatic Arthritis	
Avascular Necrosis	
Dysplasia	
Fracture	
Other	
If other, specify	

Table 17: Dorr Classification of Femoral Bone Typ

Reasons for THA	Total N = xx (%)
Type A	
Type B	
Type C	

12.4. OPERATIVE ANALYSIS

Table 18: Fluoroscopic images done

Fluoroscopic images	Total N = xx (%)
No	
Yes	

Table 19: Surgical Approach I

Surgical Approach I	Total N = xx (%)
Anterolateral	
Posterolateral	
Anterior	
Other	
If other, specify	

Table 20: Surgical Approach II

Surgical Approach II	Total N = xx (%)
Standard	
Minimal Invasive	

Table 21: Type of rasping instrument

Rasping instrument	Total N = xx (%)
Slap Hammer	
Woodpecker	
Mallet	
Combination	
If combination, specify	

Table 22: Implanted Components: Femoral Head

Femoral Head Typ	Total N = xx (%)
Ceramic Ball heads, Biolox delta	
Ceramic Ball heads, Biolox forte	
CoCr femoral head	
Other	
Femoral Head Size	**Total N = xx (%)**
28	
32	

36	

Table 23: Implanted Components: Acetabular Cup

Acetabular Cup Type	Total N = xx (%)
R3™ NO HOLE Acetabular Shells	
R3 NO HOLE HA Acetabular Shells	
R3 THREE HOLE Acetabular Shells	
R3 MULTI HOLE Acetabular Shells	
Other	
Acetabular Cup Size	**Total N = xx (%)**
28	
46	
48	
50	
52	
54	
56	
58	
60	

Table 24: Implanted Components: Acetabular Liner

Acetabular Liner Type	Total N = xx (%)
R3™ XLPE Acetabular Liners	

R3™ INTL Delta Ceramic Liners	
Other	
Acetabular Liner Size	**Total N = xx (%)**
28	
32	
36	

Table 25: Correction of final stem position necessary

Necessity of correction	**Total N = xx (%)**
No	
Yes	
If yes, method	
Smaller ball head length	
Larger ball head length	
Removal of stem and enlargement of femoral bed with last trial rasp	
Other method	
If other, specify	

Table 26: Leg Length Discrepancy

Leg Length Discrepancy	**PreOP N = xx (%)**	**PostOP[2] N = xx (%)**

[2] CRF: Operative Analysis

None			
Ipsilateral Longer			
Ipsilateral Shorter			
If Ipsilateral Longer/Shorter		**PreOP N = xx (%)**	**PostOP[3] N = xx (%)**
Ipsilateral Longer (mm)	Mean		
	Min		
	Max		
	SD		
	-95% CI		
	+95% CI		
		PreOP N = xx (%)	**PostOP[4] N = xx (%)**
Ipsilateral Shorter (mm)	Mean		
	Min		
	Max		
	SD		
	-95% CI		
	+95% CI		

Table 27: Patient Length Difference

Patient ID	lateral / standard	PreOp Leg Length Difference mm	PostOp Leg Length Difference mm

[3] CRF: Operative Analysis
[4] CRF: Operative Analysis

12.5. INDEPENDENT IMAGE REVIEW FLUOROSCOPY

Table 28: Trial rasp analysis

	Statistic	Trial Rasp Analysis N = xx
Distance X1 (mm)	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	

Table 29: Implant analysis

	Statistic	Implant Analysis N = xx
Distance X2 (mm)	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	

Table 30: Analysis of Distances

Distance	Mean	Difference	Significance
X1 (Trial Rasp)			
X2 (Implant)			

- Graph with Stem Comparison -

12.6. DEVICE DEFICIENCY

Table 31: Device Deficiency related to an AE

Relation to AE	Total N = xx (%)
No	
Yes	
If no, if intervention not made, could have let to SADE	
No	
Yes	

Table 32: Timing of Deficiency

Timing	Total N = xx (%)
Before use	
During procedural use	
After use	

Table 33: Duration, if inter-operative delay occurred

Variable	Statistic	Total N = xx
Duration of inter-operative delay (min)	Mean	
	Min	
	Max	
	SD	
	-95% CI	
	+95% CI	

Table 34: List of Deficiency

Listing

12.7. ADVERSE EVENT FORM

Table 35: List of Adverse Events

Description of AE	Total N = xx (%)

Table 36: Duration of resolved events

Description of AE	Start Date	End Date

Table 37: Severity

Severity	Total N = xx (%)
Mild	
Moderate	
Severe	

Table 38: Relationship to study device and procedure

	to study device	to study procedure
Relationship	**Total N = xx (%)**	**Total N = xx (%)**
Unrelated		
Possible		
Definite		

Table 39: Serious

Serious	Total N = xx (%)
No	
Yes	
If yes, specify	
Anticipated	
Unanticipated	

Table 40: Actions Taken

None	Total N = xx (%)
Yes	
Rest	
Yes	
Medication Therapy	
Yes	
Surgery/Procedure	
Yes	
Removal or revision surgery	
Yes	
Hospitalization or prolonged	

Yes	
Other	
Yes	
If other, specify	

Table 41: Outcome

Outcome	Total N = xx (%)
Recovered/Resolved	
Resolved with sequelae	
Recovering/Resolving	
Not recovered/Not resolved	
Fatal	
Unknown	

Table 42: Study participation discontinued due to event

Participation discontinued	Total N = xx (%)
No	
Yes	

12.8. SERIOUS ADVERSE EVENT REPORT FORM

Table 43: SAE

Description of SAE	Total N = xx (%)

Table 44: Hospitalization

Hospitalization	Total N = xx (%)
Yes	
No	
Admission Date	
Known	
Unknown	
Discharge Date	
Known	
Unknown	

Table 45: Discharge Date (Duration of hospitalization)

Discharge Date (Duration in days)	Total N = xx (%)
Mean	
Min	
Max	
SD	
-95% CI	
+95% CI	

Table 46: Involvement of study region

Study region	Total N = xx (%)
No	
Yes	

12.9. END OF STUDY

Table 47: Screen Failure

Screen Failure	Total N = xx (%)
No	
Yes	Excluded from analysis.
If yes, reason	

Table 48: Completion of study

Completed	Total N = xx (%)
Yes	
No	
If no, reason	
Subject withdrew consent after study treatment	
Subject not able to return	
Subject lost to follow-up after contact attempts were made according to protocol	
Investigator judgement	
Sponsor terminated study	
Subject deceased	

Table 49: Comments

Comment