Prospective, multicentre, single-arm, open, confirmatory trial to assess efficacy and safety of a navigation system providing personalized soft tissue balance data in medially-stabilized total knee arthroplasty.

Clinical Study Protocol

Medacta NextAR™ TKA Pivotal Trial

Study type:	Pivotal Clinical trial with Medical Device (MD)
Study categorisation:	Risk category according to HRA: C
Study registration:	The study is registered in a publicly accessible database (ClinicalTrials.gov Identifier: NCT04844879) as well as in the Swiss National Clinical Trial Portal (SNCTP via BASEC)
Study Identifier:	P02.022.02
Sponsor:	Medacta International SA Strada Regina CH 6874 Castel San Pietro (Switzerland)
Investigational device	NextAR™ TKA system (Class IIa)
Protocol Version and Date:	Version 6.0 dated 10 January 2023

10.2 Assessment, notification and reporting on the use of radiation sources

The dose from radiation sources used in this study is the same foreseen for conventional TKA procedures. No extra radiological assessment will take place in this study.

11. STATISTICAL METHODS

11.1 Hypothesis

The hypothesis of this study is that the OKS at 6 months of follow up is not inferior compared to the OKS obtained at the same time point in a benchmark study. In this respect, the null hypothesis is mean OKS at 6 months = 37. The MCID for the OKS has been demonstrated to be 5 points (33), therefore the alternative hypothesis is mean OKS at 6 months = 32.

A rejection of the alternative hypothesis would indicate that the NextAR™ TKA system provides comparable functional outcomes than the conventional operation.

11.2 Determination of Sample Size

A power analysis for a one sample t-test was performed with G-Power 3.1.9.4.
The benchmark data were gathered from an ongoing ODEP study in which the GMK® Sphere is implanted with either standard instrumentation or with patient-specific instrumentation. In that study, the mean OKS at 6 months was 37 with standard deviation of 9 (n=482).
Considering that the MCID for the OKS has been defined in the literature to be 5 points (33), we consider that a mean OKS of 32 at 6 months obtained with the NextAR™ TKA system would indicate clinically significant worse functional outcomes.
The null hypothesis of the study is H0 = 37, and the alternative hypothesis is Ha= 32. As the test is to show a discrepancy from the null hypothesis and not specifically a greater or lesser value, a two-tailed test was chosen. By choosing a significance level of 0.05 and power of 0.9, the resulting sample size is n=37, which was rounded up to n=40 patients to account for possible dropouts and patients lost to follow-up.

11.3 Statistical criteria of termination of trial

The statistical criterion for discontinuation of the trial is the occurrence of any device deficiency of the NextAR™ TKA system, prompting the investigator to complete surgery by means of the standard equipment, for:

- 3 consecutive patients operated by the same investigator, or
- 5 total patients.

In case of occurrence of either of these cases, the study will be discontinued until the causes of device deficiency are evaluated and solved. The study will resume only after the approval by the CEC and CA of all amendments. The criteria for premature study termination are reported in §2.9.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

The analysis will be performed on recruited patients who are treated with the investigational device.

The dataset will be exported from the electronic database “MyClinicalData” (see §12). Variables will be used as exported. Where necessary, variables are calculated (e.g. percentages) and additional ordinal categories, such as age groups (e.g. younger/older than 60) could be created. If applicable, delta of change (pre vs postoperative value) may be calculated for further analysis.

11.4.2 Primary Analysis

Once all included patients reach 6 months of follow-up, the mean OKS at 6 months will be calculated and compared to the OKS at 6 months of the benchmark study.

11.4.3 Secondary Analyses

For each endpoint described in §5, descriptive statistics including the mean, standard deviation, range, and median for continuous data and the count and percentage for categorical data will be calculated.

Paired Student's t-tests or Wilcoxon tests will be used to compare the continuous variables between the baseline and the follow ups.

Unpaired Student t-tests or Mann–Whitney U tests for continuous variables, and Chi-Square test or Fisher's exact test for categorical variables, will be used to compare early and late cases to evaluate the effect of the learning curve.

Comparison between the several time points are performed with the use of ANOVA with repeated measures.

The relationship between knee laxity, kinematic alignment and functional/clinical outcomes will be explored using the Spearman or Pearson correlation, or using a stratification upon knee laxity/ kinematic alignment followed by group comparison.

An alpha of 0.05 is considered significant. For PROs, MCID will be considered in addition to statistical significance. To address multiplicity, conventional non-hierarchical methods (e.g. Bonferroni correction) will be used.

11.4.4 Interim analyses

An early interim analysis is planned once the first 4 included patients reach 2 months of follow-up and undergo the radiographic evaluation (First-In-Man – FIM – cohort). Mandatory condition for this analysis is that all queries concerning missing data, SAEs and device deficiencies are resolved. The interim analysis will be notified to Swissmedic and the CEC. No other patient will be treated with the investigational device until the data have been analysed.

A second interim analysis is planned once all included patients reach 6 months of follow-up.

11.4.5 Safety analysis

All communicated AE will be evaluated by the Sponsor to establish a relationship with the investigational device.

11.4.6 Deviation(s) from the original statistical plan

Any deviation(s) from the planned analyses will be justified and reported in the annual safety report and/or clinical investigation report.

11.5 Handling of missing data and drop-outs

Every reasonable attempt should be made in order to recover all missing data. In case the patient had surgery elsewhere, the surgery report of the revision surgery is requested from the other surgeon if the patient agrees.

In case of patients lost to follow-up, available data will be used for analysis as described in §8.5.

The missing data will be assumed missing completely at random. No imputing of the missing data will be done and only available data will be analysed. With respect to the primary outcome of the study (OKS), published prescriptions for handling missing data will be followed (31). Namely, if after repeated attempts to obtain complete data from an individual, only one or two questions have been left unanswered, it is feasible to enter the mean value representing all of their other responses in order to fill the gaps. If more than two questions are unanswered, the overall score should not be calculated. If patients indicate two answers for one question the worst response is adopted (31).