Persona® Ti-Nidium® Personalized Total Knee System

A Post-Market Clinical Follow-up Study to Provide Safety, Performance and Clinical Benefits Data using the Persona Ti-Nidium Total Knee System and Instrumentation

Study Type: Post-Market Clinical Follow-up (PMCF)

CMG2020-05K

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United States

STUDY SPONSOR

Zimmer Biomet, Inc.
Clinical Affairs Department
1800 West Center Street
Warsaw, IN 46580
800-613-6131

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1. Contact Information/List of Investigators

Title	**Persona® Ti-Nidium® Personalized Total Knee System** A Post-Market Clinical Follow-up Study to Provide Safety, Performance and Clinical Benefits Data using the Persona Ti-Nidium Total Knee System and Instrumentation
Protocol Number	CMG2020-05K
Study Sponsor Contact Information	Zimmer Biomet, Inc. Clinical Affairs Department 1800 West Center Street Warsaw, IN 46580 United States 800-613-6131
Monitoring Contact Information	Zimmer Biomet, Inc. Clinical Affairs Department 1800 West Center Street Warsaw, IN 46580 United States 800-613-6131
Investigational Site Information (Clinical Investigation as per Annex XV of EU MDR)	The study will include up to 10 sites in the United States. Details regarding the sites involved will be maintained in the Sponsor's Trial Master File.

2. Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AP	Anteroposterior
ASADE	Anticipated Serious Adverse Device Effect
CI	Confidence Interval
CoCr	Cobalt Chrome
CPS	Constrained Posterior Stabilized
CR	Cruciate Retaining
CRF	Case Report Form(s)
CTA	Clinical Trial Agreement
EDC	Electronic Data Capture
EQ-5D-5L	euroQOL Five Dimensions Questionnaire
ICF	Informed Consent Form
IFU	Indications for Use
IRB	Institutional Review Board
ITT	Intent to Treat
KM	Kaplan-Meier
KSS	Knee Society Score
MC	Medial Congruent
MCL	Medial Collateral Ligament
MDR	Medical Device Regulation
ML	Medial Lateral
OA	Osteoarthritis
OKS	Oxford Knee Score
PMCF	Post-market Clinical Follow-up
PP	Per Protocol
PROM	Patient Reported Outcome Measures
PS	Posterior Stabilized
RA	Rheumatoid Arthritis
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard Deviation
TKA	Total Knee Arthroplasty
UC	Ultracongruent
USADE	Unanticipated Serious Adverse Device Effect
VEHXPE	Vivacit-E Highly Crosslinked Polyethylene

3. Study Synopsis

Complete Protocol Title	**Persona® Ti-Nidium® Personalized Total Knee System** A Post-Market Clinical Follow-up Study to Provide Safety, Performance and Clinical Benefits Data using the Persona Ti-Nidium Total Knee System and Instrumentation
Protocol Number	CMG2020-05K
Short Protocol Title	Persona Ti-Nidium PMCF
Sponsor	Zimmer Biomet, Inc. – Warsaw, IN
Manufacturer	Zimmer Biomet, Inc.
Study Device(s)	**Persona Ti-Nidium Personalized Total Knee System**
Study Objectives/Endpoints	The main objectives of this study are to evaluate overall clinical performance and safety of the *Persona* Ti-Nidium implant in total knee arthroplasty. **Endpoints**: The primary endpoint is the assessment of clinical performance and benefits by evaluating the improvement in the Oxford Knee Score between pre-operative and 2-year post-operative follow-up. This will be done by evaluating against an MCID of 7 points, according to Beard et al (2015).[1] The secondary endpoints of safety, clinical benefits, and performance will additionally be evaluated through the following: *Safety* through the assessment and evaluation of radiographic imaging at each time point and by the overall incidence and frequency of adverse events including revision of any component at each time point. *Clinical benefits* through the KSS Expectations (pre and post-op) and the euroQOL Five Dimensions Questionnaire (EQ-5D-5L). *Performance* through the evaluation of the revision, removal, or exchange of any implant component for any reason at each post-op time point using Kaplan-Meier

	estimator, and through evaluating improvements in the KSS Objective Knee Assessment.
Indications/Target Population	Patients qualifying for primary total knee arthroplasty who meet the inclusion/exclusion criteria for study participation.
Inclusion/Exclusion Criteria	**Inclusion Criteria**: *Study Inclusion Criteria:* 1. Patient is of legal age and skeletally mature 2. Patient is willing and able to provide written Informed Consent by signing and dating the IRB/EC approved Informed Consent document 3. Patient is willing and able to complete scheduled follow-up evaluations as defined in the study protocol 4. Patient qualifies for total knee arthroplasty based upon physical exam and medical history, and meets the approved indications for use of the Persona Ti-Nidium Knee System and Vivacit-E polyethylene articulating surface 5. Independent of study participation, patient is a candidate for the commercially available Persona Ti-Nidium Knee and Vivacit-E polyethylene articulating surface, implanted in accordance with product labeling *Study Device Inclusion Criteria:* *The Persona Ti-Nidium Total Knee is intended for patients with severe pain and disability due to the following:* 1. Rheumatoid arthritis, osteoarthritis, traumatic arthritis, polyarthritis. 2. Collagen disorders, and/or avascular necrosis of the femoral condyle. 3. Post-traumatic loss of joint configuration, particularly when there is patellofemoral erosion, dysfunction or prior patellectomy. 4. Moderate valgus, varus, or flexion deformities. **Exclusion Criteria:** *Study Exclusion Criteria:* 1. Patient is unwilling to sign the Informed Consent 2. Patient is currently participating in any other surgical intervention or pain management study 3. Patient is pregnant or considered a member of a protected (vulnerable) population whose inclusion

	in the study is inappropriate (e.g. prisoner, mentally incompetent) 4. Patient has a mental or neurologic condition who is unwilling or incapable of following postoperative care instructions 5. Patient has a condition which would, in the judgement of the Investigator, place the patient at undue risk or interfere with the conduct of the study 6. Patient is institutionalized or is a known drug abuser, a known alcoholic or cannot understand the requirements of study participation *Study Device Exclusion Criteria* 1. Previous history of infection in the affected joint and/or other local/systematic infection that may affect the prosthetic joint 2. Insufficient bone stock on femoral or tibial surfaces 3. Skeletal immaturity 4. Neuropathic arthropathy 5. Osteoporosis or any loss of musculature or neuromuscular disease that compromises the affected limb 6. A stable, painless arthrodesis in a satisfactory functional position 7. Severe instability secondary to the absence of collateral ligament integrity 8. Rheumatoid arthritis (RA) accompanied by an ulcer of the skin or a history of recurrent breakdown of the skin 9. The kinematic alignment surgical technique is contraindicated for patients with greater than 5° valgus deformity with MCL insufficiency
Study Design	Prospective, multi-center data collection study model for the 510(k) cleared Persona Ti-Nidium Total Knee System used in primary cemented total knee arthroplasty
Clinical Phase	Post-Market
Sample Size	A minimum of 240 patients are to be enrolled in this study (60 of each variant: PS/CPS, CR, UC, MC) • Up to 10 sites in the United States • Each site may implant no more than 33% of each variant (80 subjects)
Length of Study	12 years (2 years of enrollment, 10 years of follow-up)
Materials and Methods	Inclusion of at least 240 subjects, who meet the inclusion and exclusion criteria and are eligible for a total knee

	arthroplasty using the Persona Ti-Nidium knee system. Prospective follow-up visits will occur until each subject in the study reaches the 10 year follow-up assessment.
Data Collection	Electronic / Paper
Statistical Reporting	Data collected in the study will be summarized descriptively and will be the basis of the annual report as well as the final study reports. Continuous data (e.g. age) will be summarized through means, medians, standard deviations, minimum, maximum and 95% confidence intervals (CIs) over time periods of interest. Categorical data (e.g. gender, race) will be summarized using counts, percentages and 95% confidence limits over time periods of interest. Comparison of the primary endpoint between 2 years and baseline will be performed using paired T-tests or the Wilcoxon tests to assess the differences. Revision rates and complication data will be presented as frequencies and percentages, and Kaplan-Meier survivorship will be reported.
Scores/Performance Assessments	Oxford Knee Score (OKS) EQ-5D-5L KSS Objective Knee Assessment KSS Expectations (pre and post-op)
Standards	The PMCF is compliant with the below: • ISO 14155: 2020- Clinical investigation of medical devices for human subjects - Good clinical practice. • The Declaration of Helsinki (DoH) - Ethical principles for medical research involving human subjects • US Code of Federal Regulations 21 CFR Parts 11, 50, and 56 • ICH Guideline on Good Clinical Practice
Study Funding	Funding for this clinical study is made available by Zimmer Biomet to support clinical data collection, IRB review fees and other expenses associated with the conduct and execution of this study protocol as outlined in the fully executed Clinical Trial Agreement

4. Data Collection Overview

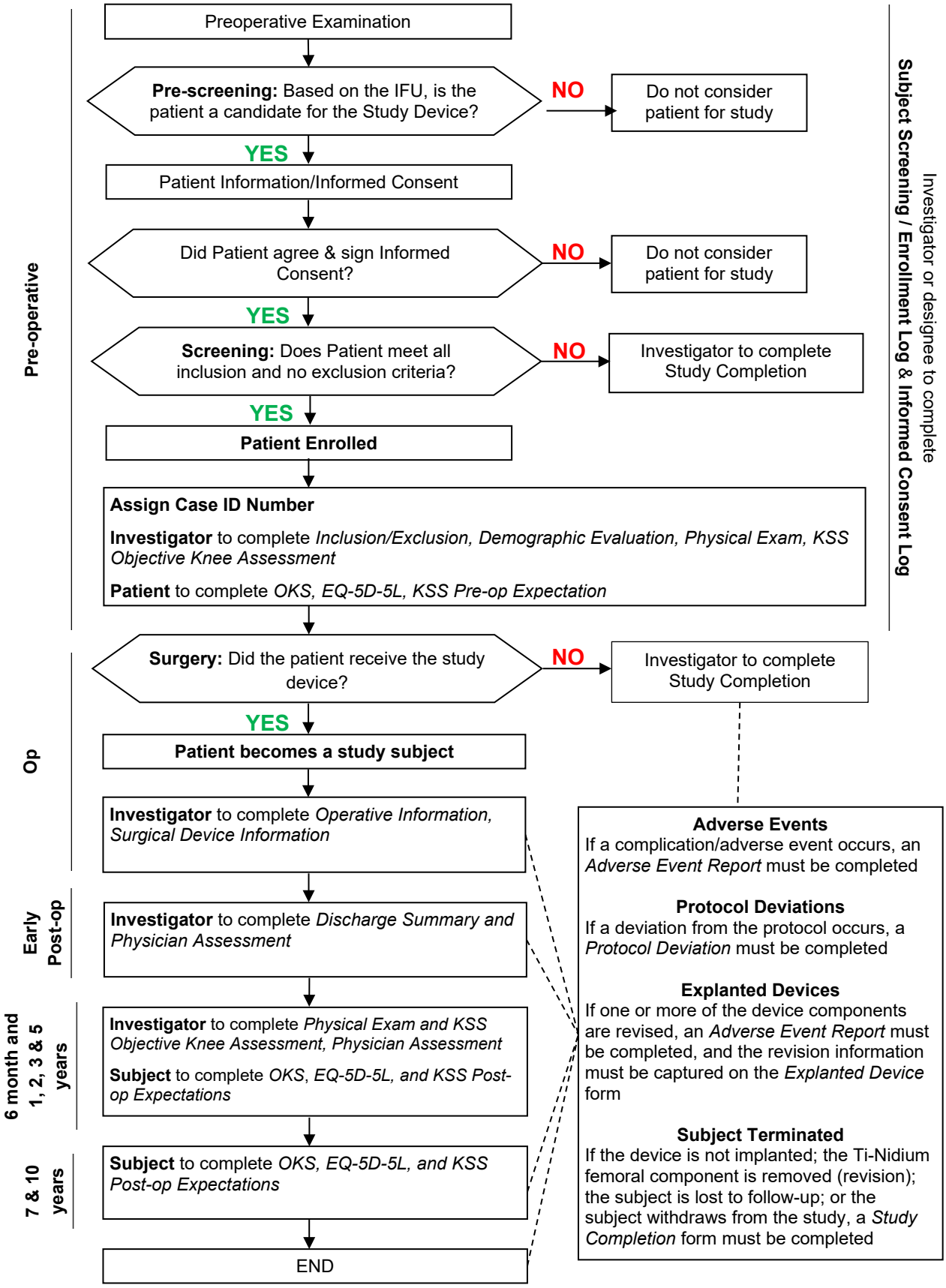
Forms and X-Ray Procedures	Pre-op	Operative	Early Post-op	Postop Follow-up Visits		
				6 month	1, 2, 3 & 5 year	7 & 10 year
Patient Information / Informed Consent	SS					
Inclusion/Exclusion Criteria	PI					
Demographic Evaluation	PI					
Oxford Knee Score	SS			SS	SS	SS*
EQ-5D-5L Questionnaire	SS			SS	SS	SS*
Physical Exam	PI			PI	PI	PI*
KSS Objective Knee Assessment	PI			PI	PI	PI*
KSS Pre-op Expectations	SS					
KSS Post-op Expectations				SS	SS	SS*
Operative Information		PI				
Surgical Device Information		PI				
Discharge Summary			PI			
Radiographs (AP and Lateral)	PI		PI	PI	PI	PI*
Physician Assessment of Radiographs			PI	PI**	PI**	PI**
Study Completion	If required					
Protocol Deviation	If required					
Adverse Event Report	If required					
Explanted Device			If required			

PI: completed by Investigator or qualified designee (required)

SS: completed by the Study Subject (required)

*: 7 and 10-year interval Patient Recorded Outcomes Forms can be completed either in office, electronically, or by mail. Therefore, the surgeon completed forms would be considered optional. If patient is reporting symptoms that warrant an in-office visit, complete the Physical Exam and KSS Objective Knee Assessment form.

**: Physician Assessment of Radiographs form is required for the Early Post-op visit. For all other visits, this form will be completed only if an abnormality is observed. Refer to Physical Exam/Radiograph form and Section 10.8 of this protocol.


Pre-operative
Preoperative Examination
Pre-screening: Based on the IFU, is the patient a candidate for the Study Device?
NO
Do not consider patient for study
YES
Patient Information/Informed Consent
Did Patient agree & sign Informed Consent?
NO
Do not consider patient for study
YES
Screening: Does Patient meet all inclusion and no exclusion criteria?
NO
Investigator to complete Study Completion
YES
Patient Enrolled
Assign Case ID Number
Investigator to complete Inclusion/Exclusion, Demographic Evaluation, Physical Exam, KSS Objective Knee Assessment
Patient to complete OKS, EQ-5D-5L, KSS Pre-op Expectation
Subject Screening / Enrollment Log & Informed Consent Log
Investigator or designee to complete
Op
Surgery: Did the patient receive the study device?
NO
Investigator to complete Study Completion
YES
Patient becomes a study subject
Investigator to complete Operative Information, Surgical Device Information
Early Post-op
Investigator to complete Discharge Summary and Physician Assessment
6 month and 1, 2, 3 & 5 years
Investigator to complete Physical Exam and KSS Objective Knee Assessment, Physician Assessment
Subject to complete OKS, EQ-5D-5L, and KSS Post-op Expectations
7 & 10 years
Subject to complete OKS, EQ-5D-5L, and KSS Post-op Expectations
END
Adverse Events
If a complication/adverse event occurs, an Adverse Event Report must be completed
Protocol Deviations
If a deviation from the protocol occurs, a Protocol Deviation must be completed
Explanted Devices
If one or more of the device components are revised, an Adverse Event Report must be completed, and the revision information must be captured on the Explanted Device form
Subject Terminated
If the device is not implanted; the Ti-Nidium femoral component is removed (revision); the subject is lost to follow-up; or the subject withdraws from the study, a Study Completion form must be completed

5. Introduction and Purpose

Osteoarthritis (OA) of the knee is one of the leading causes of knee disability among adults over 65 years of age.[2] Adults suffering from osteoarthritis likely experience significant pain during normal daily activities, often leading to a loss of productivity and quality of life. Total knee arthroplasty (TKA) procedures have the ability to manage the pain of those with OA, along with other knee related disabilities. From 2005 to 2030, TKA procedures are projected to rise approximately 673% to an estimated 3.48 million procedures performed annually by 2030.[3] Even in its current state, severe OA leading to TKA is the most commonly performed inpatient procedure in the USA.[4]

Constant design improvements, largely driven by the increasing demands of patients, are contributing to the greater longevity of total knee implants. One of the more recent design improvements came with the introduction of the Persona Total Knee System, launched in 2012. Based on its highly personalized design features, this system aims to address unmet needs and increase overall satisfaction of patients electing to undergo a TKA procedure by optimizing fit and leveraging advances in instrumentation. Indeed, early evidence has underpinned the positive impact of these design improvements.[5,6,7,8]

Beyond structural design advances, there exists an opportunity to explore solutions for patients requesting TKA procedures that may be sensitive to certain metal elements found in a traditional cobalt chrome knee system. As a result, these patients may experience hypersensitivity symptoms.[9]

Metal hypersensitivity is an immunological reaction of the body against metallic particles (ions) that are released as a result of implant wear or corrosion. This hypersensitivity in patients undergoing joint replacement may lead to complications, as the reaction can induce an immune response, leading to inflammation and sometimes implant failure.[10] The prevalence of cutaneous metal hypersensitivity in the general population is estimated to be between 10%-15%, while prevalence in patients with metallic implants may be as high as 25%.[11]

Most patients reporting a metal hypersensitivity describe a reaction against Nickel, Chromium or Cobalt; however, there are still no perfectly reliable testing methods in place to detect this hypersensitivity.[9] To strengthen patient comfort and confidence in total knee replacement procedures, several manufacturers offer zirconium or titanium alloy implants. This alternative may alleviate patient concerns surrounding hypersensitivity reactions that a

CoCr total joint implant does not, while also achieving favorable performance and longevity. Built on the clinical legacy of the NexGen Tivanium knee, which has 13 years of clinical use, the Persona Ti-Nidium knee combines the highly personalized design features of Persona with the clinically proven history of the material.[12]

6. Study Objectives

The objective of this study is to evaluate clinical performance, benefits and safety of the Persona Ti-Nidium implant in total knee arthroplasty.

Specific assessments include:

1. Confirming the long-term safety, performance and clinical benefits of the Persona Ti-Nidium total knee system and instrumentation in primary and revision TKA.
2. Verifying that, under normal use, the performance and clinical benefits of this device and its instrumentation conform to those intended by the manufacturer by recording patient-reported clinical outcomes measures (PROMs) and radiographic outcomes (if available).

7. Study Design and Endpoints

This is a prospective, multi-center data collection study for the 510(k) cleared Persona Ti-Nidium Total Knee System used in primary cemented total knee arthroplasty. The study enrollment specifics are as follows:

- A minimum of 240 patients are to be enrolled in this study to include 60 of each of the following variants: Posterior Stabilized/Constrained Posterior Stabilized (PS/CPS), Cruciate Retaining (CR), Ultra Congruent (UC), and Medial Congruent (MC)
- Up to 10 sites in the United States
- Each site may implant no more than 33% of each variant (80 subjects)

The study duration is expected to be 12 years, which corresponds to time dedicated to:

1. Obtain the Institutional Review Board (IRB) approval, if applicable.
2. Obtaining fully executed CTAs and any additional site IRB approvals.
3. Identify, obtain consent and enroll patients into the study.
4. Collect baseline information available in medical notes from the pre-op condition to the immediate post-op.

5. Invite subjects to return for their Early Post-op, 6 month, 1 year, 2 year, 3 year, 5 year, 7 year, and 10 year follow-up visits to collect patient data via verified CRFs. Patients unable/unwilling to return to the office visits will be given the option to complete PROMs remotely electronically or mail (7 & 10 year visits only).
6. Conduct data collection and analysis.
7. Draft a final study report.
8. Plan publication periods – engage surgeons for possible 2, 5, and 10 year publications/podium presentations.

The Study Endpoints are as follows:

- The primary endpoint is the assessment of performance and clinical benefits by evaluating the improvement in the Oxford Knee Score between pre-operative and 2-year post-operative follow-up. This will be done by evaluating against an MCID of 7 points, according to Beard et al (2015).[1]
- The secondary endpoints of safety, clinical benefits, and performance will additionally be evaluated through the following:
    - *Safety* through the assessment and evaluation of radiographic imaging at each time point and by the overall incidence and frequency of adverse events including revision of any component at each time point.
    - *Clinical benefits* through the KSS Expectations (pre and post-op) and the euroQOL Five Dimensions Questionnaire (EQ-5D-5L).
    - *Performance* through the evaluation of the revision, removal, or exchange of any implant component for any reason at each post-op time point using Kaplan-Meier estimator, and through evaluating improvements in the KSS Objective Knee Assessment.

Patient Reported Outcome Measures will be gathered at each follow-up time point up to 10 years for this study to ensure continued patient safety and performance of the device. This 10-year data will also be captured to help gain CE approval, and will be provided to notified bodies.

8. Study Population

The study population should be a consecutive series of subjects implanted with the Ti-Nidium Total Knee System and Vivacit-E polyethylene articulating surface that meet the inclusion and exclusion criteria. A minimum of 240 TKA procedures will be included in this

study. See the below inclusion and exclusion criteria that is to be considered.

Inclusion Criteria:

Study Inclusion Criteria:

1. Patient is of legal age and skeletally mature
2. Patient is willing and able to provide written Informed Consent by signing and dating the IRB/EC approved Informed Consent document
3. Patient is willing and able to complete scheduled follow-up evaluations as defined in the study protocol
4. Patient qualifies for total knee arthroplasty based upon physical exam and medical history, and meets the approved indications for use of the Persona Ti-Nidium Knee System with Vivacit-E polyethylene articulating surface
5. Independent of study participation, patient is a candidate for the commercially available Persona Ti-Nidium Knee and Vivacit-E polyethylene articulating surface, implanted in accordance with product labeling

Exclusion Criteria:

Study Exclusion Criteria:

1. Patient is unwilling to sign the Informed Consent
2. Patient is currently participating in any other surgical intervention or pain management study
3. Patient is pregnant or considered a member of a protected (vulnerable) population whose inclusion in the study is inappropriate (e.g. prisoner, mentally incompetent)
4. Patient has a mental or neurologic condition who is unwilling or incapable of following postoperative care instructions
5. Patient has a condition which would, in the judgement of the Investigator, place the patient at undue risk or interfere with the conduct of the study
6. Patient is institutionalized or is a known drug abuser, a known alcoholic or cannot understand the requirements of study participation

Study Device Exclusion Criteria

1. Previous history of infection in the affected joint and/or other local/systematic infection that may affect the prosthetic joint
2. Insufficient bone stock on femoral or tibial surfaces.
3. Skeletal immaturity

4. Neuropathic arthropathy
5. Osteoporosis or any loss of musculature or neuromuscular disease that compromises the affected limb
6. A stable, painless arthrodesis in a satisfactory functional position
7. Severe instability secondary to the absence of collateral ligament integrity
8. Rheumatoid arthritis (RA) accompanied by an ulcer of the skin or a history of recurrent breakdown of the skin
9. The kinematic alignment surgical technique is contraindicated for patients with greater than 5° valgus deformity with MCL insufficiency

9. Study Device Information



Figure 1: Persona Ti-Nidium Knee Ti-6Al-4V Alloy Femoral

The Persona Knee System is designed to resurface the articulating surfaces of the femoral, tibial and patellar bones. The system is comprised of porous and non-porous metal components and CR, UC, PS, CPS and MC articular surfaces. Furthermore, the Persona Tibial Stem extension can be applied to add an additional support to the Persona tibial implant non-porous baseplate. The Persona Knee system also includes patellar components for patelloplasty. The articular surfaces for this study are manufactured with Vitamin-E stabilized highly crosslinked polyethylene (VEHXPE) only, and the patellar components are manufactured with either conventional polyethylene or Vitamin-E stabilized highly crosslinked polyethylene.

The polyethylene articular surfaces match to five distinct tibial baseplate families to provide prescribed levels of kinematic constraint:

- Cruciate Retaining (CR) – A cruciate retaining articular surface may be used with a CR femur when a functional PCL exists.

- Ultracongruent (UC) – An ultracongruent articular surface may be used with a CR femur when both cruciate ligaments are excised and additional anterior constraint is needed.

- Medial Congruent (MC) – A medial congruent articular surface may be used with a CR femur when a functional PCL is present or absent.

- Posterior Stabilized (PS) – A posterior stabilized articular surface may be used with a PS femur when both cruciate ligaments are excised.

- Constrained Posterior Stabilized (CPS) – A constrained posterior stabilized articular surface may be used with a PS femur when both cruciate ligaments are excised, moderate varus/valgus constraint is needed and stems and augments are not required. CPS articular surfaces are for use with cemented non-porous tibial and femoral components only.

As indicated earlier, the Persona Ti-Nidium Knee System is to be used with *only* Vivacit-E polyethylene femorotibial inserts, which will snap into the tibial baseplate to provide an articulating surface for the femoral component.

Persona PS and CPS articular surfaces have a polyethylene intercondylar spine that provides constraint by interaction of the spine and the femoral component.

As an addition to the Persona Knee System the 510k cleared Persona® Ti-Nidium® Knee System (CR: K193223; PS: K200209) consists of a femoral component composed of a titanium alloy that has undergone a surface hardening process. This process, resulting in Ti-Nidium, involves thermal nitriding whereby nitrogen atoms are infused into the titanium lattice, which increases surface hardness and wear resistance while decreasing potential particle release.[13]

The Persona Ti-Nidium Knee System is intended for patients with painful and/or disabling knee joint issues due to the following indications:

- Rheumatoid arthritis, osteoarthritis, traumatic arthritis, polyarthritis;
- Collagen disorders, and/or avascular necrosis of the femoral condyle;
- Post-traumatic loss of joint configuration, particularly when there is patellofemoral erosion, dysfunction or prior patellectomy;
- Moderate valgus, varus, or flexion deformities.

10. Study Procedures

Prior to initiation at each particular study site, the following documents will be on file with the Sponsor (see below) and the study will be registered on clinicaltrials.gov:

- Clinical Trial Agreement (CTA): A fully executed Clinical Trial Agreement (signed by all required parties) must be on file with the Sponsor prior to any Investigator participating in this study.
- Institutional Review Board Approval: This study protocol must be submitted to and approved by the site's appropriate overseeing Institutional Review Board (IRB). A copy of the IRB approval letter must be submitted to the Sponsor. The letter should identify the following:
    - Protocol name and/or number
    - Date of IRB meeting (if available)
    - Date of approval
    - Date of expiration
    - Signature of IRB

Furthermore, once the study has been initiated, the **Site Signature/Delegation Log** (Appendix C) has to be filed with the Sponsor. This document will be maintained throughout the study and will contain the names, initials, signatures and study responsibilities including dates of all site personnel/designees involved in study procedures and data collection. If an individual no longer has any active authority with the study, the date of their removal from study activity must also be recorded.

10.1. Offer Study Participation

Study participation will be offered based on the indications and patient selection factors contained in the Information for Use (IFU) to each consecutive eligible patient presenting as a potential candidate for TKA using the Persona Ti-Nidium Knee and Vivacit-E polyethylene articulating surface. Based on the patient response, the patient may be invited to enroll in the clinical study. Prior to patient enrollment or any further patient evaluation for study eligibility, the patient must participate in the Informed Consent process (see section 10.3 below) and sign the IRB approved Informed Consent form.

For bilateral TKA candidates that agree to enroll for both operative sides, a separate Informed Consent must be signed and dated for each operative side.

10.2. Patient Screening/Enrollment Log

A **Subject Enrollment Log** (Appendix C) will be completed to document all consecutive individuals screened as potential candidates for the study. For each screening failure (patient that will not actually take part in the study) the reasons will be documented and shared with the Sponsor. The Screening/Enrollment information must be maintained throughout the study and will be part of the site Regulatory Binder. The Sponsor will review this log at each monitoring visit during the recruiting phase. The Sponsor may request copies of this log periodically during the enrollment phase of the study for reporting purposes.

10.3. Informed Consent

A Sponsor-approved Informed Consent template will be provided along with the study protocol for IRB submission and approval. Refer to the sample **Informed Consent Form** (Appendix A). A copy of the final IRB approved Informed Consent form (ICF) must be submitted to the Sponsor. All patients must sign the most recent Informed Consent Form prior to formal screening and study participation. During the Informed Consent process, the Investigator or designee - if allowed by local regulation - has to introduce the patient to the clinical study by:

- providing and explaining the Informed Consent
- describing the study procedures, alternative treatments, risks and benefits of participation
- explaining how the data will be handled and protected by both the Investigator and the study Sponsor

Candidates must be given sufficient time to read and understand the IRB approved Informed Consent form before deciding if they wish to participate in the study. The candidate must also be given the opportunity to have all questions answered. The Investigator or Designees will ask the patients to acknowledge whether all of their questions and concerns have been addressed to their satisfaction. Any questions that candidates may have will be addressed appropriately by the Investigator or Designee. No study-specific procedures will be performed in the absence of the completed informed consent process. Potential subjects will be further instructed that they are free to:

- obtain additional information from the Investigator at any time
- decline participation
- withdraw their consent and discontinue their participation at any time

After the Investigator or designee has finished explaining the informed consent process, and after the patient has had adequate time to read and agree to the Informed Consent form, she/he must complete and sign the Patient Informed Consent Form. The Investigator will not enroll patients that have not signed the Informed Consent Form. All subjects that have signed an Informed Consent to participate must be logged on the **Subject Enrollment Log** (Appendix C).

Bilateral TKA candidates that agree to enroll both operative sides *require* a separate signed and dated Informed Consent for each operative side. Each operative side will also require its own unique subject ID number.

10.4. Determination of Eligibility and Enrollment

Patient eligibility for enrollment will be determined for candidates who have signed an Informed Consent document and will be based on the inclusion/exclusion criteria. Patients must meet all of the implant-related and all of the study related inclusion criteria and none of the implant or study-related exclusion criteria in order to be offered enrollment into the study.

10.5. Baseline/Preoperative Assessment

Preoperative data will be collected for all subjects who have signed the Informed Consent form and meet the study-defined inclusion/exclusion criteria. At minimum the following information will be collected during the preoperative assessment:

- Inclusion / Exclusion Criteria

- Demographic Evaluation
- Physical Exam
- KSS Objective Knee Assessment
- KSS Pre-op Expectations
- Oxford Knee Score
- EQ-5D-5L Questionnaire

10.6. Surgical Technique

The current standard Persona TKA surgical technique will be followed by all surgeons for study implants.

10.7. Surgical / Early Post-Operative Assessment

Operative and early post-operative data will collect at minimum the following information:

- Operative Information
- Surgical Information
  - Tibial baseplate component catalog number
  - Femoral component catalog number
  - Articulating surface catalog number
  - Patellar component catalog number (if applicable)
- Discharge Summary
- Physician Assessment of Radiographs form is to be completed at the Early Post-op interval.

Post-surgical management for study subjects will follow the Investigator's standard of care for patients undergoing TKA. Post-surgical rehabilitative therapy will be as prescribed by the Investigator.

Patients that for any reasons did not receive study implants will be excluded from the study and the reason will be documented accordingly in the Study Completion Form.

10.8. Radiographic Definitions and Methods

All postoperative radiographic evaluations performed according to the protocol will be reviewed by the Investigator at the time of the evaluation and documented using the Physician Assessment of Post-op Radiographs case report form (if abnormalities are observed). This includes documentation of any significant radiographic findings. In

addition, an Adverse Event Report case report form must be completed for those findings indicated by an asterisk on the Physicians Assessment of Post-op Radiograph case report form, or for any other findings identified as an adverse event.

Required radiographic views: Standing anteroposterior (AP) and standard medial lateral radiographs (ML) of the operative knee are required to be captured at the Pre-op, Early Post-op, 6 month, 1 year, 2 year, 3 year, and 5 year follow-up visits. These views are also expected to be captured if the patient returns for an in-office visit at the 7 and 10 year intervals.

Radiographs should have similar exposure and must show the entire study device and surrounding bone. For consistency, every effort should be made to capture all radiographic views for a given subject using the same institution throughout the study. The investigative site will retain copies (hard copy/CD/digital) of all radiographs referenced for the study. It is at the Sponsor's discretion that study radiographs may be requested from the sites for independent radiographic review and assessment of appropriate parameters. Copies of certificates of registration and performance evaluations for radiographic equipment utilized in obtaining required x-rays should be maintained in the site documents for this study and must be available for review during monitoring visits. Additionally, the Sponsor may request copies of this documentation at any time during the course of this study.

The radiographic assessment definitions are as follows (according to Ewald, 1989):

Radiolucency or Radiolucent Lines: A radiographic clearing or line not exceeding 2mm in width at the bone/cement, cement/implant or bone/implant interface.

Osteolysis: A progressive radiolucency > 2mm in two or more zones not present on immediate postoperative radiographs and /or a bony destructive lesion that is progressive in nature.

Migration/Subsidence: A component migration of > 3mm or > 3º as compared to immediate post-operative radiograph may be considered a failure.[14]

10.9. Patient Reported Outcome Measures (PROMs)

The Oxford Knee Score (OKS): The OKS is a 12-item PRO specifically designed and developed to assess function and pain after TKA. This tool is short, reproducible, valid and sensitive to clinically important changes.[15]

EQ-5D-5L: The EQ-5D family of instruments has been developed to describe and evaluate health across a wide range of disease areas. Each EQ-5D instrument comprises a short

descriptive system questionnaire and a visual analogue scale (EQ VAS). The questionnaire provides a simple descriptive profile of a respondent's health state. The EQ VAS provides an alternative way to elicit an individual's rating of the individual's own overall current health.[16]

KSS Pre-op Expectations: This is a short self-report questionnaire to reflect the patient's opinion on the extent to which they expect the operation will improve their knee pain.[17]

KSS Post-op Expectations: This is a short self-report questionnaire for evaluating patient satisfaction with the outcome of hip and knee replacement surgery.[18]

10.10. Follow-Up Procedures

Clinical Interval	Follow-up Window	Target Post-op Day	Range (days)
Early Post-op (1 Month)	± 1 month	31	1 - 61
6 months	± 1 month	183	153 - 213
1 year	± 1 month	365	335 - 395
2 year	± 2 months	730	670 - 790
3 year	± 2 months	1095	1035 - 1155
5 year	± 6 months	1826	1646 - 2006
*7 year	± 6 months	2556	2376 - 2736
*10 year	± 6 months	3652	3472 - 3832

* *If patient is unable to complete onsite office visit for the 7, and / or 10 year follow up visits, these may be completed by electronically or US Postal Service. Therefore, the surgeon completed forms would be considered optional.*

Unless the study is prematurely closed by the sponsor, data will continue to be collected until each subject completes the 10-year interval, voluntarily withdraws from the study, is withdrawn from the study by the Investigator, is lost to follow-up, or undergoes removal of the Ti-Nidium femoral study component.

10.11. Minimization of Lost to Follow-Up

A study subject will be considered lost to follow-up after they have missed three consecutive interval years and attempts to locate and evaluate the subject using the procedure outlined below have failed. All attempts to contact the subject are to be documented in the subject's

medical record and on the **Study Completion** form. Missed visit(s) also must be documented using the **Protocol Deviation** form. *Attempt suggestions are outlined in the table below*. The expectation is that each site will maintain the highest rate of follow-up compliance possible throughout the study. In an effort to minimize lost to follow-up study subjects, the following recommendations and/or study requirements are essential to ensure proper patient selection and compliance:

Patient Eligibility: Subjects will be enrollment eligible according to patient criteria outlined in the inclusion/exclusion section, and are expected to return for all follow-up visits.

Patient Counselling: Patients will be counselled during the informed consent process on the importance of returning for all protocol-defined follow-up visits.

Patient Exclusion: Patients who are not willing to return for follow-up visits, unable to return for follow-up visits, or not willing to comply with the follow-up schedule will not be invited to participate in the study.

Patient Due Listings: In addition to proper patient selection, Zimmer Biomet will provide patient due notices to the sites on a regular basis in order to track each study participant and monitor adherence to the required follow-up visit timeframes.

Contact Tracking: Attempts to contact patients will be documented in the patients' medical record. It is recommended that attempts be made by telephone. If contact has not been successful after these attempts, the below are suggested prior to terminating the study patient from the study:

If	Then
a response is not received following attempts to reach the subject by phone	the Investigator could send a letter to the patient explaining the follow-up agreement per informed consent.
a response is not received from the Investigator's letter.	the Investigator could use any additional contacts provided by the subject to contact the subject.
the subject missed three consecutive visits and all attempts to contact the subject are unsuccessful, or the subject is contacted and chooses to withdraw from the study.	the **Study Completion** form will be completed and will specify the reason the patient is no longer participating in this study.

10.12. Revision Procedure

In the event that removal of *one or more* of the study related components is necessary, the Investigator will determine the best treatment and/or revision method for the subject. Once the revision surgery has been completed, the Investigator or qualified Designee must complete an **Adverse Event Report** case report form and the **Explanted Device** case report form detailing the events.

A **Study Completion** case report form is necessary to terminate the subject from the study *only if the Ti-Nidium femoral component is removed*. The Sponsor will report all revisions to an internal surveillance team, which may result in the request of additional information from the site such as op notes, surgical notes, etc.

Prior to revision, the Investigator or qualified Designee must document any significant radiographic findings related to the need for revision on the **Physician Assessment of Post-op Radiographs** form.

11. Reporting

11.1. Activities Required Prior to Initiation of the Study

Clinical Trial Agreement (CTA) and Financial Arrangements

A fully executed (signed by all required parties) CTA must be on file with the Sponsor prior to any Investigator participating in this study. This agreement must explain the financial arrangement with the investigative site.

Institutional Review Board Protocol Approval

This study protocol must be submitted to and approved by the site's appropriate overseeing IRB. A copy of the IRB approval letter must be submitted to the Sponsor. The letter should identify the following:

- Protocol name and/or number.
- Date of IRB meeting (if available).
- Date of approval.
- Date of expiration.
- Signature of IRB.

Clinicaltrials.gov Registration

The Sponsor will be responsible for registering this study on www.clinicaltrials.gov if required by local and national regulations.

11.2. Clinical Data Collection/Submission

Summary of Case Report Form Data Collection

Study data will be collected on source documents which may include study-specific worksheets provided by the Sponsor. For subjects having bilateral total knee arthroplasties, separate case report forms must be completed for each operative side.

The following source document/CRF completion guidelines should be followed:

- Complete carefully and accurately.
- Complete header information consistently across all case report forms for each individual study subject (when study-specific CRFs are used).
- Be sure that data on the source documents match that which is entered through the electronic data capture (EDC) system.
- Use the study subject's unique Case ID number assigned as instructed. Do not provide information that is not requested on the CRFs.
- Ensure that all fields are completed. For fields completed by the subject, efforts should be made to obtain any missing responses prior to the subject completing their visit.

Data Submission

Completed CRFs will be submitted directly to the Sponsor by electronic data capture and submission via a method approved by the Sponsor. Every effort must be made to ensure data submission to the Sponsor is made within 30 days of the visit completion.

Quality Assurance of Data

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports. Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All electronic systems used to create, modify, maintain, or transmit electronic study records will be validated. The Sponsor will maintain quality control systems, in accordance with the Sponsor's policies and procedures.

11.3. Reporting Requirements

Investigator Reporting Responsibilities

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of data reported to the Sponsor in accordance with this protocol. The Investigator or Designee will provide periodic reports to their IRB as required to maintain IRB approval throughout the study, and will provide any required final reporting to the IRB upon study completion/termination. A copy of all IRB re-approval letters must be submitted to the Sponsor. If the IRB terminates or suspends its approval of the study, the Investigator or Designee will suspend study-related activities and will promptly notify the Sponsor. The Investigator should also promptly provide written reports to the Sponsor and the IRB regarding any changes significantly affecting the conduct of the study, and/or increasing risk to the subjects.

Retention of Records

Clinical study records must be retained by the Investigator or Designee for at least 15 years from the Investigator's study termination date, or per applicable regulatory, local law and/or IRB requirements (whichever time period is greater). Measures shall be taken to prevent accidental or premature destruction.

Clinical study records are defined as all information in original records, certified copies of original records of clinical findings, observations or other activities in a clinical study, including source data initially recorded in an electronic format, necessary for the reconstruction and evaluation of the clinical study. This may include but is not limited to: hospital records, clinic records, laboratory notes, device accountability records, photographs, radiographs, subject casebooks, regulatory records, signed informed consents and all other study-related documents.

11.4. Management of Incurrent Events

Failure to Obtain Informed Consent

No study-specific procedures or data will be collected until the Informed Consent process and required information has been discussed with the patient and/or a legally authorized representative. The patient will also be allowed the necessary time to consider the stipulations of joining the study, and have the opportunity to have all their questions answered. Once a decision has been reached, this process will move forward when the Informed Consent form is signed and dated by the candidate. If a candidate does not wish to

participate (does not sign and date the Informed Consent form), data for that candidate will not be collected for this study.

Adverse Events

See Safety Management – Medical Events/Adverse Events section of this protocol for additional information regarding adverse event classifications.

Reporting and Documentation of Adverse Events and Adverse Device Effects

Adverse Events and Adverse Device Effects have to be documented on the Adverse Event Report form over the whole time of the investigation including information on the date of onset, treatment and resolution, as well as assessment of both the seriousness and the relationship to the study device. Further, the outcome of complications has to be documented and any changes in outcome are to be updated during the course of the study. In case of early termination of the study, further follow-up of the patient shall proceed according to the hospital's standard procedure.

Reporting and Documentation of Serious Adverse Events, Serious Adverse Device Effects, and Device Deficiencies

Serious Adverse Events and **Serious Adverse Device Effects** have to be **reported to the Sponsor as soon as possible**. The incidence has to be documented on the **Adverse Event Report** form over the whole time of the investigation including information on the date of onset, treatment and resolution, as well as assessment of both the seriousness and the relationship to the study device based on the evaluation of the Investigator. The outcome of such complications has to be documented and any changes in outcome have to be updated during the course of the study. In case of early termination of the study, further follow-up of the study subject shall proceed according to the hospital's standard procedure.

Device Deficiencies that did not lead to an adverse event but **could have led** to a medical occurrence if suitable actions had not been taken, if intervention had not been made or if circumstances had been less fortunate shall be **reported to the Sponsor as soon as possible**, as well.

The **Investigator** is responsible for reporting all SAEs, SADEs and Device Deficiencies that could have led to a SADE to the Institutional Review Board if required by national regulations or by the IRB.

Investigator Withdrawal

The Investigator can choose to withdraw a subject from the study if it is deemed to be in the subject's best interest or the subject does not consent to continue in the study after being informed of changes in the research that might affect them. The reason for the Investigator's withdrawal of the subject must be documented on the **Study Completion** case report form.

Subject Withdrawal

Study subjects may choose to withdraw from the study at any time, for any reason. If possible, a final evaluation will be completed for any subject who no longer wishes to participate in the study. The reason for the subject withdrawal must be documented on the **Study Completion** case report form.

Protocol Deviations

The Investigator should not deviate from the agreed upon protocol unless it is to eliminate hazard to the patient. However, any deviation from the protocol has to be documented on the **Protocol Deviation** Form along with an explanation for the deviation and reported to the Sponsor. Each significant deviation will be reported to the Institutional Review Board, if applicable, within the appropriate deadlines stipulated by the appropriate regulatory authorities. Significant deviations are defined as those impacting or potentially impacting patient safety.

Investigator disqualification criteria leading to exclusion from the clinical study include fraud, misconduct and serial non-compliance.

Study Termination

Study subject participation is expected to end upon completion of the subject's ten-year follow-up visit unless the subject voluntarily withdraws from the study, is withdrawn from the study by the Investigator, is lost to follow-up, undergoes revision to remove the Ti-Nidium femoral component of the study device, or expires. Reason(s) for study completion must be documented on the **Study Completion** case report form.

Note: Revision of any other device component (tibial baseplate, articular surface, or patella) will be captured in survival analyses via the case report forms, but *will not* result in study completion.

If the Sponsor decides to terminate the study early, the Sponsor will inform the Investigators of the reason for early study termination. It is the responsibility of the Investigators to inform their IRB as applicable according to local and national laws/regulations.

12. Safety Management – Medical Events/Adverse Events

Adverse events are required to be reported on the **Adverse Event Report** case report form. The completed **Adverse Event Report** case report form must be submitted to the Sponsor in a timely manner. The Investigator or Designee will also promptly provide the Sponsor with any additional requested information required for the Sponsor to comply with regulatory requirements. If applicable per their reporting requirements, the Investigator or Designee will also report applicable adverse event(s) to their IRB.

The following definitions are from ISO 14155:2020 and Medical Device Regulation (EU) 2017/745: Safety reporting in clinical investigations of medical devices.

Classification of the Event

Adverse Event (AE):
An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices or comparators.

Serious Adverse Event (SAE):
A Serious Adverse Event is an adverse event that:

a. led to death.

b. led to serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, including chronic diseases, or
    3. in-patient or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. led to fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Serious Health Threat

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibly of multiple deaths occurring at short intervals.

Adverse Device Effect (ADE):

An Adverse Device Effect is an adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment implantation, installation, or operation, or any malfunction of the medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the medical device.

Serious Adverse Device Effect (SADE):

A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)
An unanticipated adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Note 1: Anticipated serious adverse device effect is an effect which by nature, incidence, severity or outcome has been identified in the risk assessment.

Device Deficiency (DD)
A Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Note: Device Deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.

It is important to document in the study also all device deficiencies that could have led to a medical occurrence but did not lead to an adverse event.

Causality Assessment (Relation to Device)

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each adverse event will be classified according to four different levels of causality:

- Not Related
- Possible
- Probable

- Causal Relationship (Definitely related)

The sponsor and the Investigator(s) will use the following definitions to assess the relationship of the adverse event to the investigational device, the comparator or the investigation procedure.

Not related:
Relationship to the device, comparator or procedures can be excluded when:
the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device.

Possible:
The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Probable:
The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship (Definitely related):
The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt.

Note: Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

The Sponsor will review the Investigator's assessment of all reported events submitted to determine and document in writing their severity and relationship to the study device and related procedures required by this protocol. In case of disagreement, the Sponsor will consult the Investigator for clarification and correct if required. If the disagreement cannot be

resolved, the Sponsor shall communicate both options to the Post Market Surveillance team for further investigation and required reporting if applicable.

Intensity of Symptoms

Mild:
The subject is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the subject and/or little clinical significance. The event is not expected to have any effect on the subject's overall health or well-being.

Moderate:
The subject has discomfort enough to cause interference with or a change in usual activities. The event is of some concern to the subject's health or well-being and may require medical intervention and/or close follow-up.

Severe:
The event interferes considerable with the subject's usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life threatening. Hospitalization and treatment may be required.

Note: The term "severe" refers to the intensity of the event and can be used with any event, without regard to whether or not it meets the criteria for being classified as "serious" or "unanticipated". For example, a subject can have a severe headache, but it is not a serious event.

Outcome Definitions

The outcome is in relationship to the Adverse Event, not the treatment rendered for the event (if any).

Resolved:
This outcome indicates the event has improved or recuperated.

Resolved with Sequelae:
This outcome indicates the subject recuperated but retained pathological conditions resulting from the prior disease or injury.

Resolving:
This outcome indicates that the event is improving.

Not Resolved:
This outcome indicates that the adverse event has not improved or recuperated.

Fatal:
The adverse event resulted in the termination of life.

Unknown:
The outcome of the adverse event is not known, not observed, not recorded, or patient refused to provide information to make an outcome determination.

13. Monitoring

Prior to initiating the clinical study, the Sponsor may conduct a site or remote evaluation visit to ensure the Investigator(s) and study staff understands the study protocol and requirements and have adequate time and resources to implement and conduct the study. Prior to study initiation, the Investigator must have a fully executed CTA and IRB approval of the study protocol and the Informed Consent.

During the course of the study, the Sponsor will conduct periodic central monitoring and maintain contact with the study staff to monitor compliance and evidence of adverse events, in accordance with the Sponsor's policies and procedures. The Sponsor will address any identified non-compliance with the executed CTA, study protocol, and applicable regulatory requirements. Additional information may be located in the Monitoring Plan in the Sponsor's trial master files.

If onsite monitoring visit(s) are deemed appropriate by the Sponsor, the Investigator will permit representatives of the Sponsor's monitoring team to have direct access to inspect all source data/documents, study documents/binders, study subject case report forms, corresponding sections of study subject medical/hospital records, and any other documents relevant to the study.

The **Site Monitoring Visit Log** (Appendix C) will be maintained throughout the course of the study. The log will contain the visit date, monitor name/signature and the purpose of the visit (i.e. site initiation, onsite interim monitoring (as applicable), site close-out, etc. The site monitoring log will be filed in the Regulatory Binder for the study. Additional details may be found in the study Monitoring Plan.

14. Risk Analysis

GENERAL: There are no anticipated risks specific to study participation other than the potential loss of confidentiality. There are no experimental procedures in this study, and participation in this study is not anticipated to affect the medical treatment of enrolled subjects.

When used in accordance with product labelling, the risks associated with the use of the Persona Ti-Nidium Knee and Vivacit-E articulating surface are similar to those of standard knee replacement used for the same clinical indication or purpose. These risks are either general surgical risks or risks associated with the subject procedure/study device. Unanticipated adverse events can also occur.

A list of adverse events (AE) and anticipated adverse device effects (ADE) can be found in the Instruction for Use, in the section titled “Adverse Effects”. Investigators should refer to it.

15. Statistical Methods

15.1. Study Endpoints

Primary Endpoint

The primary endpoint for this study will be performance assessed by improvement in the Oxford Knee Score (OKS) from baseline to 2 years, as evaluated using the overall group mean showing greater than the minimal clinically important difference [MCID] of 7 points, according to Beard et al (2015).[1]

The OKS is a patient reported outcome measure (PROM) that has a total score ranging from 0 (most severe symptoms) to 48 (least symptoms), with 48 being the best outcome. The OKS, completed by the study subject, includes 12 questions designed to assess function and pain after TKA. Each question is scored from 0 to 4, with 4 representing the best outcome/least symptoms. This tool is short, reproducible, valid and sensitive to clinically important changes.[15]

Secondary Endpoints

1. Safety will be assessed through evaluation of radiographic imaging at each time point and by the overall incidence and frequency of adverse events including revision of any component at each time point. Adverse events will be broken out by indication and also categorized as AEs, SAEs, ADEs, and UADEs.

2. In addition to the primary endpoint, performance will also be assessed by evaluating improvements in the Knee Society Score (KSS) Objective Knee assessment, and by the evaluation of the revision, removal, or exchange of any implant component for any reason at each post using Kaplan-Meier product-limit estimator. Lastly, clinical benefits will be assessed through the KSS Post-op Expectations and the euroQOL Five Dimensions Questionnaire (EQ-5D-5L).

Exploratory Endpoints

Statistical relationships between patient demographics, comorbidities, outcome measures, device accessories and endpoints may be explored. Analyses may include regression models with the OKS as the response variable and patient demographics or device variants as the predictive variables. Cox Regression may be used to determine if there are relationships between the survival outcomes and patient demographics.

15.2. Study Hypothesis

The primary effective analysis will be performed on the Intent-to-Treat (ITT) population. The objective of the primary effective analysis is to demonstrate the mean improvement of OKS from baseline to 2-year is greater than the minimal clinically important difference (MCID) of 7 points.

$$H_0: \mu_{2-\mathrm{Year}} - \mu_{\mathrm{Baseline}} \leq \mathrm{MCID}$$

$$H_1: \mu_{2-\mathrm{Year}} - \mu_{\mathrm{Baseline}} > \mathrm{MCID}$$

Where:

$\mu_{2-\mathrm{Year}}$ = the average OKS score at 2-year

μ_{Baseline} = the average OKS score at baseline

MCID = 7

15.3. Sample Size Justification

The sample size required was calculated based on the overall group mean improvement of the Oxford Knee Score (OKS). Beard et al (2015) reports a minimal clinically important difference (MCID) of 7 points from baseline to 2 years.[1] Zimmer Biomet observed a 19.3 point mean improvement in Persona CoCr patient cohorts in

Europe, but plan to adapt to 12.2 for a more conservative approach.

With 80% power and alpha set at 0.05, 23 patients per variant would be needed for an expected change of 12.2 points with a standard deviation of 8.4. Considering an attrition rate of 40%, a minimum of 39 patients need to be enrolled per articular surface combination.

To better support conclusions drawn from secondary endpoints and respect regulatory body recommendations, 60 patients will be enrolled for each of the 4 variants (PS/CPS, CR, UC, MC). Thus, there are 240 total study subjects.

For each of the variants, the first 23 patients enrolled will be evaluated for the primary endpoint. A final analysis will be conducted once all 60 patients have OKS data at 2 years post-op.

15.4. Analysis Populations

Intent to Treat (ITT)
The intent to treat population is defined as all enrolled subjects in whom a Persona Ti-Nidium Personalized Total Knee System is implanted. The primary endpoint will be evaluated in the ITT population. For patients in the ITT population who are missing data necessary for the determination of the primary endpoints, data will be imputed as described below in the section “Missing Data and Sensitivity Analyses.”

Per Protocol (PP)
The per protocol population is defined as all subjects with a successful implant of the Persona Ti-Nidium Personalized Total Knee System, without any major protocol deviations (i.e., inclusion/exclusion violations) and with complete 2-year data. Secondary endpoints and future exploratory analyses will be conducted in the PP population. In addition, tables will be produced to evaluate differences between the ITT and PP populations and analyses will be performed as necessary to determine if there are any explanatory factors in the difference between the populations.

15.5. Missing Data and Sensitivity Analyses

Data will be considered “missing” if the primary endpoint cannot be calculated or is not available for a subject in the ITT population. Sensitivity analyses will examine the sensitivity of the results for missing values of the primary outcome using the following

analyses:

- **Last Observation Carried Forward**: Missing observations are imputed by taking the most recent outcome prior to 24 months and using it in place of the missing 2-year outcome.
- **Multiple Imputation**: This method replaces each missing value with a set of plausible values that represent the variability around the choice of which value to impute. Up to ten complete data sets will be created using multiple imputation and the sensitivity of the primary outcome will be examined based on the imputed data sets.

Data for revision cases prior to 2-years will be treated as missing and will be imputed by both Last Observation Carried Forward and Multiple Imputation. The primary analysis will be evaluated using both missing data techniques.

15.6. Statistical Analyses

Intermediate Analysis
The primary endpoint at 2 years will be compared to baseline for each variant as soon as their minimum sample size of 23 has reached the 2-year visit. Each variant will be treated as independently and analyzed as its own cohort. Paired T-Tests of Wilcoxon tests will be used to assess the differences.

Final Analysis
Comparison of the primary endpoint between 2 year and baseline will be performed using standard statistical tests and will be chosen as appropriate for the scale and distribution of the measure being analyzed. Paired T-Tests or Wilcoxon tests will be performed to assess the differences and p-values will be reported for the study hypothesis. Additionally, p-values will also be reported for the intermediate visits to examine relative improvement in the OKS over time.

Continuous variables (e.g. age or OKS) will be summarized by N, mean, standard-deviation, minimum, and maximum at each follow-up visit. Categorical variables (e.g. gender) will be summarized by frequency and percentage at each visit. As needed, subgroup summaries will be generated by strata within the study population (e.g. gender), by different cut-points (e.g. ranges of weight), by variants, or surgical approach. Intersite variability may also be analyzed using one-way ANOVA or a

random effects model.

In addition, the time to revision will be calculated for each subject. For those individuals that do not experience a revision, their survivorship outcome will be classified as censored. The last available clinical visit will be used as the censored date for subjects lost to follow-up. The death date will be used as the censored date for deceased subjects. The survivorship point estimate and 95% confidence interval about the point estimate will be calculated for each year point. Failure-free curves will summarize and illustrate the proportion of endpoint-free subjects over the course of the study. The Kaplan-Meier (KM) product-limit method will be used to construct the endpoint-free curve. Additionally and where appropriate, the KM method may be utilized to investigate the survivorship of individual components, such as the Ti-Nidium femoral component.

Each participating Investigator will receive study reports on their own pseudonymized data and the collated pseudonymized data for the whole study group. Anonymized study metrics, e.g. summary tables, graphical output and descriptive statistics will be produced and may be available as hard copy. Strict confidentiality of individual hospital data will be maintained.

15.7. Subject Accounting

Accountability tables will be generated to show, at each study visit, the number of subjects who might be expected to attend a given visit and the number of proportion who did attend. Below is the analysis window for each visit:

Visit Interval	**Follow-Up Window (Days from Surgery)**
Preoperative	≤ 0
Early Post-op	1 - 61
6 Months	153 - 213
1 Year	335 - 395
2 Years	670 - 790
3 Years	1035 - 1155
5 Years	1646 - 2006
7 Years	2376 - 2736
10 Years	3472 - 3832

The following definitions specify how the subject accountability table tracks subject

follow-up:

Theoretically Due: The number of implants that could be examined if all subjects returned on the first day of the follow-up window based on their respective initial surgery dates and the date of database closure.

Death: The number of deaths that have taken place in the course of the investigation according to scheduled follow-up visits.

Failure: The number of (re-)revisions that have taken place in the course of the investigation according to the scheduled follow-up visits.

Withdrawal of Consent: The number of subjects that have withdrawn during the course of the investigational study recorded according to the scheduled follow-up visits.

Lost to Follow-Up: The number of subjects that have lost to follow-up during the course of the investigational study recorded according to the scheduled follow-up visits.
Actual[A]: The number of subjects with complete data (i.e. primary endpoint can be determined) who are actually evaluated within the protocol-defined follow-up intervals.

Actual[B]: The number of subjects with any follow-up data (in- or out-of-window) reviewed or evaluated by Investigator.

Expected: This element is the number of subjects expected for a given time interval. These include the theoretical number of subjects who are due to be evaluated, less the number of subjects who have died, withdrawn, been revised, been lost to follow-up, or are not yet overdue in this time interval.

Follow-Up Rate: This element is the ratio of actual subjects evaluated to expected subjects, express as a percentage.

16. Quality Control & Quality Assurance

The study is conducted in accordance with the Declaration of Helsinki, ISO 14155:2020, US Code of Federal Regulations 21 CFR Parts 11, 50, and 56, as well as the ICH Guideline on Good Clinical Practice.

The Investigator will be required to permit representative(s) of the Sponsor's monitoring team to inspect all Case Report Forms and corresponding sections of the study patients' office records and/or hospital original medical records. These audits will be done for quality assurance purposes, i.e. verifying adherence to the clinical investigation plan/protocol, and the completeness and accuracy of the data being entered on the Case Report Forms.

The Clinical Investigation Plan will be provided to all participating study centers. The Investigators will be fully trained in the proper reporting and submission of trial data prior to patient enrollment. Completed Case Report Forms may be reviewed by the Sponsor before the data is compiled into a central database.

The Clinical Study Manager is responsible for generating data queries for missing or unclear data if needed. It is the responsibility of the Clinical Study Manager to ensure data quality.

There will be regular meetings between the Investigators and Zimmer Biomet Clinical Affairs staff. Written correspondence to all sites will be used to inform the Investigators of routine study details and to update them on study status.

17. Suspension or Premature Termination of the Clinical Investigation

Zimmer Biomet may decide to suspend or prematurely terminate the clinical study at one or more investigational sites if, for example, information becomes available that the risk to study subjects is higher than initially indicated and/or interim analysis indicates that the results significantly differ from the study objectives or statistical endpoints.

In the case of an early termination of the study, the IRB and regulatory authorit(ies) should be informed in accordance with regional and/or national laws/regulations, and IRB requirements. The reasons for termination should be provided and documented.

Further follow-up of the study subjects shall proceed according to the Investigator's standard of care or hospital's standard procedures.

18. Vulnerable Populations

Patients that are within one or more inappropriate vulnerable populations, including children, prisoners, and pregnant women are to be excluded from this study. Steps to safeguard the well-being of other vulnerable populations likely to participate (such as elderly individuals) include a robust voluntary Informed Consent process, and oversight by a local or central IRB. These individuals are allowed to participate in that they are the most likely to benefit from the study's conclusions and their data is critical to evaluation of the study objectives for their population.

For all appropriate included populations, the Investigator and/or designee will provide an oral presentation of the Informed Consent document and answer any questions. The patient (and their legally authorized representative) will be given adequate time to decide whether or not to participate. The Informed Consent document is written at an 8th grade level, and in a language that is understandable to the subject or representative.

19. Amendments / Modifications to the Clinical Investigation Plan

All amendments to this clinical protocol shall be agreed to by the Sponsor and be recorded with a justification for the amendment prior to implementation. Approval from the IRB must be obtained prior to implantation of the amended protocol, if required by regional and/or national laws/regulations. In the case of an amendment to the protocol, the revision history will be documented in the Document History section of this protocol.

20. Publication Policy

Both the Investigator and the Sponsor have the right to publish or allow the results of the clinical trial to be published. The Investigator recognizes that the Sponsor has a special interest in the results of the clinical study and will submit manuscripts to the Sponsor prior to publication. If the Sponsor desires changes to be made, these are communicated to the Investigator within 30 days of submission. Pooled data may be used for training and meetings.

In the event there is a restriction on the total number of authors, priority will be given to the Investigators who provided the most data for the article. The order of names will be based on the amount of input, time and effort put into the article.

21. Document History

Version Number	Date	Description of Change	Person in Charge of Change
1.0	January 29, 2021	Initial Document	Tim Swanson
1.1	March 22, 2021	• Change in enrollment per site • Require 15yrs of record retention • Various formatting and language additions in line with new protocol template	Tim Swanson
1.2	April 15, 2021	• Adapting to CDASH / CDISC language for reporting adverse events • Addition of Explanted Device case report form • Various formatting changes	Tim Swanson
1.3	July 15, 2021	• Adjusted incorrect follow-up windows to align with the EDC	Tim Swanson
1.4	July 29, 2021	• Added CPS sku #'s to the appendix	Tim Swanson

Note:

- **Administrative Changes** (CIRC review/approval not required) updates the Protocol Version to an incremental decimal, e.g. 1.0 → 1.1
- **Substantive Changes** (CIRC review/approval required) updates the Protocol Version to the next incremental integer, e.g. 1.0 → 2.0

22. References

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23 Appendices

Appendix A - Sample Informed Consent (and Patient Information Sheet if applicable)

Appendix B - Case Report Forms

Appendix C - Study Logs

- Informed Consent Log
- Site Monitoring Visit Log
- Site Signature/Delegation Log
- Patient Screening/Enrollment Log

Appendix D – Instructions for Use

Appendix E – Device Catalog Numbers

Appendix F – Investigator Amendment Acknowledgement Statement

The following information is provided in the Regulatory Binder:

- Sponsor contact information
- Return information for explanted devices